Identifier: O01

SYSTEMIC INFLAMMATION, LYMPHOPROLIFERATION AND VASCULOPATHY IN A PATIENT WITH ARHGAP10 MUTATION

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Introduction: Inborn errors of immunity can underline genetic conditions with a predominant inflammatory phenotype. Early childhood vasculitis are rare rheumatic diseases characterized by infiltration of the blood vessel wall by immune cells driving cell damage, blood flow disruption and ischemia or hemorrhages . ARHGAP10 is a member of Rho GTPase-activating proteins (RhoGAP). It contributes to the regulation of actin cytoskeleton dynamics, cell proliferation, and apoptosis by inhibiting Rho family GTPases, including RhoA and CDC42.

Objectives: We present a novel genetic condition observed in a patient characterized by systemic inflammation with increased serum IL-6 and vasculitis presenting with stroke, intestinal ischemia, non-malignant lymphoproliferation and short stature.

Methods: Peripheral blood mononuclear cells (PBMCs) and fibroblasts derived from patients were used for in vitro experiments. Cell migration was assessed by transwell assay and scratch test. Actin polymerization was quantified via FACS analysis. Zebrafish hemorrhages and vascular abnormalities were detected by fluorescence microscopy in transgenic lines.

Results: Histological samples revealed sarcoidosis-like granuloma, medium size vessel vasculitis and blood wall abnormalities. The disease partially responded to anti-IL6 therapy with progression of the vasculopathy and exitus in the second decade of life. Whole exome sequencing revealed a homozygous missense mutation in ARHGAP10. The mutation was predicted to be damaging in silico, with no homozygous variant reported in databases. Experiments performed in patient's primary cells, documented increased RhoA activation, altered in vitro migration and actin polymerization. Silencing of ARHGAP10 expression in zebrafish resulted in growth restriction, CNS hemorrhages, blood vessel abnormalities, defective neutrophil migration and increased IL6 mRNA transcripts. A rescue of the phenotype was possible in vivo using a RhoA inhibitor.

Conclusion: Alteration of ARHGAP10 protein leads to defects in RhoA pathway and cytoskeletal and vascular abnormalities.

Disclosure of Interest: None declared

Identifier: O02

BIOLOGICS IN THE TREATMENT OF PEDIATRIC BEHÇET'S DISEASE: RESULTS OF AN INTERNATIONAL COLLABORATIVE STUDY BY THE PRES VASCULITIS WORKING PARTY

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Introduction: Behçet's Disease (BD) is a variable vasculitis affecting arteries and veins of all sizes. Pediatric cases represent 4%-26% of all BD cases, with similar incidence between genders but different clinical presentations. The treatment of pediatric Behçet's Disease (pedBD) is tailored to the severity of the disease and the organs involved, based on adult recommendations such as the The European Alliance of Associations for Rheumatology (EULAR) 2018 guidelines. Goals include controlling inflammation, relieving symptoms, and preventing complications through individualized approaches.
Objectives: The objective of this study is to examine the preferences of pediatric rheumatologists with regard to the use of biologic therapy in the treatment of BD. In addition to assessing the efficacy, side effects and remission rates of such therapy, the study also seeks to compare the demographic and clinical characteristics of Turkish and European cohorts.
Methods: This study is a multicentre, retrospective analysis conducted within the vasculitis study group of the Pediatric Rheumatology European Society (PReS). Data were collected from 19 centres in six countries, focusing on 109 patients diagnosed with pedBD before the age of 18 years.
Results: The study included 109 pedBD patients, comprising 45 in the European cohort and 64 in the Turkish cohort. The median age at diagnosis and mean age were similar between cohorts. Males comprised 64.2% of the total group, 55.5% in the European cohort, and 70.3% in the Turkish cohort (p=0.11). Across the entire cohort, ocular involvement (40.4%) was the most common indication for biologics, followed by mucocutaneous (22.9%) and neurological involvement (17.4%). Tumor necrosis factor-α (TNF-α) inhibitors were predominantly used (90.8%), with adalimumab (ADA) being the most common first-line treatment (59 cases), followed by infliximab (IFX) (38 cases).
In the European cohort, IFX was mostly used (44.4%), followed by ADA (35.6%) and apremilast (8.9%). In contrast, the Turkish cohort preferred ADA (67.2%), followed by IFX (28.1%) and ETN (3.1%). In the European cohort, IFX (50%) was mostly used for ocular involvement, while ADA (71.9%) was more frequently preferred in the Turkish cohort for ocular involvement. For neurological involvement, both ADA and IFX were preferred in both cohorts. In the European cohort, IFX was used in 8 of 9 patients (88.9%), while in the Turkish cohort, both agents were equally preferred, with 5 patients receiving ADA and 5 receiving IFX. (Table 1)

While remission rates were similar between ADA and IFX groups, patients receiving ADA achieved remission more quickly. In the European cohort, 2 patients achieved drug-free remission, 22 were in drug-on remission, in the Turkish cohort, 1

patient achieved drug-free remission, 49 were in drug-on remission. The frequency of adverse events was similar between the groups.

Table 1. Biologic agent selection according to organs/systems in Turkish and European cohorts

	Turkish cohort (n=64)	**European cohort (n=45)**	***p***
Ocular involvement, n (%)	**32 (50)**	**13 (26.7)**	0.11
Adalimumab, n (%)	23 (71.9)	5 (41.7)	
Infliximab, n (%)	8 (25)	6 (50)	
Neurological involvement, n (%)	**10 (15.6)**	**9 (20)**	0.06
Adalimumab, n (%)	5 (50)	1 (12.5)	
Infliximab, n (%)	5 (50)	8 (88.9)	
Vascular involvement, n (%)	**3 (4.7)**	**5 (11.1)**	0.68
Adalimumab, n (%)	1 (33.3)	1 (20)	
Infliximab, n (%)	2 (66.7)	3 (60)	

Conclusion: This study highlights the predominant use of TNF-α inhibitors, particularly ADA and IFX in pedBD with comparable efficacy and safety profiles. While the overall remission rates and adverse event frequencies were similar across Turkish and European cohorts, drug-free remission remained rare, underscoring the need for sustained biologic therapy in most patients. These findings provide valuable insights into the demographic, clinical, and therapeutic characteristics of pedBD in diverse geographic regions.

Disclosure of Interest: None declared

Identifier: O04

COFILIN-1 IS A REDOX SENSOR REGULATING THE NLRP3 INFLAMMASOME

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Introduction: NLRP3 has a pivotal role in nucleating the inflammasome, a cytoplasmic multiprotein complex that mediates the maturation of the proinflammatory cytokines interleukin-1β (IL-1β) and IL-18 by activating caspase-1. Mutations in the gene encoding human NLRP3 cause a spectrum of autoinflammatory disease, the cryopyrin-associated periodic syndromes (CAPS). The NLRP3 inflammasome also has been reported to be involved in the pathogenesis of other inflammatory conditions, including gout, type 2 diabetes mellitus, atherosclerosis, and Alzheimer's disease. Reactive oxygen species (ROS) are a major factor for NLRP3 inflammasome activation induced by many extracellular activators. However, the molecular mechanism by which a change in cellular redox state leads to NLRP3 inflammasome activation, as well as the molecular pathogenesis of CAPS, has not been elucidated. Here we found that cofilin-1, an actin severing protein, is a negative regulator of the NLRP3 inflammasome that is released by ROS.
Objectives: To investigate how ROS activates the NLRP3 inflammasome and the molecular pathogenesis of CAPS.
Methods: Bone marrow-derived macrophages (BMDMs) from wild-type (WT) and NLRP3 knockout (KO) mice were used for screening NLRP3-interacting proteins through co-immunoprecipitation and mass spectrometry. Inflammasome activation was analyzed by ELISA or immunoblotting to detect the released active forms of IL-1β and caspase-1. Intracellular ROS were measured with MitoSox green. The interaction between cofilin-1 and NLRP3, as well as the knockdown of *Cfl1*, was analyzed using BMDMs. J774.1 cells were used to ectopically express wild-type (WT) or mutant cofilin-1 proteins. The NLRP3-binding motif of cofilin-1 was identified through GST-pull down assay. WT or mutant peptides containing the NLRP3-binding motif of cofilin-1 were synthesized and transfected into mouse BMDMs or peripheral blood mononuclear cells (PBMCs) from CAPS patients with various *NLRP3* mutations.
Results: In the absence of NLRP3 inflammasome activators, cofilin-1 directly bound to the nucleotide-binding domain (NBD) of NLRP3 protein in LPS-primed mouse BMDMs. When the cells were stimulated with NLRP3 inflammasome activators, cofilin-1 was oxidized and dissociated from NLRP3. On the other hand, oxidation-resistant C39A/C80A mutant cofilin-1 was not dissociated from NLRP3 and suppressed inflammasome activation by NLRP3 inflammasome activators. The dissociation of cofilin-1 from NLRP3 in inflammasome-activated cells was inhibited by extracellular potassium and MCC950, known inhibitors of the NLRP3 inflammasome. Knockdown of *Cfl1* induced spontaneous IL-1b release, which was dependent on the NLRP3 inflammasome but not NLRC4, AIM2, or pyrin inflammasomes. The binding of cofilin-1 to CAPS-associated mutant human NLRP3 was substantially decreased relative to binding to wild-type NLRP3. Four amino acid residues of cofilin-1 were identified as essential for its interaction with NLRP3. A peptide synthesized with 33 amino acids of cofilin-1 containing the NLRP3-binding motif suppressed IL-1β release induced by CAPS-associated NLRP3 mutations as well as NLRP3 inflammasome activators.
Conclusion: Taken together, these results demonstrate that cofilin-1 is a key component in regulating the NLRP3 inflammasome in response to ROS and that the spontaneous activation of the inflammasome in myeloid cells of patients with CAPS may be due to reduced suppression of NLRP3 activation by cofilin-1. Peptides containing the NLRP3-binding motif of cofilin-1 could be developed into treatments not only for CAPS but also several acquired inflammatory diseases in which the NLRP3 inflammasome has been implicated.
Disclosure of Interest: None declared

Identifier: O05

SGT1 CONTROLS NLRC4 INFLAMMASOME ACTIVATION IN AUTO-INFLAMMATORY DISEASES

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Introduction: Autoinflammatory diseases (AIDs) are characterized by recurrent episodes of multi-system inflammation, including chronic fever, skin rashes, and arthralgia. Genetic defects underlying certain AIDs often involve gain-of-function (GOF) mutations in inflammasome components, such as NLRP3 and NLRC4, leading to spontaneous inflammasome activation and the release of proinflammatory cytokines like IL-1β and IL-18. NLRC4-GOF mutations are associated with a range of autoinflammatory diseases, including Macrophage Activation Syndrome (MAS), and Familial Cold Autoinflammatory Syndrome (FCAS). However, the detailed molecular mechanisms driving inflammasome assembly and activation in AIDs remain incompletely understood.
Objectives: This study aims to elucidate the molecular mechanisms and signaling pathways that drive and regulate autoinflammation, with a particular focus on defining the essential signaling components involved in NLRC4 activation.
Methods: To achieve these objectives, we developed human cellular models that recapitulate NLRC4-AIDs. These models were used to perform functional genetic screening to identify novel regulators of NLRC4 inflammasome complex formation induced by GOF-mutations. Additionally, we employed biochemical approaches to assess the contribution of each identified component, utilizing CRISPR-Cas9 to delete specific candidates' genes.
Results: We developed human monocyte-derived cellular models incorporating a doxycycline-inducible NLRC4-S171F system, which serves as a representative model of NLRC4-AID. Activation of NLRC4-S171F induced the formation of inflammasome-ASC specks, leading to the cleavage of IL-1β and GSDMD, and resulting in subsequent cell death. A genome-wide CRISPR screen identified SGT1 as a critical regulator of NLRC4-GOF inflammasome formation. Further investigation revealed that SGT1 interacts with both GOF and wild-type (WT) NLRC4 via its LRR domain. Notably, SGT1 is essential for NLRC4-GOF activity and regulates WT NLRC4 activation following bacterial infections. Mechanistically, SGT1 acts upstream of ASC recruitment, and is required for NLRC4 oligomerization, as SGT1 impairs these processes.
Conclusion: Our findings highlight the pivotal role of SGT1 in regulating NLRC4 function, providing novel insights into NLR oligomerization mechanisms and their role in inflammation. This study underscores the potential of functional genetics to identify key regulators of inflammasome activation, offering promising avenues for therapeutic intervention in autoinflammatory diseases.
Disclosure of Interest: None declared

Identifier: O06

GSDMD AND GSDME AMPLIFY NLRP3 ACTIVATION IN AUTOINFLAMMATION

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Introduction: Neutrophils play a key role in CAPS pathogenesis in mice, yet the nature of their response to activation in human patients, the relative roles of gasdermin (GSDM) D and GSDME in IL-1β(Interleukin-1β) production, and capacity to undergo pyroptosis are unknown.

Objectives: This study aims to investigate: (1) the activation status and nature of the neutrophil response to cold-triggered autoinflammation in CAPS patients; and (2) the roles of GSDMD and GSDME in regulating IL-1β processing and pyroptosis in neutrophils from CAPS mouse models. Specifically, we study neutrophil heterogeneity in a CAPS case series, and the kinetics of the neutrophil response to cold-induced NLRP3 activation. Using mouse models of CAPS, we then evaluate the impact of GSDMD and GSDME loss on disease progression and the cellular, biochemical, and biophysical changes accompanying NLRP3 activation in mouse neutrophils.

Methods: Peripheral blood samples were obtained from patients with confirmed NLRP3 mutations after written informed consent was provided. A subset of patients underwent a cold challenge, and blood samples were analyzed before and after the challenge by mass cytometry (CyTOF). We used our two murine CAPS models, MWS (*Nlrp3A350V*) and FCAS (*Nlrp3L351P*), crossed with *S100a8-Cre* (neutrophil-specific), *LysM-Cre* (myeloid-specific), or *Esr1-Cre* (tamoxifen-inducible). These mice were intercrossed with *Asc-/-*, *Gsdmd-/-*, and *Gsdme-/-* strains to compare survival and record lesion number and size of neonates. For *ex vivo* studies, bone marrow neutrophils were isolated and cultured for 2 or 6 hours in Pam2CSK4 or LPS. For studies with *Esr1-Cre* cells, neutrophils were incubated with tamoxifen for 6h prior to stimulation to trigger expression of the mutant *Nlrp3* allele. Pyroptosis was tracked by flow cytometry and live-cell imaging using Annexin V and PI. The localization of GSDMD and GSDME was studied using lattice SIM super-resolution microscopy, and the impact of these gasdermins on ultrastructure was captured by transmission electron microscopy. Changes in the biophysical properties of pyroptotic neutrophils were analyzed using atomic force microscopy. IL-1β secretion was measured by ELISA. Western blotting was used to track Inflammasome proteins.

Results: Neutrophils from CAPS patients are highly heterogeneous including 3 subsets expressing differing levels of IL-1β, and they undergo rapid phenotypic changes during autoinflammatory flares. In mice, the combined deletion of both GSDMD and GSDME improved survival and resolved skin lesions typically associated with the disease. This was associated with a significant reduction in Caspase-1 cleavage and pro-IL-1β processing. Surprisingly, the loss of GSDMD alone resulted in increased cleavage of GSDME, suggesting a compensatory mechanism. In activated neutrophils from CAPS mice, GSDMD and GSDME pores could be visualized at the plasma membrane forming higher-order structures that disrupted membrane integrity.

Conclusion: The coordinated actions of GSDMD and GSDME are critical for amplifying NLRP3 inflammasome activation and mediating pyroptosis in neutrophils during CAPS. The combined loss of both GSDMD and GSDME prevents IL-1β secretion and mitigates autoinflammation, highlighting the essential and non-redundant roles of both gasdermins in CAPS pathogenesis. Targeting the gasdermin pathway may be beneficial as an alternative to IL-1 therapies in some disease settings, however these data highlight the potential need to target multiple gasdermins for neutrophilic autoinflammation.

Acknowledgments: National Institutes of Health grant R01AI155869 (BC & HMH)

National Institutes of Health grant P01HL152958 (BC, HMH, SDC, CH)

American Heart Association Career Development Award (YPZ)

National Institutes of Health grant NINDS P30NS047101

National Institutes of Health grant S10OD030505

Disclosure of Interest: None declared

Identifier: O07

PROTEIN ARRAY PROFILING IDENTIFIES DISTINCT AUTO ANTIBODY SIGNATURES IN SYSTEMIC AUTO INFLAMMATORY DISEASES

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Introduction: Systemic auto inflammatory diseases (SAIDs) encompass a diverse group of chronic, often debilitating disorders characterized by immune dysregulation in which the immune system involving multiple cell types, cytokines, and, notably, auto-antibodies. Understanding the precise auto-antibody patterns associated with different SAIDs is essential for advancing diagnostic precision, elucidating disease mechanisms, and developing personalized therapeutic strategies.

Objectives: (1) delineate distinct antibody profiles within the SAID population, (2) assess the heterogeneity of immune responses across and within SAID subtypes, and (3) investigate correlations between auto-antibody reactivity and clinical parameters. We hypothesize that specific auto-antibody signatures will be differentially associated with SAID phenotypes and disease progression, offering insights into potential mechanisms of pathogenesis and guiding future therapeutic interventions.

This research is part of the PerSAIDs (PERsonalised medicine for SAIDs) project, funded by “ERA PerMed JTC2021: Multidisciplinary Research Projects on Personalised Medicine – Development of Clinical Support Tools for Personalised Medicine Implementation” and co-funded by the European Union (grant agreement No 101137129).

Methods: Leveraging AITs in-house developed 16k protein microarray —a comprehensive technology that enables the simultaneous profiling of Antibody responses against over 7390 of human proteins—we analyzed serum samples from a well-characterized cohort of 114 individuals. This method allowed for an expansive profiling of auto-reactivity, capturing both known and novel antigen-specific antibodies.

We profiled autoantibody signatures using protein microarrays, applying background correction, quantile normalization, and batch correction. Group comparisons were conducted with linear models for microarray analysis, with significance thresholds of adjusted p-value < 0.05 and log2 fold-change >1 or <-1. Machine learning (ML) models, including Elastic-Net Regularized Generalized Linear Models and Naïve Bayes, were employed with performance criteria of AUC ≥ 0.7, and sensitivity and specificity ≥ 0.6. Dimensionality reduction and visualization were performed using UMAP.

Results: Distinct antibody profiles were identified across disease groups, revealing unique patterns of immune reactivity. Notably, antibodies against USP5—a deubiquitinating enzyme involved in protein degradation and cellular stress regulation—emerged as a potential marker of disease-specific immune dysregulation. Key reactive proteins, for which significant autoantibody responses were detected, will be highlighted. Using machine learning for feature selection further refined these markers, enhancing the robustness and specificity of our findings.

Conclusion: We identified unique auto-antibody profiles associated with different monogenic and polygenic SAIDs by employing a high-throughput immunomics approach. The immunological signatures reveal the heterogeneity of immune responses among SAID patients, offering valuable markers for differentiating subtypes, improving diagnostic precision, and identifying new therapeutic targets aligned with specific disease mechanisms. This work enhances our understanding of disease-specific immune pathways and supports the development of novel diagnostic and prognostic

tools. Ultimately, our findings underscore the potential of such immunologic signatures to guide personalized therapeutic interventions, improving patient outcomes and advancing autoinflammatory disease management.
Disclosure of Interest: None declared

Identifier: O08

VALIDATION OF HUMAN PHENOTYPE ONTOLOGY (HPO) TERMS AND DEVELOPMENT OF AN AI-BASED DIAGNOSTIC TOOL FOR SAIDS USING THE EUROFEVER REGISTRY: THE ODINO PROJECT

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Introduction: Accurate classification is crucial for the early diagnosis and therapy optimization of systemic autoinflammatory diseases (SAIDs). The overlapping and complex phenotypes of SAIDs make classification challenging. The Human Phenotype Ontology (HPO) project provides a standardized terminology for describing phenotypic features of genetic diseases. In 2022 the AutoInflammatory diseases section was revised and updated, but the accuracy of the new terms has not yet been validated in real patients. HPO help clinicians prioritize diagnosis by ranking diseases based on similarity scores between HPO terms and patient's symptoms, through its associated prediction tool, *Phenomizer*. However, the tool's accuracy has not yet been validated in real-world datasets.

Objectives: i) to evaluate the diagnostic accuracy of HPO terms in a cohort of real patients, ii) to evaluate the accuracy of *Phenomizer* compared to different machine-learning algorithms based on a provided real-life patients' dataset. iii) to develop a novel diagnostic tool for SAIDs

Methods: Our dataset included 2,866 patients from the Eurofever Registry, diagnosed with Familial Mediterranean Fever (FMF), Cryopyrin-Associated Periodic Syndrome (CAPS), Mevalonate Kinase Deficiency (MKD), Periodic Fever, Aphthous Stomatitis, Pharyngitis, Adenitis (PFAPA), or Tumor Necrosis Factor Receptor-Associated Periodic Syndrome (TRAPS). Eurofever clinical variables were codified with HPO terms, and missing terms were retained. The patients' dataset was split into training (n=2,005) and test sets (n=861). Four machine learning classifiers were evaluated: Elastic Net regression (EN), k-Nearest Neighbors (kNN), Random Forest (RF), and eXtreme Gradient Boosting (XGBoost), comparing their performance to *Phenomizer*

Results: 224 Eurofever variables (215 clinical, 5 laboratory, 4 demographic) were codified into HPO terms. Of these,195 had full HPO correspondence, 12 partial, and 17 no correspondence. XGBoost emerged as the best-performing algorithm in assigning the correct diagnosis to the analyzed patients, achieving an average accuracy of 0.80, and significantly outperforming *Phenomizer*, even when *Phenomizer* was trained on Eurofever HPO terms' frequencies. The addition of the terms "fever duration" and "ethnicity" (present in Eurofever but absent in HPO) improved the algorithm accuracy, highlighting the need for new HPO codes. Additionally, the number of HPO terms per patient showed a reversed U-shaped association with classification accuracy, indicating that either too few (low characterization) or too many terms (low specificity) reduced accuracy, underscoring the importance for clinician to carefully select HPO terms in order to optimize classification. Finally, based on the best-performing algorithm, a user-friendly web app where clinicians can input HPO terms to receive the probability of each SAID diagnosis (among those used in the training model) was developed

Conclusion: Our results suggest that the HPO database should be updated including Eurofever patients' term frequencies. The developed web app correctly identifies the two most probable SAIDs in over 85% of cases, offering a valuable tool for early diagnosis. Further updates will refine the model as additional data from underrepresented diseases become available

Disclosure of Interest: None declared

Identifier: O09

ASSESSING THE IMPACT OF FAMILIAL MEDITERRANEAN FEVER (FMF) ON PHYSICAL ACTIVITY IN CHILDREN USING THE PHYSICAL ACTIVITY QUESTIONNAIRE FOR CHILDREN (PAQ-C): A COMPARATIVE PRELIMINARY STUDY WITH HEALTHY CONTROLS

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Introduction: Familial Mediterranean Fever (FMF) is the most common inherited autoinflammatory disease, characterized by recurrent episodes of fever, abdominal pain, chest pain, and arthritis. These recurrent attacks were previously observed to impair the physical activity levels in pediatric patients. However, there is no such study evaluating the relationship between physical activity and disease activity in children with FMF.
Objectives: The primary aim was to assess the physical activity levels of pediatric patients with FMF who are stable under colchicine treatment and compare these levels with age- and sex-matched healthy controls. The secondary aim was to examine the correlation between the physical activity levels and the acute phase reactants (APRs) and the disease activity scores of the patients.
Methods: This cross-sectional study enrolled pediatric FMF patients aged 9-14 years, who had at least 6 months of follow-up duration. Those without exon 10 mutation in the Mediterranean fever (*MEFV*) gene, and those having inadequate colchicine adherence were excluded. The FMF diagnosis was made according to the Eurofever/PRINTO classification criteria. Disease activity is assessed using the Pras score and the International Severity Scoring System for FMF (ISSF), while the Physical Activity Questionnaire for Children (PAQ-C) was used to assess the physical activity levels of the subjects. The participants were monitored for one month with weekly PAQ-C score. APRs including C-Reactive protein (CRP), erythrocyte sedimentation rate (ESR), and serum amyloid A (SAA) were measured before and after this observation period.
Results: A total of 142 participants were included (71 in the control group, and 71 in the patient group) (male/female=70/72). The mean PAQ-C score of FMF patients (2.79 ± 0.73) was found to be significantly lower than that of the control group (3.36 ± 0.57) ($p< 0.05$). Furthermore, FMF patients with exercise-induced leg pain were demonstrated significantly lower PAQ-C scores compared to those without leg pain (2.57 ± 0.58 vs. 3.02 ± 0.81, $p < 0.05$). PAQ-C scores were evaluated for their correlations with demographic characteristics, inflammatory markers, and disease activity scores. A statistically significant negative correlation was observed between patient age and PAQ-C scores ($r = -0.368$, $p = 0.002$). A statistically significant negative correlation was observed between PAQ-C scores and ISSF scores at both 0 months ($r=-0.307$, $p < 0.05$) and 1 month ($r = -0.298$, $p < 0.05$). Additionally, PAQ-C scores were also evaluated across PRAS disease severity categories (mild, moderate, severe) at 0 and 1 months, but no statistically significant differences were found.
Conclusion: This study demonstrates that children with FMF exhibit higher propensity for reduced physical activity. Among the patients, those experiencing exercise-induced leg pain were observed to engage in less physical activity. These findings suggest that children with FMF may intentionally limit their physical activity as a protective measure against activity-induced attacks. Moreover, patients of increasing age demonstrated decreased physical activity, which may be attributed to the heightened awareness of activity-induced attacks that develop with age. To investigate the relationship between physical activity and disease activity in patients over time, we planned a three-month prospective study employing disease activity scores and PAQ-C scores as monitoring tools.
Disclosure of Interest: None declared

Identifier: O10

INCORPORATION OF RECENT SELECTION SIGNALS IMPROVES VARIANT IMPACT PREDICTION IN IMMUNE-MEDIATED GENES

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Introduction: The diagnostic yield for rare immune diseases, including autoinflammatory conditions, remains disproportionately low at ~20%, compared to ~40% for other rare diseases (Poker et al., 2023; Wright et al., 2023). This gap reflects ongoing challenges in accurately annotating variants in immune-related genes, where conventional variant impact prediction tools frequently misclassify pathogenic variants as benign. Most tools assume that conservation positively correlates with functional importance. We hypothesize that the unique selection pressures acting on immune-related genes—characterized by swift and recurrent episodes of positive and negative selection, along with pleiotropic effects—disrupt this relationship, resulting in a higher false negative rate for these genes.
Objectives: To systematically evaluate the performance of existing variant impact prediction tools, identify their limitations for immune disease genes, and develop a novel variant impact prediction model tailored to address these challenges.
Methods: We analyzed variants across multiple datasets, including ClinVar, Infevers, HGMD, gnomAD, and MAVE, and assessed the performance of 45 variant prediction tools (32 individual and 13 ensemble models) using ROC analysis and AUC metrics. Differences in classification thresholds between immune and non-immune genes were examined, revealing discrepancies in prediction accuracy. To overcome these limitations, we developed a machine learning model that integrates eight distinct recent selection signals, capturing positive selection, neutrality, and negative selection for all genes; in addition to 18 other structural and evolutionary conservation features.
Results: Our analysis demonstrated that immune-related genes require lower classification thresholds for accurate variant prediction. We found that the optimal point between sensitivity and specificity for each tool tested was lower for immune genes (Infevers and IUIS) compared to non-immune genes (ClinVar and OMIM). When comparing Infevers to ClinVar, the optimal thresholds for REVEL and CADD were 0.324 and 17.24, compared to 0.735 and 24.15, respectively. Further, we found that optimal thresholds were significantly lower for variants associated with genes under positive selection - which were enriched with immune genes – both innate and adaptive. These findings highlight a systematic underestimation of pathogenic variants in immune genes when using conventional pathogenicity prediction criteria, likely due to strong selection signals.
We present Freyja, an ensemble random forest model, which incorporates recent selection-based signals. We demonstrate state-of-the-art predictions across a wide range of genetic and experimental benchmarks. Freyja achieves an AUC of 0.96 on ClinVar variants, compared to an AUC of 0.91 and 0.83 for REVEL and CADD. We further assessed the performance of our model on IUIS defined disease genes, and achieved an AUC of 0.88 compared to 0.79 for the next best performing tool, CADD. Our model enhances variant impact prediction in known autoinflammatory genes, such as *NLRP3*, where pathogenic variants have historically been misclassified. Application of our approach to inflammatory disease sequencing cohorts identified previously missed pathogenic variants in known autoinflammatory genes and revealed novel gene-disease associations, including findings in *STAT4* (Baghdassarian et al., 2023).
Conclusion: By integrating selection-informed features our model improves prediction accuracy, reduces false negatives, and identifies overlooked pathogenic variants. Further, we provide immune-specific variant curation guidelines for widely used tools. This framework directly improves molecular diagnostics, uncovers novel gene-disease associations, and advances precision medicine strategies for inflammatory conditions, ultimately addressing a fundamental limitation in rare disease research.
Disclosure of Interest: None declared

Identifier: O11

IMPROVED MACHINE LEARNING MODELS FOR PREDICTING COLCHICINE RESISTANCE IN FAMILIAL MEDITERRENEAN FEVER

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Introduction: Familial Mediterranean Fever (FMF) is the most common hereditary autoinflammatory syndrome, and colchicine resistance remains a significant challenge in its treatment. The ability to predict colchicine resistance in advance could greatly impact treatment management. Recently, machine learning algorithms have emerged as powerful tools for predicting this resistance. These algorithms are capable of forecasting colchicine resistance based on various patient features, enhancing clinical decision-making.
Objectives: To enhance the performance of baseline models by incorporating new features and technically improving the models.
Methods: In this study, a cohort of 965 patients was examined, with various clinical and genetic features used as inputs for the models. The patients with missing data on new features were eliminated. The features included mutation type (homozygous, heterozygous, compound heterozygous), presence of specific mutations (M694V, M680I, E148Q, V726A, R761H), presence of recurrent arthritis, presence of arthralgia, presence of oligoarthritis, age of diagnosis and frequency of attacks. Two machine learning techniques were employed: Deep Learning and Logistic Regression. These models were trained on the dataset to predict colchicine resistance based on the newly introduced features.
Results: The deep learning model achieved an AUC of 0.79, while the logistic regression model reached an AUC of 0.78. These results were compared with baseline models, and the comparison is shown in Table 1.

Table 1. Comparison of Baseline and Current Machine Learning Models

Model	Features (Baseline Model)	Features (Current Model)	AUC (Baseline Model)	AUC (Current Model)
Logistic Regression	Presence of compound heterozygous mutations in the MEFV gene, Chest pain during attacks, Number of attacks per month before treatment, M694V homozygous mutation, Presence of recurrent arthritis	Mutation type (Homozygous, heterozygous, compound heterozygous), Presence of specific mutations (M694V, M680I, E148Q, V726A, R761H), Presence of recurrent arthritis, Presence of arthralgia, Presence of oligoarthritis,	0.76	0.78

		Age of diagnosis, Frequency of attacks,		
Deep Neural Network	Number of attacks per month before treatment, Presence of M694V homozygous mutation, Presence of recurrent arthritis	Mutation type (Homozygous, heterozygous, compound heterozygous), Presence of specific mutations (M694V, M680I, E148Q, V726A, R761H), Presence of recurrent arthritis	0.75	0.79

Conclusion: The incorporation of new features and technical enhancements has led to significant improvements in the predictive performance of our models. These models show a promising ability to predict colchicine resistance more accurately and can be further refined for even better performance.

Disclosure of Interest: None declared

Identifier: O12

DIAGNOSIS OF CRYOPYRIN-ASSOCIATED PERIODIC SYNDROME (CAPS) IN ADULTHOOD: LESSONS FROM A FRENCH COHORT

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Introduction: Cryopyrin-associated periodic syndrome (CAPS) is a rare autoinflammatory disorder associated with a pathogenic gain-of-function mutation in the *NLRP3* gene, which was characterised in 2001. The key symptom of the disease is the presence of dermatological involvement, most commonly cold-induced pseudo-urticarial lesions. Other associated symptoms include fever, rheumatological, ophthalmological, neuroinflammatory symptoms and hearing loss. More recently, atypical cases of CAPS without cutaneous symptoms have been described. Although the disease most commonly manifests in childhood, it is not uncommon to be diagnosed in adulthood, with the risk of inflammatory complications, particularly AA amyloidosis.

Objectives: The aim of this study is to identify the reasons for diagnosis in adulthood in patients with CAPS.

Methods: Patients were recruited through the Reference Centre for Autoinflammatory Diseases and AA Amyloidosis at Tenon Hospital. Patients with genetically proven CAPS diagnosed in adulthood and who had been seen at least once in consultation were identified using the AP-HP Clinical Data Warehouse authorized by the French Data Protection Authority (Commission Nationale de l'Informatique et des Libertés, number 1980120). Clinicobiological data were collected retrospectively for each patient, including the *NLRP3* variant, symptoms associated with the disease, age at diagnosis and age at onset of symptoms. Criteria to explain the delay in diagnosis were defined as follows: atypical presentation without skin involvement, age of onset after 18 years, diagnosis of the disease within 10 years of its initial characterisation.

Results: A total of 47 patients were recruited. The median age of symptom onset in the cohort was 3 years, ranging from 0 to 32 years, and the median age at diagnosis was 42 years, ranging from 18 to 73 years, with a median delay in diagnosis of 32 years, ranging from 5 to 73 years. The most common symptoms in the cohort were arthralgia in 74.5% of cases (35/47), urticaria in 57.4% of cases (27/47), headache in 48.9% of cases (23/47), conjunctivitis in 46.8% of cases (22/47) and fever in 34% of cases (16/47). One patient in the cohort had AA amyloidosis.

82.9% of patients (39/47) had only one criterion that could explain the diagnosis of CAPS in adulthood, 14.8% (7/47) had two and 2% (1/47) had three. The majority of patients diagnosed in adulthood had an atypical presentation without skin involvement, accounting for 42.6% of patients (20/47). 27.7% (13/47) of them were diagnosed before 2011, i.e. within 10 years of disease description. 6.4% (3/47) of them had developed the disease in adulthood. In 27.7% of cases (13/47), none of the above criteria were met.

Conclusion: CAPS is still under-diagnosed, with many cases of long diagnostic delay in patients diagnosed in adulthood despite symptoms beginning in childhood. The results suggest that the delay in diagnosis is largely explained by atypical presentation of the disease without skin involvement, with the latter being one of the key symptoms of the disease. It is important for clinicians to consider CAPS even in the absence of skin involvement, and even more so if there is a family history of inflammatory symptoms or unexplained hearing loss. Early genetic analysis is necessary to avoid a long delay

in diagnosis with the risk of complications such as AA amyloidosis, significant hearing loss requiring hearing aids and impact on the patient's quality of life.

Disclosure of Interest: None declared

Identifier: O13

NEUTROPHIL EXTRAVASATION AND BBB DISRUPTION IN MURINE NOMID: INSIGHTS INTO NEUROINFLAMMATION

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Introduction: Neonatal-Onset Multisystem Inflammatory Disease (NOMID) is a severe autoinflammatory disorder caused by mutations in the NLR family Pyrin domain containing 3 (*NLRP3*) gene, resulting in chronic systemic inflammation with neuroinflammation. However, the mechanisms leading to Central-nervous system (CNS) disease remain poorly understood.
Objectives: This study aimed to characterize the neutrophilic inflammation in the brains of murine NOMID neonates and identify specific involvement in CNS inflammation. We sought to examine the integrity of the blood-brain barrier (BBB) and evaluate the potential therapeutic effects of an NLRP3 inhibitor and IL-1Ra on these processes.
Methods: We generated *Nlrp3*$^{D301N/+}$ Zp3 Cre mice to model the germline *NLRP3* D303N mutation in patients with NOMID. Experiments were performed on postnatal day 10 (P10). Super-resolution microscopy (Airyscan LSM 780/880) stained for Hoechst (nuclei), IBA1 (microglia), IL-1β, and Ly6G (neutrophils), with images 3D rendered in Imaris. To visualize BBB leakage, NOMID pups were injected with FITC-dextran and processed for IF after 5 minutes. Vascular permeability was evaluated with Evans blue injections, followed by brain homogenization and spectrophotometric quantification of extravasated dye in the supernatant. IL-1Ra or MCC950 (10mg/kg) was administered every other day, with vehicle controls. On P10, leukocytes, endothelial cells, and microglial cells were isolated from homogenized brains using a Percoll gradient and analyzed by flow cytometry and single-cell multiomics (RNA transcriptome and antibody-oligo immunophenotyping using BD Rhapsody).
Results: NOMID brains contained an abundance of infiltrating monocytes and neutrophils, as well as neutrophil and monocyte progenitors supportive of extramedullary myelopoiesis. Super-resolution microscopy showed interactions between IBA1+ IL-1b+ microglia and extravasating IL-1b+ neutrophils at the BBB, and neutrophils clustering around microglia in the white/grey matter. FITC-dextran leakage confirmed vascular compromise and Evans blue staining was elevated in NOMID brains. Single-cell multiomics revealed activated microglia with upregulated complement activation pathways (C1QB, C1QA, C1QC, and C4B) and other activation markers for microglia including Apoe, Clec4a1, Cd74, Ctss, CysLTR1, Trem2, and Otulin1. NOMID microglia also displayed a specific upregulation of IL-18 and P2RX7, along with CCR2, CCL9, and CCR5. IL-1- and NLRP3-targeted therapies reduced neutrophil presence in the brain.
Conclusion: This study provides mechanistic insights into immune cell expansion in NOMID and suggests that interactions between resident brain cells and infiltrating myeloid cells and progenitors may play a role in the development of chronic CNS inflammation. The identification of key immune cell types interacting at the BBB and in the cortex provides a new understanding and roadmap to specifically interfere with initial damage at the BBB and preserving BBB integrity in NOMID and other neutrophil-driven autoinflammatory conditions.
Acknowledgments: National Institutes of Health grant R01AI155869 (BC & HMH)

National Institutes of Health grant P01HL152958 (BC, HMH, WBK)

Disclosure of Interest: None declared

Identifier: O14

IRAK2 DEFICIENCY CAUSES A NEW IMMUNE DYSREGULATION DISORDER

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Introduction: Interleukin 1 receptor-associated kinase 2 (IRAK2) plays a critical role in immune response by participating in the formation of the Myddosome complex in Toll-like receptor (TLR) signaling pathways. IRAK2 is composed of a death domain (DD), a proline, serine, and threonine-rich (ProST) linker, a kinase domain (KD), and a C-terminal domain (CD), with the DD being critical for Myddosome assembly. Patients with loss-of-function mutations in either *MyD88* or *IRAK4* are highly susceptible to pyogenic infections due to impaired TLR and interleukin 1 (IL-1) signaling. Moreover, many patients with IRAK4 deficiency also develop autoimmune disease, suggesting a more complex pathological mechanism of Myddosome deficiency.

Objectives: To determine the correlation between the *IRAK2-Δex2* mutation and the clinical manifestations observed in three patients.

Methods: Whole-exome sequencing (WES) was performed on the two patients to identify pathogenic mutations. Sanger sequencing was conducted to confirm the copy number variant (CNV) in *IRAK2* in three patients and their family members. Cytometric Bead Array, RNA sequencing, Cytometry by time of flight (CyTOF), and single-cell RNA sequencing (scRNA-seq) were performed on samples from the patients. Functional studies were carried out in HEK293T cells and bone marrow-derived macrophages (BMDMs) from *Irak2*$^{\Delta ex2/\Delta ex2}$ mice to assess the impact of the *IRAK2-Δex2* mutation.

Results: We first identified a homozygous loss-of-function mutation (*IRAK2-Δex2*), a CNV, in the *IRAK2* gene in three patients exhibiting immune dysregulation, including systemic lupus erythematosus (SLE) and Behçet's disease. This mutation results in a partial deletion of the DD in the IRAK2 protein, disrupting the interaction between IRAK2 and IRAK4, but with no significant change in its interaction with tumor necrosis factor receptor-associated factor 6 (TRAF6), as demonstrated by co-immunoprecipitation in HEK293T cells. We overexpressed either wild-type IRAK2 (IRAK2-WT) or IRAK2-Δex2 in a stable HEK293T-TLR4 cell line. After stimulating the TLR4 complex, IRAK2-Δex2 failed to enhance the phosphorylation of p65, p105, JNK, and p38 compared with IRAK2-WT. Defective NF-kB and MAPK signaling was further observed in patients' PBMCs and BMDMs from *Irak2*$^{\Delta ex2/\Delta ex2}$ mice. Using CyTOF and scRNA-seq, we found that impaired NF-kB signaling specifically occurred in patients' myeloid cells following LPS stimulation. Despite reduced NF-kB signaling, an aberrantly upregulated type I IFN response was observed in patients' PBMCs following LPS stimulation, primarily in the monocyte-macrophage lineage. The upregulated type I IFN response was further confirmed in BMDMs from *Irak2*$^{\Delta ex2/\Delta ex2}$ mice.

Conclusion: We identified a homozygous loss-of-function mutation, *IRAK2-Δex2*, in three patients exhibiting immune dysregulation disorders. The mutation resulted in impairments in NF-kB and MAPK signaling pathways and an upregulation of type I IFN signature in both patients and mice. Our study highlights the critical role and dual function of IRAK2 in regulating inflammatory responses and provides insights in the pathogenesis of immune dysregulation disorders due to IRAK2 deficiency.

Acknowledgments: We thank the patients, their families and the unaffected controls for their support during this research study.
Disclosure of Interest: None declared

Identifier: O15

CHANGING THE LANDSCAPE OF ACQUIRED SAIDS - REPORT FROM THE UK REFERENCE GENETIC LABORATORY

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Introduction: Genetic mosaicism has emerged as a significant molecular mechanism of systemic autoinflammatory diseases (SAIDs). In SAIDs somatic mutations typically originate in myeloid cells and are reported in patients without a family history and/or with a late presentation. To date, somatic mutations have been reported in the following genes: *NLRP3, NLRC4, TNFRSF1A, NOD2, STING, TLR8, and UBA1*.
Objectives: As the UK reference laboratory for diagnoses of SAIDs we aimed to establish the prevalence of mosaicism in patients who were referred for genetic testing.
Methods: Between 2018 and 2024, 4409 patients were referred with a suspicion of SAIDs and underwent analysis of targeted NGS autoinflammatory gene panel, which has been validated to detect a very low mutant allele, at a frequency down to 3% (min amplicon coverage ≥200X). All variants were classified according to the American College of Medical Genetics and Genomics (ACMG) guidelines and in line with the pathogenicity reported on the Infevers database and ClinVar. Clinical information for each patient was provided by the referring clinician and the outcome of genetic testing was discussed at multidisciplinary team (MDT) meetings.
Results: Genetic testing led to diagnosis of SAIDs in 308 patients (7%). Of these, mosaic variants were identified in 53 patients (17%): 32 (31M:1F) had VEXAS; 17 (8M:9F) CAPS; 4 (3M:1F) TRAPS; 1 Blau syndrome and 1 NLRC4 associated autoinflammatory disease. 4 patients presented either at birth or early infancy (all diagnosed with CAPS), the remaining reported disease onset typically in adulthood (median age at presentation 60 years).

Of the 17 patients in whom we found mosaic variant in the *NLRP3* gene 13 reported their symptoms started in adulthood (median age at presentation 50 years). Three had been diagnosed AA amyloidosis.

In total 20 different mosaic variants (classified as pathogenic/likely pathogenic by one or more of the online tools mentioned above) were found: 11 variants in the *NLRP3* gene; 4 in *TNFRSF1A* gene; 3 in the *UBA1* gene; 1 in *NOD2* gene and 1 in *NLRC4* gene. In 6 patients the mutant allele frequency (MAF) was ≤5%. Of the 11 mosaic variants detected in the *NLRP3* gene, 7 were clustered in the HD2 domain, which is a known hotspot for mosaic variants, the remaining 4 in NBD domain.

In the past 4 years, we received 112 requests for patients in whom the referring clinician suspected a diagnosis of VEXAS; of those 24 (21%) had a pathogenic variant in the UBA1 gene. We identified 8 further patients with VEXAS in whom the referring clinician had not suspected VEXAS, but upon receipt of the genetic results, the clinical features were reviewed and ultimately the diagnosis of VEXAS was made in each patient.

Conclusion: The results from our specialised diagnostic laboratory, show that that 17% of patients who had been diagnosed with SAIDs carry a mosaic variant. Notably, disease is not mild and carries risks including AA amyloidosis. Interestingly, one patient diagnosed with the late-onset CAPS had the acquired p.(Tyr570Cys) variant with the MAF of 3.3%, yet this low level somatic mosaicism was sufficient to cause sustained acute phase response.

This series highlights the importance of deep sequencing targeted NGS approach to detect very low-level mosaic mutations in patients with suspected SAIDs, even in the classically inherited types not only CAPS where mosaicism is well recognised, but also the other dominant diseases of TRAPS, Blau and NCLR4 associated autoinflammatory disease. The landscape of acquired genetic diseases in older adults has been transformed by the discovery of VEXAS by Beck et al. in 2020 and in line with this our results show a dramatic and persistently increasing change in demographics with the majority of somatic mosaicism now resulting in diagnosis of patients over the age of 50 with an overlapping autoinflammatory

features and hematological abnormalities consequent on VEXAS, suggesting that this disease is still significantly underdiagnosed.

Disclosure of Interest: None declared

Identifier: O16

RARE TNFAIP3 HYPOMORPHIC VARIANTS ARE A MASSIVELY UNDERESTIMATED DRIVER OF HUMAN AUTOINFLAMMATORY DISEASE GLOBALLY

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Introduction: *TNFAIP3* encodes the ubiquitin editor A20, which inhibits multiple proinflammatory signaling pathways. High-penetrance heterozygous germline mutations in *TNFAIP3* cause the early-onset autoinflammatory disease HA20 (Haploinsufficiency of A20). The prevalence of HA20 is thought to be low, with only 200 reported cases. However, HA20 is clinically heterogeneous and has variable severity, leading us to hypothesize that prevalence might be underestimated due to ascertainment bias.
Objectives: To determine the contribution of rare *TNFAIP3* variants to immune disease at a population-wide level using genotype-to-phenotype pipelines.
Methods: To determine the collective prevalence of rare (MAF<0.01%) predicted pathogenic *TNFAIP3* variants, we analyzed three population-wide genomic databases, gnomad v4 (730,947 exomes; 76,215 genomes), the All of Us database (244,845 genomes), and the UK Biobank (500,000 genomes). To test variant function, we generated mutations in full-length A20 (Addgene), transfected WT vs. mutant *TNFAIP3* plasmid into A20-deficient HEK293T cells, and measured TNF-induced NF-kB activation (Cignal luciferase, Qiagen). Clinical association analyses were performed on paired electronic health record data using standardized pipelines (PheWAS, PheRS). For the HA20 “referral cohort,” we also measured A20 expression (Western) and interferon gene score (Nanostring) in patient-derived samples.
Results: Rare predicted loss-of-function (pLOF) variants (frameshift, truncating, splice null) had a mean prevalence of 1:14403. Rare predicted pathogenic missense (pPM)variants (CADD>30; SIFT deleterious; PolyPhen probably damaging) had a mean prevalence of 1:2782. *In vitro*, pLOF and pPM variants reduced A20 stability and/or TNF-induced NF-kB activation. Variants were significantly associated (PheWAS) with Behcet’s disease, chronic hepatitis, and respiratory disease, all of which can be seen in HA20. Subjects with pLOF and pPM variants were significantly more likely to carry multiple autoimmune and autoinflammatory diagnoses than subjects in a "virtual control" cohort. To further study the role of hypomorphic missense variants in HA20, we investigated a “referral cohort” of patients seen at the University of Pittsburgh for autoinflammatory disease related to pLOF (48 subjects, 17 variants) or missense (14 subjects, 9 variants) *TNFAIP3* mutations. All pLOF variants and 8 of 9 missense variants (89%) were fully penetrant. Patients with pLOF and missense variants exhibited clinical autoinflammation and/or autoimmunity as well as evidence of basally activated TNF-NFkB, inflammasome-IL-1ß, and/or Type I interferon signaling. Variants either increased A20 protein degradation, resulted in production of an A20 protein unable to suppress TNF-induced NFkB activation, or reduced both protein stability and function. Some individual missense variants had allele frequencies > 0.01% (mean prevalence > 1:3609). Patients exhibited >90% response to therapies targeting A20-regulated pathways.
Conclusion: Our findings suggest that rare hypomorphic *TNFAIP3* variants are a massively underrecognized cause of inflammatory disease with a high global disease burden. Enhanced recognition and expanded genetic testing could potentially improve disease outcomes by directing these patients towards HA20-related therapies.
Acknowledgments: We thank our collaborators for their input and referrals. We thank our patients for enthusiastic participation in this study.
Disclosure of Interest: D. Schwartz Grant /Research support from: Eli Lilly, Sobi, Consultant for: Sobi, D. Lee: None declared, U. Karri: None declared, Y. Luo: None declared, K. Cetin Gedik: None declared, P. Chhibbar: None declared, P. Guha Roy: None declared, J. Das: None declared, M. Carpio Tumba: None declared

Identifier: O17

JAK INHIBITORS ARE EFFECTIVE IN PEDIATRIC REFRACTORY NLRC4 GAIN OF FUNCTION MUTATION

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Introduction: NLRC4 gain of function mutation (GOFM) leads to an hyperinflammatory state with aberrant levels of interleukin IL-18 and IL-1-beta. Blocking these cytokines does not always lead to clinical remission. Other pathways induced by the excess production of IL-18, notably IFN-gamma, may be downregulated by Janus kinase inhibitors (JAKi).
Objectives: Report two patients with refractory NLRC4 GOFM who reached remission on JAKi.
Methods: Case report design.
Results: These are the first patients reported with NLRC4 GOFM treated with a JAKi. Patient 1 is a 7-year-old male with a de novo heterozygous mutation in the nucleotide binding domain of NLRC4 (c.1021G>C, p.Val341Leu). He presented at 2 weeks of age with severe enterocolitis and macrophage activation syndrome. Total IL-18 levels measured early in the disease course were elevated: 82844 pg/mL at 7 weeks old and 13305 pg/mL at 7 months old. His course was characterized by multiple severe disease flares and exposure to prolonged high dose corticosteroids. He received multiple lines of immunosuppressive therapies with partial or no effect: anakinra, sirolimus, infliximab, adalimumab. He achieved near complete disease remission and was weaned off steroids with a combination of canakinumab 150 mg/kg subcutaneous (SC) q 2 weeks, adalimumab 20 mg SC q week and an IL-18 specific blocker. The latter medication became unavailable and baricitinib 2 mg twice daily was added to canakinumab and adalimumab. Complete disease remission (CDR) was achieved within 1 month, adalimumab was stopped and canakinumab is being tapered.

Patient 2 is a 19-year-old male. He presented at 1 month of life with severe enterocolitis. He was diagnosed with food protein-induced enterocolitis syndrome. He remained with poor weight gain, frequent regurgitations and unformed stools until 6 years old. He was symptom-free from age 6-12. He represented at age 13 years with severe fistulizing ileocolitis and was diagnosed with Crohn's disease. He failed to achieve remission despite systemic corticosteroids, infliximab, azathioprine and vedolizumab. He underwent genetic testing at age 16 and was found to have an heterozygote mutation in NLRC4 (c.1005G>A, p.Met335Ile). IL-18 level was elevated at 2568 pg/mL (normal ≤ 266 pg/mL). Tofacitinib 10 mg po BID was started alongside ustekinumab 90 mg SC monthly. The patient achieved CDR four weeks post initiation of tofacitinib/ustekinumab. Temporary interruption of tofacitinib, while continuing ustekinumab, led to a severe disease flare. Tofacitinib was resumed and CDR was reachieved. Endoscopic remission of his severe colitis was confirmed 6 months later.

IL-18, IL-1-beta, CXCL9, and INF-gamma were measured in both patients but at different timepoints during their disease course. Patient 1 cytokine/chemokine assay was performed at 4 years old while on canakinumab, adalimumab and an IL-18 specific blocker (prior to starting JAKi). It shows elevated level of IL-18 (1247 pg/mL; normal ≤ 164 pg/mL), IL-1-beta (373 pg/mL; normal 2.4-59.6 pg/mL), CXCL9 (7250 pg/mL; normal 38-4817 pg/mL), but not IFN-gamma (2.2 pg/mL; normal ≤ 8.2 pg/mL). It is possible that IFN-gamma was partially inhibited by therapy ongoing at that time and/or lack of sensitivity of the assay to detect the overall/intra-tissular burden of IFN-gamma. A cytokine/chemokine assay was performed for patient 2 at 16 years old, two months after starting JAKi and ustekinumab. It showed elevated levels of IL-18 (2568 pg/mL; normal ≤ 266 pg/mL), IL-1-beta (193 pg/mL; ≤ 34.1 pg/mL), normal level of CXCL9 (1374 pg/mL; normal 318-5193 pg/mL) and elevated level of IFN-gamma (19.8 pg/mL; normal ≤ 7.9 pg/mL).

Conclusion: NLRC4 GOFM is a severe multisystemic autoinflammatory disease. When targeted anti-IL-1 and/or anti-Il-L8 therapies are ineffective or unavailable, JAKi should be considered as a treatment option.
Disclosure of Interest: None declared

Identifier: O18

DOMINANT NEGATIVE ADA2 MUTATIONS CAUSE ADA2 DEFICIENCY IN HETEROZYGOUS CARRIERS

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Introduction: Human ADA2 deficiency (DADA2) is an inborn error of immunity with a broad clinical phenotype encompassing vasculopathy including livedo racemosa and lacunar strokes as well as hemato-immunological manifestations. Combination of decreased serum ADA2 activity and the identification of biallelic deleterious alleles in the *ADA2* gene are used for diagnosis. DADA2 carriers harbor a single pathogenic variant in *ADA2* and are mostly considered healthy and asymptomatic. However, some DADA2 carriers present a phenotype compatible with DADA2 (1–4).

Objectives: We sought to investigate whether being heterozygote for specific variants in *ADA2* could explain the patients' DADA2 phenotype.

Methods: A HEK293T cell overexpression system was used to evaluate impact of ADA2 variants on WT ADA2 protein expression/secretion and enzymatic activity. Finngen, UK biobank and the Bio*Me* Biobank were used to assess population genetics and evaluate correlation with DADA2 phenotypes. ADA2 enzyme activity was measured in a colorimetric assay adapted from Giusti et al (5).

Results: In addition to diseased DADA2 carriers in literature (1–4), we report and investigate a cohort of 10 heterozygous carriers of pathogenic *ADA2* variants presenting with DADA2 clinical features. To study the potential effect of heterozygous pathogenic variants in ADA2 on WT ADA2 protein expression, secretion and enzymatic activity, we performed transient transfection of each *ADA2* variant together with WT *ADA2* to mimic carrier status. In vitro study of the *ADA2* variants identified in this patient cohort revealed that R169Q, H424N and Y453C variants affect secretion of WT ADA2 protein. Moreover, we demonstrate a dominant negative effect on the enzymatic activity of WT ADA2 by variants G47A, G47R, G47V, R169Q, E328K, H424N and Y453C both intracellularly and extracellularly. Data from PheWAS show that the heterozygous state for pLOF variants in *ADA2* is associated with phenotypes that align with DADA2. When studying the most frequent allele, R169Q, the enriched phenotypes are even more striking, despite the overall low number of cases.

Conclusion: Here, we describe how specific heterozygous variants cause ADA2 deficiency through distinct dominant negative effects on either ADA2 enzyme activity, dimerization and/or secretion. At the protein level, heterozygosity for these variants mimics what is observed in DADA2. We conclude that humans with heterozygous dominant negative missense variants in *ADA2* are at risk of DADA2.

Acknowledgments: Funding:

IM is as supported by FWO and by the Jeffrey Modell Foundation. This project has received funding from the European Research Council under the European Union's Horizon 2020 research and innovation programme. This work is supported by ERN-RITA. LE was supported by a PhD Fellowship from the Research Foundation FWO – Flanders and is a fellow of the BIH Charité Junior Clinician Scientist Program funded by the Charité – Universitätsmedizin Berlin, and the Berlin Institute of Health at Charité. MEK and YI were funded by the Charles Bronfman Institute for Personalized Medicine at Icahn School of Medicine, Mount Sinai, supported by Scientific Computing and Data at the Icahn School of Medicine at Mount Sinai and supported by the Clinical and Translational Science Awards grant from the National Center

for Advancing Translational Sciences. This research was conducted using the UKBiobank. WVE acknowledges funding of FWO was used for this research. RS is supported by an FWO senior clinical investigator fellowship.

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Disclosure of Interest: None declared

Identifier: O19

PULMONARY ARTERIAL HYPERTENSION WITH STILL'S DISEASE: A NEW PULMONARY MANIFESTATION ASSOCIATED WITH HLA-DRB1*15

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Introduction: Inflammatory lung disease (ILD) in Still's disease (SD) has recently been described. Pulmonary arterial hypertension (PAH) is another rare and life-threatening associated event, with only a few case reports published.
Objectives: To report the largest cohort of PAH occurring in the context of SD.
Methods: We identified 16 adult SD patients with PAH (PAH+ group, PAH was confirmed by right heart catheterization in all patients) by a call for observations from the CRIIMIDIATE network and a search of the French PH network registry. Patient characteristics and disease evolution were retrospectively compared with those of 111 SD controls without PAH (PAH-) followed in a reference centre.
Results: The profile of patients in the PAH+ and PAH- groups differed: 100% versus 69.4% female(p=0.006), 75% versus 17.1% Black (p<0.0001), more active SD both at diagnosis and throughout the disease course, and more likely to present MAS (62.5% vs 14.4%, p<0.0001), which was recurrent (i.e. ≥ 2 episodes) in most cases (7/10 patients), and exhibit eosinophilia during the disease course (68.7% vs 7.2%, p<0.0001). For the 84/127 patients with genetic typing, the HLA-DRB1*15 allele was more prevalent in PAH+ than PAH- patients (8/11 [72.7%] vs 22/51 [30.1%], p=0.014). The groups did not differ in treatment, except for methotrexate (81.2% vs 50.4%, p=0.029), canakinumab (50% vs 21.6%, p=0.026) or immunosuppressant agents (56.2% vs 10.8%, p<0.0001) that were more often used in the PAH+ group, reflecting a more active underlying SD. There was higher frequency of drug reactions tointerleukin 1 (IL-1) and/or IL-6 inhibitors in PAH+ than PAH- patients (37.5% vs 7.2%, p=0.002). Mortality was higher in PAH+ than PAH- patients (37.5% vs 0.9%, p<0.0001), all deaths related to SD flare.

Table. Comparison of demographics and characteristics of SD patients with and without PAH

	Still's disease with PAH (n=16)	Still's disease without PAH (n=111)	p-value (PAH vs no PAH)
Still's disease onset ≥ year 2010	13 (81.3)	88 (79.3)	1
Female, n (%)	16 (100)	77 (69.4)	**0.006**
Ethnicity, n (%) - Caucasian - Black	3 (18.7) 12 (75.0)	64 (57.7) 19 (17.1)	**<0.0001**

Modified Pouchot score at Still's disease diagnosis, median (IQR)	(data available for 15 patients) 7 (6–8)	(data available for 67 patients) 6 (5–7)	**0.031**
MAS ever during disease course, n (%)	10 (62.5)	16 (14.4)	**<0.0001**
Eosinophilia ever during disease course, n (%) Maximum eosinophil count, median (IQR), /mm^3	11 (68.7) 2616 (1765–3460)	8 (7.2) 937 (850–1100)	**<0.0001** **0.002**
HLA-DRB1*15-positive, n/N available (%)	8/11 (72.7)	22/73 (30.1)	**0.014**
History of drug reactions to IL-1 or IL-6 inhibitors, n (%)	6 (37.5)	8 (7.2)	**0.002**
Deaths directly attributed to Still's disease complications, n (%)	6 (37.5)	1 (0.9)	**<0.0001**

Conclusion: PAH is a specific manifestation, different from SD-related lung disease, but develops on the same background (i.e., in patients with MAS, especially when recurrent, eosinophilia and carrying the HLA-DRB1*15 allele). The proximity between PAH and LD in SD reinforces the association of the HLA-DRB1*15 allele with severe forms of SD and raises the question of treatment optimisations to better control both SD and its complications.

Acknowledgments: The authors thank the CRIIMIDIATE clinical research network (https://cri-net.com/) for its support and for making the national survey possible as well as the French PH network PulmoTension.
Disclosure of Interest: None declared

Identifier: O20

FUNCTIONAL ANALYSIS OF C- AND N-TERMINAL CDC42 VARIANTS REVEALS DISTINCT PATHWAYS OF AUTOINFLAMMATION RESPONSIBLE FOR DIFFERENT CDC42-ASSOCIATED AUTOINFLAMMATORY DISEASES

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Introduction: Autoinflammatory actinopathies are monogenic disorders characterized by dysregulation of actin cytoskeleton homeostasis, particularly in immune cells. CDC42, a key RHO GTPase, plays a critical role in actin dynamics and pyrin inflammasome activation. C-terminal *CDC42* variants (R186C, C188Y, *192C*24) are linked to severe autoinflammatory phenotypes, known as NOCARH syndrome (Neonatal Onset Cytopenia, Autoinflammation, Rash, and Hemophagocytosis). In contrast, the N-terminal Y64C variant causes dysmorphic features and several malformations, neurodevelopmental delay, macrothrombocytopenia, and mild inflammatory symptoms, as initially described as the Takenouchi-Kosaki syndrome. To date, functional defects have mainly been characterized for the C-terminal R186C CDC42 variant. This study aimed to explore shared cytoskeletal abnormalities and signaling alterations across these variants.

Objectives: To functionally characterize the inflammatory pathways and cytoskeletal abnormalities of the different C- and N-terminal CDC42 variants.

Methods: Using flow cytometry and imaging techniques, we performed analyses of actin cytoskeleton, NF-kB nuclear translocation/activation, and pyrin-dependent pyroptosis in patients' cells and both THP-1 or U937 monocytic cell lines expressing CDC42 variants. Primary fibroblasts obtained from patients were also used to study cell migration during a wound-healing assay.

Results: The N-terminal Y64C CDC42 variant localized normally, and showed no defects in pyrin-dependent pyroptosis, or NF-kB activation. Interestingly, although there were no defects in actin filaments content at the basal state, a wound-healing assay revealed a defect in migration capacity. In contrast, all three C-terminal variants exhibited aberrant subcellular localizations (Golgi or nuclear accumulation) and shared functional alterations, including reduced actin filament polymerization, defects in migration capacity, and increased NF-kB nuclear translocation and phosphorylation. Using a pharmacological approach, reduction in cellular actin filaments content by specific depolymerizing drugs was not sufficient to hyperactivate NF-kB, indicating that there is no causal relationship between these two events. Moreover, both Golgi-trapped CDC42 variants (R186C and *192C*24) showed increased pyrin-dependent pyroptosis whereas the nuclear C188Y one did not.

Conclusion: Altogether, this study expands the spectrum of defects identified in *CDC42*-associated autoinflammatory diseases and highlights the functional heterogeneity of *CDC42* variants. Defects in basal actin filaments dynamics and/or cell migration probably explain the various malformations that may be present in these patients, particularly in the body midline. The differential activation of inflammatory pathways among these variants shows that there is no single 'NOCARH' syndrome, but several different inflammatory pictures associated with *CDC42* variants, which could be called

"*CDC42*-associated autoinflammatory diseases". Thus, these findings highlight the importance of developing tailored therapeutic strategies to treat these severe autoinflammatory disorders.

Disclosure of Interest: None declared

Identifier: O21

CURRENT TREATMENT OF MACROPHAGE ACTIVATION SYNDROME WORLDWIDE: THE METAPHOR PROJECT, A PRES/PRINTO REAL-LIFE INTERNATIONAL SURVEY

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Introduction: Despite significant improvement in its management, macrophage activation syndrome (MAS) treatment is still not standardized, due to lack of robust evidence and differences in access to medications. This holds especially true for MAS related to rheumatologic conditions other than systemic juvenile idiopathic arthritis (sJIA)

Objectives: To capture the current therapeutic approaches to MAS worldwide and to evaluate major unmet needs and treatment challenges

Methods: In context of the METAPHOR project, a PReS/PRINTO initiative to optimize treatment in sJIA and MAS, a survey on MAS treatment was developed. Topics addressed were based on a systematic literature review, and selected by a panel of 22 experts, including 1 patient representative and 2 pediatric hematologists. The survey consisted of: a) demographic section, including country of practice; b) clinical section, investigating real-life approaches to MAS; c) patient focused section, developed with patient representatives and exploring major unmet needs. Physicians part of the PReS/PRINTO network and of the Histiocyte Society were invited to anonymously complete the web-survey from Oct 5th to Dec 15th2023

Results: A total of 287 replies from 64 countries worldwide were collected. Respondents were mostly pediatric rheumatologists (90%), while 10% were pediatric hematologists. Methylprednisolone (MPN) pulses were the commonest glucocorticoid (GC) in all subtypes of MAS. In addition to GC, ciclosporin (CsA) and anakinra were the cornerstones of treatment in sJIA-MAS, used by 91% and 74% of physicians, respectively. Anakinra was the most selected agent beside GC as 1st line, and only 2% of respondents indicated not to consider the use anakinra in sJIA-MAS. However, access to anakinra is a major gap across countries: almost all physicians would use it in North America and Western Europe (1st line for 66 and 50% of respondents, respectively) but it is still unavailable for more than 65% and

70% of physicians in Asia and South America. Systemic erythematosus lupus (SLE)-associated MAS represents the condition with the highest heterogeneity of therapeutic approaches across centres and countries. Besides MPN, which was largely the 1st line choice worldwide (98%), 58% of physicians would use anakinra as 1st line in North America and 63% as 1st/2nd line in Western Europe, while CsA and immunoglobulin would be the medications of choice in all the other countries. Etoposide was globally the agent most frequently selected as 3rd line/rescue, followed by JAK-inhibitors, mainly ruxolitinib. Emapalumab was potentially chosen as 2nd/3rd line treatment across all subtypes of MAS; however, its access is still drastically limited in all countries, except North America and partially Western Europe.

Conclusion: A wide heterogeneity in the approach to MAS still exists, with relevant discrepancies in its management worldwide. An international effort is needed to optimize therapeutic options, reduce gaps in access to medications and harmonize treatment.

Disclosure of Interest: F. Minoia Consultant for: SOBI, Speaker bureau of: Novartis, F. Baldo: None declared, G. Rogani: None declared, R. Erkens: None declared, C. Bracaglia Consultant for: SOBI, Novartis, GSK, D. Foell Consultant for: Novartis, Sobi and Boehringer, M. Gattorno: None declared, M. Jelusic: None declared, J. Anton: None declared, P. Brogan: None declared, S. Canna: None declared, S. Chandrakasan: None declared, R. Cron Consultant for: Pfizer, Abbvie, Sobi, F. De Benedetti: None declared, A. Grom Consultant for: Novartis, Sobi, Kiniksa, M. Heshin-Bekenstein: None declared, A. Horne Consultant for: Sobi, Novartis, R. Khubchandani: None declared, M. Mizuta: None declared, S. Ozen Consultant for: SOBI, Novartis, P. Quartier: None declared, A. Ravelli: None declared, M. Shimizu: None declared, G. Schulert Grant /Research support from: IpiNovyx, Consultant for: SOBI and Boehringer Ingelheim, C. Scott: None declared, R. Sinha: None declared, N. Ruperto: None declared, J. Swart: None declared, S. Vastert Consultant for: SOBI, Novartis

Identifier: O22

MANAGING PATIENTS WITH CRYOPYRIN ASSOCIATED PERIODIC SYNDROME (CAPS). HOW DOES INITIATING TREATMENT WITH IL-1 MEDICATIONS AFFECT PATIENT'S SYSTEMIC INFLAMMATION, SYMPTOM REPORTING AND QUALITY OF LIFE. EXPERIENCE OF A SPECIALISED UK CENTRE.

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Introduction: Cryopyrin Associated Periodic Syndrome (CAPS) is an autoinflammatory disease associated with overproduction of interleukin-1 (IL-1), resulting in high levels of systemic inflammation. Patients can experience symptoms of fatigue, fever, myalgia, inflammation of the skin, eyes, joints, and meninges. Patients have access to IL-1 therapy, Canakinumab (Ilaris) and Anakinra (Kineret), which should reduce systemic inflammation, resulting in a remission of symptoms and improve quality of life. However, patients treated with IL-1 therapy may still be affected by the damage caused from their disease, impacting on their quality of life.
Objectives: To review and compare the quality of life outcomes, inflammatory blood results and reported symptoms of patients diagnosed with CAPS before and after commencing IL-1 therapy.
Methods: Patients aged over 16, diagnosed with CAPS and treated with IL-1 therapy, Anakinra and Canakinumab by the UK CAPS and Autoinflammatory Service were included in the review. Outcome data from patient's follow-up visits, prior to starting IL-1 therapy and 3 months after IL-1 therapy were collected and analysed.

Systemic inflammation was reviewed using blood test results of C-Reactive Protein (CRP mg/L) and Serum Amyloid A (SAA mg/L). Symptoms were scored using a CAPS assessment score of 10 CAPS symptoms reported as Absent (0), Mild/Moderate (1) or Severe (2). Quality of life was reviewed using SF-36 health questionnaires.

Results: During the study period, 114 patients diagnosed with CAPS and treated with IL-1 therapy were included in the study.

There was a significant reduction in CRP and SAA levels when commencing IL-1 therapy. The median result before commencing treatment CRP 26 and SAA 91. The median result after commencing treatment: CRP 2 and SAA 5. A median reduction in CRP of 92% and SAA of 94%.

There was a reduction in reported symptoms. The median result before treatment was a score of 13/20. The median result after treatment was a score of 3/20. The most common ongoing symptoms were Fatigue (40/114) and Arthralgia (26/114).

Patients scored their overall health. Prior to treatment: Excellent 0/114, Very Good 7/114, Good 39/114, Fair 55/114 and Poor 13/114. After treatment: Excellent 25/114, Very Good 43/114, Good 39/114, Fair 6/114 and Poor 1/114. Patients either improved their score 105/114 (92%) or remained the same 9/114 (8%). No patients reported their general health being worse after commencing treatment 0/114.

Patients reported tiredness/fatigue. This improved following treatment but remained a reported health complaint in 54% patients. Patients reported bodily pain. This improved following treatment but remained a reported health complaint in 24% patients. Patients reported feeling low. This improved following treatment but remained a reported health complaint in 29% patients. Patients reported if they were feeling happy. This improved following treatment but remained a reported health complaint in 20% patients.

Conclusion: CAPS Patients treated with IL-1 therapy have a significant improvement in reducing systemic inflammation, resolving symptoms and an overall improvement in their quality of life.

However, despite being on treatment, some patients quality of life is still negatively impacted, likely due to damage caused by exposure from active CAPS disease prior to treatment. Other factors such as comorbidities are also likely to be contributing to these reported outcomes. Both physical and emotional wellbeing are affected.

It is important to start patients with CAPS on IL-1 treatment promptly to reduce active disease, but once started on treatment, ongoing support is required to address ongoing physical and emotional wellbeing, address potential damage from disease and contribution from other comorbidities.

Disclosure of Interest: None declared

Identifier: O23

PROGRESS REPORT ON IL6 INHIBITION IN ROSAH AUTOINFLAMMATORY DISEASE

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Introduction: ROSAH (retinal dystrophy, optic nerve edema, splenomegaly, anhidrosis, headache) is a rare systemic disease characterized by inflammation and progressive vision loss, which can lead to blindness by early adulthood. Caused by NF-κB activating mutations in the innate immune sensor ALPK1, an initial report indicated that intra-ocular inflammation in ROSAH may respond to treatment with the IL6 receptor antagonist tocilizumab (TCZ).

Objectives: This study aims to evaluate the efficacy, durability and generalizability of TCZ in treating ocular inflammation in early-stage ROSAH.

Methods: We conducted a retrospective cohort study to assess impact of TCZ on ocular inflammation in patients with genetically confirmed ROSAH. Inclusion criteria required empiric treatment with TCZ and evidence of active intraocular inflammation (demonstrated by cellularity on slit lamp biomicroscopy, cystoid macular edema (CME) on ocular coherence tomography (OCT) and/or retinal vasculitis on fluorescein angiography (FA)), without blindness or advanced retinal degeneration (based on funduscopic exam and/or full-field electroretinogram (ffERG)) prior to initiation of TCZ.

Results: Five patients (aged 9-36 years) with ROSAH met the inclusion criteria and were included in this analysis. All 5 patients showed improvement in intraocular inflammation while on TCZ.

- **Patient 1**: After 32 months of TCZ, sustained structural improvements were observed in retinal vasculitis, CME, and retinal nerve fiber layer (RNFL) thickness. Additionally, TCZ was associated with function improvement, evidenced by improved visual acuity.
- **Patient 2**: After 16 months of TCZ, there were structural improvements in retinal vasculitis and RNFL thickness. No CME was present at baseline and visual acuity was normal.
- **Patient 3**: After 8 months of TCZ, there were structural improvements in CME, and RNFL thickness. The patient declined FA. TCZ was also associated with function improvement, evidenced by improved visual acuity.
- **Patient 4**: After 6 weeks of TCZ, there was improvement of the retinal vasculitis in the right eye. Assessment of the left eye was limited secondary to prior retinal detachment limiting the left eye to light perception only.
- **Patient 5**: Despite TCZ treatment interruptions due to neutropenia, there were improvements in CME during periods of consistent TCZ treatment.

Conclusion: These findings from 5 early-stage patients with a rare, blinding disease of innate immune activation support our hypothesis that TCZ treatment can improve ocular inflammation in ROSAH. Crucially, this work demonstrates that the impact of TCZ is generalizable to additional patients with early-stage ocular disease and indicates that prolonged treatment can be associated with improvements in both structural and functional outcomes. Additionally, our results highlight the need for autoinflammatory providers to be aware of ROSAH and be prepared to support timely introduction of potentially vision-sparing therapy for this systemic disease.

Disclosure of Interest: None declared

Identifier: O24

PROSPECTIVE FOLLOW UP OF 37 PREGNANCIES IN WOMEN RECEIVING IL1 INHIBITORS FOR SYSTEMIC AUTOINFLAMMATORY DISEASES: AN MULTICENTRIC FRENCH STUDY FROM THE GR2 COHORT.

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Introduction: Interleukin-1 (IL-1) inhibitors, including anakinra and canakinumab, are effective treatments for autoinflammatory diseases such as adult-onset Still's disease (AOSD) and familial Mediterranean fever (FMF). These diseases often affect women of reproductive age, raising concerns about the safety of anti-IL1 therapies during pregnancy. Althoughdata suggest no significant malformation or neonatal risks, prospective evidence remains limited (1)

Objectives: To prospectively evaluate maternal and neonatal outcomes in pregnancies exposed to anti-IL-1 inhibitors, focusing on complications, preterm birth and long-term infant health.

Methods: This study analysed women from the GR2 cohort, a French multicentre prospective registry of women with rare and/or rheumatological diseases. Pregnancies with periconceptional (canakinumab in the two months before conception and anakinra at the theoretical date of conception) or gestational exposure to anakinra or canakinumab were included. The prospective registry began in 2014 and we froze inclusions in February 2024 for this work. Data included disease activity, treatment, pregnancy outcomes and neonatal health, with follow-up data on child development.

Results: We included 37 pregnancies (including 3 twin pregnancies) in 31 patients exposed to anti-IL-1 (anakinra in 33 and canakinumab in 4). The underlying maternal autoinflammatory diseases were AOSD (n=17), FMF (n=16), unspecified systemic autoinflammatory disease (n=2), cryopyrin-associated autoinflammatory syndrome (n=1), TNF receptor associated periodic syndrome (n=1), recurrent pericarditis (n=1), respectively. One patient had both FMF and AOSD.

Pregnant women were exposed to anti-IL-1 for a median duration of 26 weeks [6; 37.4], with the majority of patients treated in the periconceptional period and continuing into the third trimester for anakinra.

Fifteen patients (41%) had at least one pregnancy-related complication. Eight women had infections (appendicitis, COVID infection, pneumopathy, otitis externa, sialadenitis and pyelonephritis and no required intensive care treatment reported (22%), 5 gestational diabetes (14%), 5 intrahepatic cholestasis (14%), 3 threatened preterm delivery (8%) but pregnancy finally carried to term,1 intrauterine growth retardation (3%) and one woman presented pre-eclampsia (3%). One patient with uncontrolled FMF had two early spontaneous miscarriages (5%), both at the time of the crisis. Preterm delivery occurred in 14% of cases, all between 32 and 37 weeks of amenorrhea, with no extreme prematurity.

Despite treatment, disease flares occurred in 72% of the pregnancies.

Neonates had weighted 3 220 grams [2873; 3398], with only one singleton classified as small for gestational age. No malformations were observed.

During the first days of life, one infant had an infection associated with stained amniotic fluid, one had neonatal still's disease, and one had neonatal jaundice. All the 31 neonates followed until the 6-month follow up, were healthy, three were reported to have infections, one had laryngomalacia and one required surgery for an inguinal hernia. Twenty patients were followed more than six months with a median of 23 months after birth [11; 40]: all children were reported to be in good health with normal psychomotor development. Twenty mothers (57%) breastfed (mixed and exclusive).

Conclusion: Anti-IL-1 therapy during pregnancy in women with systemic autoinflammatory diseases appears to be safe, particularly for anakinra for which we have had the vast majority of pregnancies exposed to anti IL1 with low maternal and neonatal risks. Control of the underlying disease is a key factor in preventing complications. These findings provide reassuring evidence for the use of anakinra and canakinumab in pregnancy.
Disclosure of Interest: None declared

Identifier: O25

THE LONG JOURNEY OF CONGENITAL SYPHILIS DIAGNOSIS: THROUGH MALIGNANCY AND AUTOINFLAMMATORY DISEASE SUSPICION

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Introduction: This case report describes the diagnostic challenge of congenital syphilis, highlighting how this rare disease can present with non-specific symptoms, especially in young infants. The patient was addressed to our reference center for autoinflammatory diseases after malignancy was ruled out by the oncology and hematology department. The patient's case involved an unusual progression of symptoms, including a persistent inflammatory syndrome, anemia, hepatosplenomegaly, and skin manifestations. Despite many investigations, the final diagnosis was only reached after 18 months. This case underlines the importance of maintaining congenital syphilis in differential diagnoses.
Objectives: A two-and-a-half-month-old infant was admitted at the emergency department with a range of symptoms: a bicytopenia, inflammation, and a skin rash (Picture1).

Medical history shows at three weeks old, she had exhibited a non-itchy macular pinkish rash on her scalp, trunk, and extremities, which later became scaly. Initial consultations at six weeks at a different hospital noted symptoms of rhinorrhea, cough, decreased appetite, weight stagnation, nosebleeds, mild respiratory distress, tachycardia, hepatosplenomegaly, and wheezing, with no fever.

At the time of admission, laboratory results included:

- Hemoglobin: 5.9 g/dL
- White blood cells: 11.18 G/L
- Platelets: 118 G/L
- C-reactive protein : 85 mg/L
- Ferritin: 611 µg/L
- Normal liver and kidney function
- Negative tests for influenza, RSV, SARS-CoV-2

She was hospitalized and treated with IV fluids and a blood transfusion. Antibiotics were started due to the uncertainty of her condition. Follow-up blood tests indicated stabilized hemoglobin and an improved inflammatory response, although platelet levels fluctuated. Imaging and tests ruled out major infections but the underlying cause remained undetermined.

Methods: She was transferred to a hematology unit, where her condition gradually improved, with the rash subsiding and the inflammatory response decreasing. Several additional tests were performed, including imaging, metabolic studies, and skin biopsies. The results ruled out malignancy. Skin biopsy excluded malignancy but pointed to a possible autoinflammatory condition. She was transfered to our department for further investigations. Despite extensive testing, including genetics, no specific diagnosis was reached, and she was discharged with regular follow-up.
Results: During follow-up, clinical picture improved, yet she continued to present mild hepatosplenomegaly and intermittent inflammatory markers in follow-up visits. At 18 months she still presented with persistent symptoms

including developmental delay, chronic rhinitis, and lymphadenopathy. Her mother announced a new pregnancy. Due to the social background, an extensive sexually transmitted disease search was performed. Serology test for syphilis returned positive confirming the mother had syphilis. The child had a test as well with a VDRL titer of 1/128, which confirmed the diagnosis of congenital syphilis. Additional tests with bone scintigraphy, revealed bone lesions indicative of congenital syphilis, while other systemic evaluations remained normal.

Penicillin G treatment was started and the patient's condition gradually improved.

Conclusion: This case underscores the diagnostic difficulty of congenital syphilis, which can mimic various pediatric conditions. Although it is rare, congenital syphilis should be considered in infants with unexplained febrile rashes, anemia, hepatosplenomegaly, and other inflammatory symptoms. Syphilis remains an underdiagnosed disease, likely due to non-mandatory reporting and its resemblance to other conditions. Nevertheless, we see a rise in congenital syphilis in recent years. The delay in diagnosis also highlights the need for continued follow-up and reevaluation in complex pediatric cases.

Disclosure of Interest: None declared

Identifier: O26

CLINICAL PRESENTATION AND COURSE OF PULMONARY INVOLVEMENT IN CHRONIC NONBACTERIAL OSTEOMYELITIS

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Introduction: Chronic nonbacterial osteomyelitis (CNO) is a non-infectious autoimmune/inflammatory disease that primarily affects bones. While all age groups can develop CNO, it most commonly affects children and adolescents with a peak onset between 7 and 12 years. CNO covers a clinical spectrum with sometimes singular self-limiting bone lesions at one end, and chronically active or recurrent multifocal lesions at the other end which are then also referred to as chronic recurrent multifocal osteomyelitis (CRMO). However, in addition to bones, further organs may be affected. Among extraosseous manifestations, skin (pustulosis, psoriasis, acne, pyoderma, etc.), gut (chronic bowel inflammation) and joint involvement have been most frequently reported.

In the published literature, pulmonary involvement in CNO (pCNO) has been reported in seven children/adolescents and two adults. Because of its rarity, little is known about demographic, clinical and imaging characteristics of pCNO, its clinical course and outcomes. Thus, limited awareness and understanding of pCNO may result in an incorrect diagnosis and aggressive anti-proliferative treatments.

This manuscript describes demographic, clinical, and morphologic features of pCNO, response to treatment and outcomes in a national cohort of 22 patients.

Objectives: Pulmonary involvement in chronic nonbacterial osteomyelitis (CNO) is rare. Limited awareness results in diagnostic challenges, especially as malignancy or infection need to be considered.

Methods: Based on a survey shared among centers participating in the *Kerndokumentation Deutsches Rheumaforschungszentrum* (Germany), this study investigated clinical and imaging presentations, demographic features, treatment response and outcomes of pulmonary involvement in CNO (pCNO). MRI and CT images were read centrally by an experienced pediatric radiologist.

Methods: Based on a survey shared among centers participating in the *Kerndokumentation Deutsches Rheumaforschungszentrum* (Germany), this study investigated clinical and imaging presentations, demographic features, treatment response and outcomes of pulmonary involvement in CNO (pCNO). MRI and CT images were read centrally by an experienced pediatric radiologist.

Results: Twenty-two patients with pCNO were included in this study. Among CNO patients, pulmonary involvement was more common in girls (91% versus 62.8%, p=0.006) and patients with multifocal bone lesions (95% versus 65%, p<0.001), but did not associate with systemic inflammation or additional organ involvement. Forty-two pulmonary lesions were counted with a median of 2 per patient (2-6). They displayed a median size of 1.8 cm (0.3-4.0 cm), followed mono- (40%) and oligo-focal (60%) patterns, representing consolidations or nodules, abutting the pleura in 50%. While prominent hilar lymph nodes were present (in 19%), no pathological enlargement (>1cm) was seen. Where available (3/22), histology revealed granulomatous inflammation with lymphocyte infiltration. Development and courses of pCNO did not associate with treatments chosen. Complete remission was reported in 60%, partial remission in 20%.

Conclusion: Pulmonary CNO is usually asymptomatic. While more common in girls and patients with multifocal CNO, pCNO is not associated with systemic inflammatory parameters or specific organ involvement. Prognosis of pCNO is favorable, and most lesions resolve over time. Thus, a careful watch-and-wait strategy may be appropriate.
Acknowledgments: The authors thank all patients and their families as well as the wider teams involved in the care of CNO patients at their centers
Disclosure of Interest: None declared

Identifier: O27

RETROPERITONEAL FIBROSIS (RPF) IN A CASE OF H SYNDROME – A DIAGNOSTIC CHALLENGE AND LITERATURE REVIEW

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Introduction: H syndrome, a rare autosomal recessive disorder caused by biallelic pathogenic mutations in *SLC29A3* is characterized by diverse clinical manifestations, including **H**yperpigmentation, **H**ypertrichosis, **H**epatosplenomegaly, **H**eart anomalies, **H**ypogonadism, **H**earing loss, **H**yperglycemia, and **H**allux anomalies. A notable aspect of H syndrome is its association with autoinflammatory and lymphoproliferative features which can complicate diagnosis and treatment. Retroperitoneal fibrosis (RPF), though exceedingly rare, is a severe manifestation that can encase vital retroperitoneal structures, causing life-threatening complications. Diagnosing RPF in H syndrome is particularly complex in tuberculosis(TB)-endemic regions, as these can share overlapping features or coexist. We present a pediatric case of H syndrome with RPF and an interesting clinical sign.

Objectives: To highlight RPF as a potential complication of H syndrome and briefly review literature/differential diagnosis of this entity in H syndrome.

Methods: Case :

A 13-year-old female, born to non-consanguineous parents with an uneventful birth history (birth weight: 2.7 kg), presented with failure to thrive, hyperglycemia, and exocrine pancreatic insufficiency at age 4.5 years. Clinical findings included hyperpigmentation, hypertelorism, hearing loss, hypothyroidism, and enamel hypoplasia. Investigations for celiac disease, islet cell antibodies, and insulin antibodies were negative, but GAD antibody was positive. Based on clinical features, a diagnosis of H syndrome was confirmed via homozygous pathogenic mutation in the *SLC29A3* gene.

She was treated intermittently with steroids for prolonged fever and retroorbital infiltration. At age 12, she developed prolonged fever, weight loss, and a strongly positive Mantoux test without an identifiable focus. CT chest was normal. She improved rapidly with secondary prophylaxis using two anti-tuberculosis drugs.

Six months later, she experienced a urinary tract infection with sonographic evidence of calculi. There was no mention of retroperitoneal fibrosis, though ESR was elevated. After a month again, she presented with a few weeks of abdominal pain and a visibly prominent and tortuous abdominal vessel on the right flank. It showed rapid unidirectional filling. A persistently elevated ESR along with the dilated flank vein prompted further evaluation and imaging was done which revealed retroperitoneal fibrosis encasing the distal ureters and left iliac vein, resulting in bilateral hydronephrosis, chronic pyelonephritis, and ureteral obstruction. Chronic veno-occlusive liver disease, splenomegaly, diffuse pancreatic atrophy, and features of chronic pyelonephritis were also identified. Biopsy could not be done as the site was inaccessible and IGG and IGG4 levels were normal.

The patient was managed with tocilizumab and stent placement for obstructive uropathy. Repeat investigations to assess treatment response are awaited.

Results: Discussion:

RPF in H syndrome is rare, with fewer than seven cases reported, only two in children. The pathogenesis involves chronic inflammation driven by defective nucleoside transport due to *SLC29A3* mutations, leading to persistent immune dysregulation, fibroblast activation, and extracellular matrix deposition. RPF can also result from other conditions such as TB, IgG4-related disease, chronic granulomatous disease, or autoimmune processes, which may exacerbate fibrosis.

Conclusion: We present a child of H Syndrome with an impressive clinical sign that led to the rare diagnosis of RPF causing bilateral hydronephrosis.

Disclosure of Interest: None declared

Identifier: O28

UNMASKING DIAGNOSTIC CHALLENGES: H SYNDROME MISTAKEN FOR CAPS

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Introduction: H syndrome is a rare autosomal recessive disorder caused by mutations in the SLC29A3 gene, encoding the human equilibrative nucleoside transporter 3 (hENT3). This protein functions as a nucleoside transporter critical for lysosomal and mitochondrial metabolism. The syndrome manifests with a broad spectrum of systemic symptoms, including cutaneous hyperpigmentation, skin sclerosis, hepatosplenomegaly, hypertrichosis, hypogonadism, cardiac anomalies, short stature, sensorineural hearing loss, and systemic inflammation.
Objectives: To describe the clinical course of a 24-year-old patient with genetically confirmed H syndrome who was misdiagnosed as having CAPS (Cryopyrin-Associated Periodic Syndromes).
Methods: Patient records were reviewed. Plasma cytokine levels were measured using the Ella method. IL-1β secretion was assessed in the supernatant of patient peripheral blood mononuclear cells (PBMCs) and healthy donor (HD) controls. A type I interferon signature analysis was performed on the patient's peripheral blood.
Results: The patient was first evaluated at age 24, presenting the following clinical history: during infancy, he experienced recurrent episodes of non-itchy urticarial-like rashes, conjunctivitis, episcleritis, and febrile episodes accompanied by fluctuating hearing loss. Although oral steroid treatment improved his hearing temporarily, progressive damage resulted in permanent hearing loss. He also reported episodes of extremity swelling and paresthesia, triggered particularly by cold exposure, and two episodes of hemolytic anemia associated with fever. He experienced abdominal pain episodes leading to two colonoscopies—one in childhood and one in adulthood—both diagnosing undifferentiated colitis. Type 1 diabetes mellitus was diagnosed in adolescence.

Initial treatment with colchicine was ineffective. Given the clinical suspicion of cryopyrinopathy, anakinra was started, which initially alleviated inflammatory symptoms but was subsequently replaced by canakinumab. A genetic panel for recurrent fever syndromes (IL1RN, LPIN2, MEFV, MVK, NLRP12, NLRP3, NOD2, PSMB8, PSTPIP1, TNFRSF1A) was negative. IL-1β secretion was increased and exhibited an accelerated kinetic profile compared to healthy controls. The interferon signature was positive, while plasma cytokine levels (IL-18, IL-1RA, IL-6, TNFRI) were within normal ranges. Whole-exome sequencing with an extended autoinflammatory disease panel revealed a biallelic deletion in the exon 2 of the SLC29A3 gene.

Conclusion: This case presents the diagnostic challenges of H syndrome due to overlapping autoinflammatory phenotypes, which can lead to misdiagnosis. Notably, the patient lacked typical cutaneous features of H syndrome, such as hyperpigmentation, induration, and hypertrichosis, observed in approximately two-thirds of cases. This contributed to years of misclassification, even after the syndrome's identification. The clinical presentation, including hearing loss, initially suggested CAPS. However, alternative diagnoses should be considered in the presence of atypical symptoms (e.g., diabetes mellitus, hemolytic anemia) and an incomplete response to IL-1 blockade therapy.
Disclosure of Interest: S. Palmeri: None declared, A. Agrusti: None declared, V. Natoli: None declared, C. Conti: None declared, E. Drago: None declared, F. Penco: None declared, R. Bertelli: None declared, P. Bocca: None declared, R. Papa Conflict with: Speaking from SOBI. , S. Volpi Conflict with: SV received speaker's fee from SOBI and consultancies Boehringer. , R. Caorsi Consultant for: from SOBI, Conflict with: Speaking fee from SOBI, M. Gattorno Conflict with: MG received consultancy and speaker fee from Novartis, Sobi, Fresenius Kabi, Kiniksa

Identifier: O29

BEYOND NOONAN SYNDROME: QUESTIONING THE ROLE OF PTPN11 MUTATION IN PEDIATRIC AUTOINFLAMMATORY DISEASE: A CASE REPORT

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Introduction: The protein-tyrosine-phosphatase Shp2,encoded by the *PTPN11* gene,plays an important role in regulating cell proliferation and differentiation.Germline *PTPN11* mutations are implicated in Noonan syndrome(NS).Somatic *PTPN11* mutations have been identified in some sporadic juvenile leukemia.However,the role of SHP2 in inflammatory and autoimmune diseases remains poorly understood.
Objectives: We describe the case of a child presenting with an undifferentiated autoinflammatory disease,in whom genetic analysis revealed a mutation in the *PTPN11* gene.
Methods: The case was reported based on the information from the patient's medical record.
Results: A 4-year-old boy,born to consanguineous parents,was referred to our unit with a history of recurrent fevers,macrocephaly and persistent biological inflammation.The patient's brother died at the age of 5 due to ventricular tachycardia complicating a dilated cardiomyopathy.He also experienced recurrent fever episodes associated with a biological inflammation,hepatosplenomegaly,epilepsy and macrocephaly.Trio exome sequencing identified a *PTPN11* variant.Since the age of 11 months,our patient experienced recurrent febrile episodes lasting 3 to 7days and recurring 1–2 times per month.Fever was either isolated or accompanied by cervical lymphadenopathy,abdominal pain or headaches.He exhibited persistent raised inflammatory markers.At 12 months,he developed progressive psychomotor developmental delay and an increase in head circumference(+2-3SD).Brain MRI revealed enlargement of cerebral spaces and a left frontoparietal subdural collection;CT scan showed no calcifications.At the age of 3 years old,he experienced aseptic meningitis,presenting with fever,headache and biological inflammatory syndrome(CRP 169 mg/L,anemia,leukocytosis),hypergammaglobulinemia,elevated SAA(25 mg/L)IL-10(7.3 pg/ml;nv<3.8)and TNF(20;vn<12).Mevalonic acid during febrile episodes was negative.A 5-day corticosteroid course(~1.5mg/kg/day)was initiated in October 2023,leading to fever resolution,but CRP persisted elevated(118 mg/L).Anakinra(2 mg/kg/day)was introduced in November 2023,with initial clinical and biological improvement.However,owing to recurrence of fever two weeks after in the context of otorrhea,anakinra was discontinuated.In December 2023(age:3 years)the patient was admitted to our unit.Clinical findings included macrocephaly(+2–3SD),hepatosplenomegaly.No rash,aphthae, uveitis or arthritis were observed.MRI revealed stable pericerebral space enlargement and left subdural collection.Spectroscopy,fundoscopy,EEG/ENMG were normal.Laboratory findings showed elevated inflammatory markers(CRP 169 mg/L),anemia,and leukocytosis,elevated IL-18(292 pg/mL);normal interferon signature and ADA2 activity.CSF analysis revealed lymphocytic-predominant aseptic meningitis.Metabolic workup was normal.Exome sequencing *in quatuor* revealed a *PTPN11*(c.1020C>A, p.Asp340Glu)mutation,also identified in the asymptomatic mother and in the deceased brother.We decided to introduce colchicine(0.5 mg/day).Three months after,we observed a marked reduction in crisis recurrence(AIDAI score:3).Due to residual biological inflammation,colchicine was increased to 0.75 mg/day.After six months,the patient exhibited resolution of fever episodes,normalization of inflammatory markers,regression of hepatomegaly,stable macrocephaly and MRI findings,negative CSF analysis.
Conclusion: Mutations in *PTPN11* lead to NS and leukemia.Recent studies suggest that SHP2 also regulates the inflammasome pathway,as its inhibition in macrophages intensifies NLRP3 activation.We report a case of a child with an undifferentiated autoinflammatory disease carrying a *PTPN11* mutation.We hypothesize that the *PTPN11* mutation may play a role in disease pathogenesis.Functional studies are required to confirm this hypothesis.
Disclosure of Interest: None declared

Identifier: O30

OGFRL1 GENE MUTATIONS MAY LINK CHERUBISM TO CHRONIC RECURRENT MULTIFOCAL OSTEOMYELITIS (CRMO)

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Introduction: Cherubism (OMIM 118400) is characterized by destructive bilateral jawbone expansion due to inflammatory fibrous lesions. Recently, autosomal recessive loss-of-function variants in the *OGFRL1* (opioid growth factor receptor-like 1) gene were identified in two families from Syria and India with cherubism. These families carried homozygous frameshift mutations, presumed highly pathogenic. Despite attempts to model the disease in *OGFRL1* knockout mice, the human phenotype could not be replicated

Objectives: To investigate the relationship between OGFRL1 gene mutations and the co-occurrence of cherubism and chronic recurrent multifocal osteomyelitis (CRMO) in a newly identified family, and to explore the molecular mechanisms underlying this phenotype by analyzing genomic variants and proteomic profiles.

Methods: We identified a new family with a phenotype linking cherubism and CRMO. Whole genome sequencing (WGS) was performed on both parents and two affected brothers. Proteomics analysis using SomaScan 7K from blood plasma compared the blood proteome of one patient to CRMO patients and controls from the IMMUNAID cohort. Only proteins significant in both comparisons were analysed further.

Results: The younger brother developed recurrent fevers, developmental delay, sterile pyogenic arthritis, and severe abscesses post-vaccination at the age of 1, along with jawbone osteitis and diffuse CRMO lesions. Imaging revealed mandibular osteosclerosis with heterogeneous osteolytic lesions and multifocal metaphyseal involvement on whole-body MRI. A major inflammatory syndrome was noted (leukocytes 16,000, CRP 180 mg/L, ESR 110 mm). The older brother displayed a milder phenotype with post-vaccination abscesses and osteoarticular pain starting at age 10. MRI identified a single epiphyseal-metaphyseal lesion in the right clavicle, suggesting CRMO. Inflammatory markers were moderately elevated (CRP 7 mg/L, ESR 40 mm). Cherubism-related features were absent.

WGS revealed a rare missense variant in *OGFRL1* exon 7, p.(Arg241His), predicted deleterious *in silico* in both brothers. Proteomics analysis of the younger brother highlighted a higher abundance of proteins involved in osteoclast differentiation (NOTCH2, EFNA2, FOSL2, PIAS3), cartilage development (FOSL2, RUNX3, DLX2), and immune function (TXN, ITGB2/ITGAL, HERC1, ULBP1). Conversely, anti-inflammatory proteins BCHE, SIGLEC5, and SIGLEC14 were less abundant.

Conclusion: This report extends the spectrum of *OGFRL1*-related disorders to include a phenotype combining cherubism and CRMO. Unlike previously reported cases, our patients exhibit CRMO, pyogenic arthritis, and skin pathergy. We investigated the KEGG pathways involving significant proteins and known cherubism-related genes. Our results suggest that the *OGFRL1* mutation in our patients may affect the MAPK signaling pathway, shedding light on the potential molecular mechanisms underlying this condition.

Disclosure of Interest: None declared

Identifier: O31

EFFICACY AND TOLERABILITY OF BISPHOSPHONATES IN THE MANAGEMENT OF CHRONIC RECURRENT MULTIFOCAL OSTEOMYELITIS (CRMO) IN CHILDREN: A 30-PATIENT RETROSPECTIVE COHORT STUDY

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Introduction: Chronic recurrent multifocal osteomyelitis (CRMO) is a rare inflammatory disease primarily treated with non-steroidal anti-inflammatory (NSAIDs) drugs to reduce pain, inflammation, and disability. In NSAID-resistant cases, bisphosphonates (BPs) are used for their analgesic effects, though their impact on radiological lesions remains controversial. Treatment decisions rely on clinical judgment due to the absence of standardized guidelines.
Objectives: This study aims to evaluate the clinical, biological, and radiological response to BPs at 12 ± 3 months and at the last follow-up visit, as well as to identify predictive factors of response. Assessing BPs safety constitutes a secondary objective.
Methods: This single-center retrospective study was conducted in children (<16 years) with CRMO treated with intravenous BPs (pamidronate: 3-day regimen – 0.5 mg/kg on Day 1, 1 mg/kg on Day 2, and 1 mg/kg on Day 3) at a tertiary university hospital between 2010 and 2023. Data on pain, biological inflammation, radiological involvement (number and location of lesions on whole-body MRI (WB-MRI)), and treatment (doses and tolerance) were collected at BPs initiation (T1), 12 ± 3 months (T2), and last follow-up visit (T3). Complete remission was defined as the absence of pain, inflammatory syndrome, and lesions on WB-MRI. Partial remission was defined as the absence of improvement in one of the parameters. A multivariate analysis was conducted to identify factors predictive of response to BPs.
Results: Thirty patients (F/M ratio = 1.73:1, median age at diagnosis: 10.9 years [8–17]) were included in the study. Clinically, 24 patients (80%) presented with inflammatory pain, primarily affecting the lower limbs (66.7%) and/or the spine (40%), with an average of 2.7 ± 2.33 affected sites. Vertebral fractures were identified in 9 patients (30%), including one posterior wall collapse. Over a mean follow-up of 50.9 ± 26.9 months, patients received an average of 2.9 BP courses by T2 and 4.8 by T3. Complete remission increased from 15% at T2 to 33.3% at T3, while severe pain decreased from 44.8% at T1 to 13.3% at T2 ($p < 0.001$) and 3.7% at T3 ($p < 0.001$). Total clinical remission (absence of pain) was observed in 46.7% at T2 and 66.7% at T3. Treatment failure was rare (33.3% at T2, 11.1% at T3).

Radiologically, lesion counts remained stable. At T2, 57% (8/14) of patients in clinical remission had asymptomatic lesions, decreasing to 27% (5/18) at T3. All vertebral fractures at T3 were sequelae, with no new fractures or complications. Multivariate analysis linked BPs courses to reduced pain, fewer clinical lesions, and lower inflammatory markers, but not lesion counts. BPs tolerance was good, with flu-like syndrome (60%) and asymptomatic hypocalcemia (60.7%) as the most common side effects.

Conclusion: BPs appear to be indicated in the treatment of CRMO, particularly for pain management and vertebral fractures. All vertebral fractures were in the sequelae stage, with no new fractures or complications observed. However, their long-term impact on radiological lesions remains uncertain, raising questions about therapeutic targets in the context of a 'treat-to-target' approach. A prospective, placebo-controlled study would be necessary to confirm these findings.
Disclosure of Interest: None declared

Identifier: O32

TRANSCRIPTOMIC INSIGHTS INTO PFAPA SYNDROME: RNA-SEQUENCING ANALYSIS OF FLARE RELATIVE TO NON-FLARE STATES

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Introduction: While the etiology of Periodic Fever, Aphthous Stomatitis, Pharyngitis, and Adenitis (PFAPA) is unclear, emerging evidence suggests a strong genetic component and dysregulation of innate immunity.

Objectives: To identify differentially expressed genes (DEGs) distinguishing PFAPA flare from non-flare and explore molecular mechanisms in PFAPA flares with machine learning.

Methods: Paired blood samples were collected during flare and non-flare from 10 PFAPA patients fulfilling the inclusion criteria of the Childhood Arthritis Rheumatology and Research Alliance PFAPA Consensus Treatment Plans[1]. Differences in laboratory parameters were analyzed utilizing the paired t-test and RNA sequencing (RNA-Seq) was performed. DEGs were analyzed with standard RNA-Seq pipelines, including quality control, alignment to the reference genome (hg39), and quantification of transcript levels (STAR). Genes with significant differential expression were identified (DESeq2) and analyzed for pathway enrichment (gseapy). We trained a random forest (RF) on gene counts to classify flare and non-flare, obtaining a final model area under the curve=0.75. Top-ranked features' biological relevance was further analyzed to understand key pathways driving disease flares.

Results: The PFAPA cohort was 70% male with a median age of onset of recurrent fevers at 32 (IQR; 12-78) months (mos), age of enrollment during flare at 100 (IQR: 78-134) mos, maximum temperature of 104.9 (IQR 103.4-105.2) Fahrenheit, fever duration of ~4 (IQR:3-4) days with intervals every 36 (IQR 24-46) days between attacks, and an 8 out of 10 in severity with how an episode feels and affects function (IQR: 6-8; 6-9, respectively). When evaluated with flares, 90% had pharyngitis, 80% had cervical lymphadenopathy, and 50% had oral aphthae. Laboratory parameters from paired samples showed statistically significant leukocytosis, neutrophilia, monocytosis, lymphopenia, and increased CRP ($p < 0.01$). RNAseq Principal Component Analysis (PCA) showed a clear separation between flare and non-flare. The top 50 DEGs by adjusted p-value included upstream regulators of immune pathways (*CD177*, *GPR84*, *C1QC*, and *CARD17P)*. Gene Set Enrichment Analysis (GSEA) identified key pathways such as the inflammatory responses, including interferon (IFN) signaling pathways (type I IFN, IFN-gamma); neutrophil degranulation; viral defense; protein processing (translational initiation and SRP-dependent co-translational protein targeting to membrane). The top 20 features from the RF of flare versus non-flare were related to cell cycle arrest and microtubule polymerization. The highest-ranking feature was microRNA 5195, a regulator of post-transcriptional gene expression.

Conclusion: We identified distinct gene expression profiles associated with PFAPA flare versus non-flare states in a well-characterized PFAPA cohort. This provides a global overview of the immune dysregulation associated with PFAPA flares and suggests that they resemble an inflammatory response at the transcriptional level. The flare state was associated with differences in interferon signaling, innate immune mechanisms, and heightened cellular activity manifesting as cell cycle arrest and microtubule polymerization (modulated by colchicine used in PFAPA). The MicroRNA 5195 gene was identified as the highest-ranking predictive feature of PFAPA flares demonstrating the utility of machine learning models in prioritizing biologically relevant markers and advancing our understanding of the molecular drivers of PFAPA flares.

Acknowledgments: References:

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Disclosure of Interest: S. Lapidus Grant /Research support from: The Shotmeyer Family Foundation, The Hearst Foundation , T. Ambooken Conflict with: The work described in this publication was completed while Dr Tresa Ambooken was employed at Hackensack University Medical Center. The opinions expressed in this article do not reflect the views of the Food and Drug Administration, the Department of Health and Human Services, or the United States government. , E. Hakim : None declared, T. Lozy Shareholder of: Eli Lilly; low potential conflict. , E. Golalipour: None declared, S. Adonimohammed : None declared, J. E. Weiss : None declared, S. Li : None declared, A. Nowakowski: None declared, A. Lejtman: None declared, A. Sebbag: None declared, A. A. Aptekmann: None declared, J. V. Desai: None declared

Identifier: O33

STRUCTURE AND FUNCTION OF PYRIN INFLAMMASOME: MECHANISTIC LINK BETWEEN FMF AND NOCARH SYNDROME

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Introduction: 27 years after the discovery of *MEFV,* the gene mutated in familial Mediterranean fever (FMF), a complete account of the structure and function of the pyrin inflammasome is still lacking. The B30.2 domain where the majority of FMF variants are located has long been thought to hold the key for understanding the activation mechanism. On the other hand, the dominant inheritance pattern of the autoinflammatory phenotype from rare P373L, H478Y, and T577N FMF patients emphasizes the importance of the B-box and coiled-coil domains. Meanwhile, neonatal-onset cytopenia, autoinflammation, rash, and hemophagocytic lymphohistiocytosis (NOCARH) syndrome has been recently added to the ever-growing list of pyrin-mediated autoinflammatory diseases. Mechanisms how mutations on the C-terminus of CDC42 trigger the inflammasome activation of pyrin however remain enigmatic. We previously demonstrated that in PAPA syndrome, mutant PSTPIP1 aberrantly activates the pyrin inflammasome in a noncanonical pathway that is independent of pyrin phosphorylation or 14-3-3 interaction, opening possibilities for the existence of other regulatory mechanisms of the pyrin inflammasome.

Objectives: We sought to explain the function of each domain of pyrin and how their functions translate into the activation of the pyrin inflammasome. At the same time, we will provide mechanistic insight into inflammasome activation by FMF and NOCARH syndrome variants.

Methods: We utilized U-937 human monocytic stable cell lines that express wildtype and mutant *MEFV* and *CDC42*. For immunofluorescence imaging, COS-1 cells were transiently transfected with plasmids encoding either pyrin and CDC42 fused with fluorescent molecules for live imaging or tagged pyrin and CDC42 for fluorescence imaging on fixed cells. The pyrin homo-trimer model was built by homology to 5IEA using Schrodinger software. The multimer mode of AlphaFold2 was used to predict the structure of the B30.2-CDC42 dimer.

Results: To investigate possible common mechanisms of activation, we studied the oligomerization of pyrin. Tripartite motif (TRIM) family proteins are known for the formation of aggregates called cytoplasmic bodies by overexpression. We found that pyrin also forms its own cytoplasmic body by overexpression, which is mediated by the B-box and coiled-coil domains. AlphaFold2 predicted that the B-box domain of pyrin homo-trimerizes with other pyrin molecules. The predicted structure was confirmed by site-directed mutagenesis of key residues. We also demonstrated that disruption of B-box homo-trimerization suppressed inflammasome activity, indicating that oligomerization is critical for pyrin inflammasome activation. NOCARH variant CDC42 is known to localize at the Golgi apparatus. When coexpressed, pyrin was colocalized with mutant CDC42 at the Golgi. Only the coiled-coil and B30.2 domains were necessary for the colocalization. Deleting the B30.2 domain or the Ile692 residue abrogated the colocalization. The B30.2 domain and CDC42 were predicted to directly interact by AlphaFold2. In the predicted structure, residues known to be mutated in FMF such as Met680, Ile692, and Met694 were located on the interacting surface with CDC42. We validated the predicted structure by introducing the M45E mutation on CDC42, the residue expected to be critical for the interaction, and observed that the colocalization was disrupted. The B30.2 binding site on CDC42 overlapped with the CRIB motif binding site of CDC42. We observed that pyrin competes with PAK1-CRIB for interaction with CDC42, and that pyrin preferentially interacts with the inactive form of CDC42.

Conclusion: For the first time, we present a comprehensive mechanism of the pyrin inflammasome activation based on domain-wise structural and protein-protein interaction analysis. This knowledge also provides valuable insight on understanding the pathogenesis of both FMF and NOCARH syndrome.
Disclosure of Interest: None declared

Identifier: O34

MEVALONATE KINASE DEFICIENCY – AN AUTOINFLAMMATORY DISEASE OF DYSREGULATED NK CELLS

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Introduction: Mevalonate kinase deficiency (MKD) is caused by loss-of-function variants in the mevalonate kinase (*MVK*) gene. Infection is a common trigger for inflammatory flares, although the mechanism is unclear. Lack of mevalonate kinase prevents the prenylation of small GTPases, long thought to cause inflammasome over-activation. However, it is also clear that MKD is a multi-cytokine disorder with some patients presenting with features of hemophagocytic lymphohistiocytosis (HLH) or macrophage activation syndrome (MAS).
Objectives: We sought to elucidate the underlying mechanisms of inflammation in MKD by creating the first genetic mouse models of MKD with a variety of biallelic loss-of-function mutations in *Mvk*.
Methods: Inflammasome activation in $CD11b^+$ monocytes was measured by ASC speck staining. Immune cell populations in PBMC were examined used single cell RNA sequencing. Findings were validated by flow cytometry and extended to PBMC from MKD patients. Immune cell function was analysed by confocal imaging of live single cells.
Results: We found no evidence that $CD11b^+$ monocytes from *Mvk* mutant mice were more sensitive to NLRP3 or pyrin inflammasome activation. However, scRNA-seq analysis of PBMCs revealed a significant decrease in NK cells. Flow cytometric analysis confirmed a profound decrease in the most mature subset of NK cells ($NK1.1^+CD27^-CD11b^+$) in spleen and blood from three different lines of *Mvk* mutant mice. This effect was cell intrinsic and was retained in wildtype chimaeric mice transplanted with *Mvk* mutant bone marrow. Importantly, we also found a significant decrease in the frequency of the most mature subset of circulating NK cells ($CD57^+CD56^{dim}$) in 8 MKD patients compared to healthy controls. Prenylated Rab GTPases are essential for cytotoxic granule formation and trafficking in NK cells. We confirmed that the prenylation of Rab GTPases was profoundly deficient in purified NK cells from *Mvk* mutant mice and that these NK cells had a significant increase in the number and dispersion of cytotoxic granules and a ~40% reduction in target cell killing. A similar, mild decrease in NK cell cytotoxicity was observed in 2 MKD patients. High-resolution live cell microscopy of NK/target cell interactions revealed that, in NK cells from mutant mice and 2 MKD patients, cytolytic granules failed to migrate to the immunological synapse with a target cell. Furthermore, activation of *Mvk* mutant mouse NK cells also led to a significantly higher proportion of $IFN\gamma^+$ NK cells and elevated IFNγ release. Since NK cells respond to viral infection, we further examined the effect of MCMV infection *in vivo*. *Mvk* mutant mice had significantly higher viral load after 7 days compared to infected control mice, with worsened liver pathology and increased inflammatory cell infiltrate. NK cells in *Mvk* mutant mice failed to expand during infection, with significantly lower numbers of total and $Ly49H^+$ NK cells (that recognise MCMV-infected cells) 7 days post-infection. Whilst serum cytokines in infected control mice were at baseline 7 days after infection, multiple serum cytokines and chemokines were significantly increased in infected *Mvk* mutant mice, particularly IFNγ.
Conclusion: These observations reveal that a dysregulated anti-viral response of defective NK cells in mouse models of MKD results in insufficient viral clearance, cytokine-mediated macrophage activation (likely via IFNγ) and systemic inflammation. NK cells also appear to be defective in patients with MKD. We propose that the inflammatory flares in MKD are caused by an underlying defect in cytotoxic cell function, reminiscent of the mechanisms of inflammation in HLH/MAS caused by abnormalities in cytotoxic cells.
Disclosure of Interest: None declared

Identifier: O35

INFLAMMATORY AND DYSIMMUNE MANIFESTATIONS IN T/NK-CELL TYPE CHRONIC ACTIVE EBV INFECTION: A DESCRIPTION OF 14 CASES OF A RARE AND HETEROGENEOUS CLONAL LYMPHOID HEMATOLOGICAL DISORDER

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Introduction: Systemic chronic active Epstein-Barr virus infection (CAEBV) of T/NK cells is a rare EBV-positive T/NK lymphoproliferative disease often associated with somatic genetic alterations. Its heterogeneous phenotypes can mimic dysimmune or inflammatory diseases, posing diagnostic challenges. Improved awareness and early diagnostic tools are essential to address its poor prognosis.

Objectives: To describe the phenotypic diversity, diagnostic challenges, and somatic genetic events linked to systemic CAEBV presenting with dysimmune or autoinflammatory symptoms.

Methods: We analyzed and reported the inflammatory or dysimmune presentations of 14 patients from a cohort of 60 individuals diagnosed with EBV-positive T/NK-cell lymphoproliferative disorders. Diagnosis was based on detecting EBV-infected T or NK cells via EBER flow-FISH assays on peripheral blood or histological analysis. Targeted NGS and optical genome mapping after bead-based sorting of infected lymphocyte was carried out in 7 patients to identify somatic alterations.

Results: Fourteen patients were included. The median age at onset was 11.4 years (range: 3.5–51.7 years), with a median diagnostic delay of 2.8 years (range: 0.03–13.3 years). Median follow-up duration was 4 years (range: 0.2–25.9 years). Median EBV DNA load was 5 log (range: 4.7–7.1 log), with a median duration of EBV PCR positivity of 2 years (range: 0.1–22.4 years); no patient presented PCR negativity without chemotherapy or hematopoietic stem cell transplantation (HSCT).

Chronic organ involvement included skin (n=5, severe ulcers, isolated facial edema, subcutaneous nodules), nephrotic syndrome (n=1), systemic vasculitis (n=5, affecting large or medium vessels), diffuse myositis (n=2), inflammatory bowel disease (n=2), infiltrating meningitis (n=2), and laryngeal stenosis (n=2). New organ involvement was rare over follow-up. Before CAEBV diagnosis, patients were diagnosed with or suspected to have Behçet's disease, Kawasaki disease, polyarteritis nodosa, Takayasu disease, granulomatosis with polyangiitis, Whipple disease, myositis, inflammatory bowel disease, or systemic granulomatous disorders. These diagnoses often exhibited atypical features, such as absent disease-specific antibodies or a spontaneous relapsing-remitting course.

CRP levels were inconsistently elevated; while some patients with vasculitis or inflammatory bowel-like disease had high CRP levels during flares (150–300 mg/L), others showed normal or mildly elevated CRP (0–60 mg/L), even during exacerbations. Clues suggestive of lymphoid hemopathy, such as cytopenia, lymphadenopathy, or elevated LDH, were

often absent or mild at onset and during follow-up.
Somatic alterations were identified in the 7 patients tested, including mutations in the *KMT2D, PTPRC, ARID1A, STAT3, CD58, DDX3X* genes and a chromosomal rearrangement affecting the *PDL1/PDL2* genes, highlighting the clonal nature of CAEBV.
Outcome was unpredictable: while some patients remained stable with minimal treatment, five out of ten who did not undergo allogeneic HSCT died from uncontrolled organ damage or hemophagocytic lymphohistiocytosis (HLH), sometimes after years of indolent disease. All four allogeneic HSCT recipients died (one relapse, three toxicity-related deaths). These outcomes contrast with the better survival reported in Japanese cohorts, where earlier diagnosis led to more successful treatments (especially HSCT).
Conclusion: Systemic T/NK CAEBV is a lymphoid hematological disorder with unpredictable outcomes, driven by somatic genetic events in many cases. Symptoms can mimic atypical autoinflammatory or dysimmune diseases, complicating diagnosis. In such cases, a markedly elevated EBV DNA load should prompt diagnostic confirmation through EBER flowfish or histology to enable timely treatment, including consideration of allogeneic HSCT.
Disclosure of Interest: None declared

Identifier: O36

EMERGING TREATMENT STRATEGIES FOR VEXAS SYNDROME: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Introduction: VEXAS syndrome is a monogenic autoinflammatory disorder with significant morbidity and mortality. Pathogenic variants in the UBA1 gene have been established as the key etiological factor. Common manifestations include skin lesions, fever, weight loss, lung involvement, chondritis, arthralgia, fatigue, cytopenia, myelodysplastic syndrome (MDS), thrombosis, and hematologic malignancies. Furthermore, the disease is associated with significant mortality and morbidity. Numerous treatment options including azacytidine, JAK inhibitors, IL-6 inhibitors, anti-IL-1, and anti-TNF agents have been proposed. However, no consensus on treatment algorithm for VEXAS syndrome has been reached.

Objectives: This study aims to evaluate the efficacy and safety of these treatments through a meta-analysis of existing data to help establish clearer guidelines for managing VEXAS.

Methods: The study protocol was registered in PROSPERO (CRD42024590134). MEDLINE and EMBASE were screened from inception until September 2024. We included patients with VEXAS syndrome who received treatment with azacitidine, JAK inhibitors, IL-6 inhibitors, anti-IL-1, or anti-TNF agents. The primary outcomes were proportion of complete responders and patients who experienced adverse events. Secondary outcomes were the proportion of partial responders and the occurrence of serious adverse events. Given the lack of standardized response criteria for VEXAS syndrome, we defined complete response as being clinically asymptomatic, normalization of inflammatory/hematological parameters, prednisolone <10mg/day or independence, or genetic remission (VAF <1%). Partial response was marked by symptom improvement, laboratory parameter normalization, and reduced prednisolone or VAF.

Results: A total of 15 studies and 291 patients with VEXAS syndrome were included. Among the included patients, 116 (39.9%) were reported to have MDS. Azacitidine treatment resulted in complete and partial inflammatory response in 66% [95% CI (0.55,0.77)] and in 77% [95% CI (0.67,0.87)] of cases, respectively. Complete and partial hematological responses were achieved in 65% [95% CI (0.54,0.75)] and 81% [95% CI (0.70,0.92)] of the patients treated with azacitidine, respectively. Infections were frequently reported during azacytidine treatment. JAK inhibitors provided complete responses in 49% [95% CI (0.39,0.58)] and partial responses in 78% [95% CI (0.70,0.86)]. Cardiovascular adverse events were the most commonly reported serious adverse events during JAK inhibitor treatment. IL-6 inhibitors led to a complete response in 27% [95% CI (0.18,0.36)] and partial response in 62% [95% CI (0.52,0.71)]. Anti-IL-1 treatment did not yield any significant increase in the proportion of complete responders [10%, 95% CI (0,0.21)]; however, a partial response to anti-IL-1 treatment was achieved by 35% [95% CI (0.22,0.48)] of the patients. Anti-TNF agents did not significantly increase the number of complete responders [9%, 95% CI (-0.04,0.22)] and the proportion of patients who partially responded to anti-TNF treatment was 27% [95% CI (0.09,0.45)].

Conclusion: Azacitidine and JAK inhibitors may be the treatment of choice for patients with VEXAS syndrome and concomitant MDS. IL-6 inhibitors may be favorable for patients with high inflammatory activity and no hematological involvement. The elevated risk of infections and cardiovascular adverse events should not be overlooked, and these patients must be closely monitored throughout the course of treatment.

Disclosure of Interest: None declared

Identifier: O37

ROLE OF IL-18 AS A BIOMARKER IN MONITORING PEDIATRIC PATIENTS WITH STILL'S DISEASE

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Introduction: Still's disease is a chronic systemic inflammatory disorder characterized by nonspecific clinical signs and symptoms, as well as laboratory markers, which pose diagnostic challenges at onset (e.g., Kawasaki disease, leukemia, HLH). Interleukin-18 (IL-18) has emerged as a promising biomarker for Still's disease, supporting diagnosis and monitoring. Although IL-1 inhibitors are the first-line therapy, the longitudinal trends and predictive value of IL-18 levels in treated patients remain poorly characterized.
Objectives: To evaluate IL-18 plasma levels in pediatric patients with Still's disease before treatment initiation (baseline) and during treatment with IL-1 inhibitor therapy. We aimed to assess the relationship between IL-18 levels and disease activity and to establish IL-18 cut-off values predictive of clinical inactive disease (CID) at 6- and 12-months post-treatment initiation.
Methods: A total of 81 episodes of pediatric Still's disease (67 disease onset and 14 flares) were analyzed. All patients began IL-inhibitor therapy and were followed for at least 12 months. Demographic, clinical and laboratory data were collected at the baseline (T0), at 3 (T3), 6 (T6) and 12 (T12) months post-treatment initiation. Disease status was assessed according to the new EULAR/PReS recommendation. Statistical adjustments were made for potential confounders, including macrophage activation syndrome (MAS) and concomitant treatments.
Results: At baseline, the median IL-18 level was 42.956 pg/ml (range 7.628–136.559), CXCL9 was 533 pg/mL (range 300–3.687), and ferritin was 1.375 ng/ml (range 399–4.928). MAS was present in 26 patients at the onset of the disease. 71 patients were treated with anakinra (87,6%) and 10 patients with canakinumab (12,4%). 75,3% received glucocorticoids (54,3% with intravenous pulses) for a median time of 72 days, and 18,5% patients received cyclosporin. IL-18 levels showed a significant reduction over time, regardless of disease status [median values (pg/ml) at T0: 42.956, T3: 1.984, T6: 969 and T12: 753,5; p<0,0001]. At T3, 54/78 patients (69.2%) achieved CID, with no significant difference in IL-18 levels between CID and active disease (AD) patients (median: 1,498 vs. 3,318 pg/mL, p = NS). At T6, 60/79 patients (75%) were in CID, while 19/79 (25%) had AD; IL-18 levels were significantly higher in AD patients compared to those in CID (median: 3,138 vs. 819 pg/mL, p = 0.01). Baseline IL-18 levels were markedly elevated in patients with AD at T6 compared to those achieving CID (median: 121,800 vs. 29,695 pg/mL). At 12 months, 65/79 patients (82,2%) were in CID, and 14/79 (17,7%) had AD; IL-18 levels were significantly higher in patients with AD compared to those in CID (median 49.909 vs 721 pg/mL, p=0,0001). By ROC analysis, a 12-month IL-18 cut-off of 1,150 pg/mL identified CID patients with an AUC of 90% (sensitivity 91%, specificity 79.5%, p<0.0001). Additionally, patients with AD at T12 exhibited significantly higher baseline IL-18 levels than those in CID (median: 121,800 vs. 29,695 pg/mL, p = 0.003). A baseline IL-18 cut-off of 43,898 pg/mL predicted CID at T12 with an AUC of 73.5% (sensitivity 91.6%, specificity 58%).
Conclusion: IL-18 levels are strongly associated with disease activity in pediatric Still's disease, independent of MAS or IL-1 inhibitor therapy. IL-18 demonstrates significant potential as a biomarker for monitoring disease progression and predicting CID, offering a valuable tool for tailoring treatment strategies and improving patient outcomes.
Disclosure of Interest: None declared

Identifier: O38

EVALUATING SIGLEC-1 EXPRESSION ON MONOCYTES AS A DIAGNOSTIC BIOMARKER FOR TYPE I IFN-RELATED PEDIATRIC AUTOINFLAMMATORY DISEASES

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Introduction: Type I interferons (IFN-α and IFN-β) are cytokines critical for antiviral immune responses. Dysregulated or excessive activation of the IFN-I pathway can lead to a group of diseases collectively referred to as “interferonopathies”. These disorders include monogenic interferonopathies, such as Aicardi-Goutières Syndrome (AGS), STING-Associated Vasculopathy with Onset in Infancy (SAVI), Chronic Atypical Neutrophilic Dermatosis with Lipodystrophy and Elevated Temperature (CANDLE), and systemic autoimmune diseases like Systemic Lupus Erythematosus (SLE), Juvenile Dermatomyositis (JDM), and Sjögren's Syndrome. Diagnosing IFN-I-related diseases is challenging due to overlapping clinical features. The identification of an "IFN signature" (IS) through gene expression profiling has become an important tool in diagnosis and monitoring. However, this method, based on quantitative RT-PCR, is time-consuming, expensive, and not widely accessible. The expression of sialic-acid-binding Ig-like lectin 1 (Siglec-1, also known as CD169) on monocyte surface has emerged as a promising alternative biomarker for diagnosing and monitoring interferonopathies.
Objectives: This study aimed to evaluate whether SIGLEC-1 expression on monocytes, assessed by flow cytometry (FACS), could serve as a reliable and efficient biomarker for IFN-I activation-related diseases. Specifically, we evaluated its diagnostic accuracy compared to the current gold-standard IS obtained via RT-PCR.
Methods: We retrospectively analyzed peripheral blood mononuclear cells (PBMCs) from 32 pediatric patients with interferonopathies (7 SAVI, 11 JDM, 14 SLE) and 15 healthy controls. SIGLEC-1 expression was measured by FACS on CD14+ CD16+ monocytes (classical and intermediate subsets). Both the percentage of SIGLEC-1+ monocytes and their mean fluorescence intensity (MFI) were measured and correlated with the IS, determined by evaluating six IFN-stimulated genes (*IFI27, IFI44L, IFIT1, ISG15, RSAD2, SIGLEC1*) via RT-PCR in whole blood. To validate the diagnostic performance of Siglec-1 measurement, a prospective cohort of 84 patients with suspected interferonopathy was also analyzed, with concurrent analyses of SIGLEC-1 expression (FACS) and IS (RT-PCR).
Results: In the retrospective cohort, the percentage of SIGLEC-1+ monocytes and the SIGLEC-1 MFI strongly correlated with the IS ($r = 0.8747$ and $r = 0.8716$, respectively; $p<0.0001$). Receiver operating characteristic (ROC) curve analysis revealed that both the percentage of SIGLEC-1+ monocytes (area under the curve [AUC] = 0,98, $p < 0.0001$) and the SIGLEC-1 MFI (AUC = 0.9979, $p < 0.0001$) reliably discriminated patients with interferonopathies from healthy controls. Optimal cut-offs were established at 3.5% for SIGLEC-1+ monocytes and 513 MFI, yielding diagnostic accuracies of 93.75% and 96.87%, respectively. In the prospective cohort, 54 of 84 patients met the 3.5% SIGLEC-1+ monocyte cut-off, of whom 47 (87.04%) also exhibited a positive IS, resulting in a positive predictive value (PPV) of 87.04% and a negative predictive value (NPV) of 80.0%, with an overall diagnostic accuracy of 84.52%. Similarly, using the MFI cut-off, 56 of 84 patients were positive, with 49 out of 56 (87.5%) showing a positive IS, resulting in a PPV of 87.5%, NPV of 85.71%, and an overall diagnostic accuracy of 86.9%.
Conclusion: Our findings demonstrate that SIGLEC-1 is a reliable, cost-effective, and time-efficient biomarker for diagnosing and monitoring interferonopathies. This method offers a practical alternative to the labor-intensive IS analysis by RT-PCR, enhancing diagnostic accessibility and improving clinical management of IFN-I-related diseases.
Disclosure of Interest: None declared

Identifier: O39

DEEP PHENOTYPING IDENTIFIES INFLAMMATORY PATHWAYS ASSOCIATED WITH DISEASE ACTIVITY OF VEXAS SYNDROME

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Introduction: VEXAS syndrome (VS) is a newly discovered autoinflammatory disease caused by somatic mutations in the *UBA1* gene. VS is characterized by recurrent inflammation, particularly during steroid tapering, leading to low remission rates and a high prevalence of complications. There is an urgent need for effective therapeutic strategies to control disease activity. Our group has recently published a disease activity index (DAI) known as the VEXAS current activity form (VEXASCAF). However, the clinical significance of VEXASCAF remains uncertain, and reliable biomarkers to assess disease activity or guide treatment decisions are yet to be established.
Objectives: To identify molecules correlated with DAI to search for potential biomarkers of VS, and to elucidate the mechanisms driving disease flares through deep phenotyping (DP).
Methods: We measured VEXASCAF during each outpatient visit and extracted RNA and plasma from peripheral blood. Longitudinal RNA-seq was performed as part of DP. cDNA was synthesized from the remaining RNA, and variant allele frequency (VAF) of *UBA1*-mutant was quantified. As controls, we analyzed samples from patients with *UBA1* mutation-negative VS-like diseases and healthy individuals. Detailed clinical information, laboratory data, and treatment records were carefully collected throughout the study. In addition to whole blood, peripheral blood samples from VEXAS patients and healthy controls were fractionated into PBMCs, monocytes, and neutrophils for RNA sequencing (RNA-seq). Single-cell RNA-seq was also performed. Plasma samples underwent proteomic analysis. Furthermore, disease model cell lines harboring *UBA1* mutations (p.Met41Val, p.Met41Thr, p.Met41Leu) were generated using gene-editing techniques. These models were analyzed for phenotypic changes, RNA-seq, and ATAC sequencing to examine gene expression and chromatin accessibility.
Results: Thirteen VS patients were included in DP. The collected RNA-seq samples from VS were divided into discovery samples (n=38) and validation samples (n=41), both of which identified *RNASE1* as one of the genes most strongly correlated with VEXASCAF ($r = 0.7$, FDR < 0.05). *RNASE1* was consistently upregulated in VS compared to controls across multi-omics data. Additionally, *RNASE1* expression showed a positive correlation with *UBA1* mutant VAF ($r = 0.58$, FDR < 0.05) and a negative correlation with hemoglobin ($r = -0.64$, FDR < 0.05). Plasma/serum concentrations of RNASE1 were elevated in VS patients and partially decreased following corticosteroid dose escalation. While previous studies have reported *UBA1* genotype-dependent differences in prognosis, our established cell lines revealed genotype-specific variations in ubiquitination, cell death, and cytokine secretion. Validation using disease model cell lines revealed *RNASE1* upregulation associated with cell death, and *UBA1* genotype-specific expression patterns. Further analyses elucidated the epigenetic mechanisms regulating *RNASE1* expression.
Conclusion: RNASE1 was identified as a potential biomarker for disease activity in VS, through comprehensive multi-omics analysis based on DP. Disease pathogenesis patterns following ubiquitination appear *UBA1* genotype-specific, potentially influencing prognosis.
Disclosure of Interest: None declared

Identifier: O40

IMPROVEMENT OF REFRACTORY STILL'S/SYSTEMIC JUVENILE IDIOPATHIC ARTHRITIS LUNG DISEASE IN 6/7 CHILDREN TREATED WITH A NOVEL, BI-SPECIFIC IL-1BETA/IL-18 NEUTRALIZING ANTIBODY

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Introduction: Despite major advances in the understanding, diagnosis, and treatment of Still's disease (including Systemic Juvenile Idiopathic Arthritis, sJIA), many patients experience a refractory course despite maximal therapy. Among potential organ-involvements, sJIA-associated lung disease (sJIA-LD) has arisen as a major comorbidity of refractory Still's, prompting some patients to seek stem cell transplantation.

Objectives: We report on the safety and efficacy of an investigational bi-specific IL-1β/IL-18 neutralizing antibody (αIL-1β/18, MAS825) in seven refractory Still's patients.

Methods: All patients received bimonthly αIL-1β/18 infusions via single-patient extended-use protocols at The Children's Hospital of Philadelphia (CHOP), University of Pittsburgh, or Hackensack University Medical Center. Parents/guardians provided informed consent for a registry study approved by The CHOP Institutional Review Board. Clinical, laboratory, radiologic, and pathologic information were extracted from patient electronic medical records.

Results: Disease onset was observed between 13 months and 11 years of age. All patients met provisional classification criteria for refractory sJIA prior to αIL-1β/18 treatment. Other baseline characteristics included a predominantly systemic course with at least one Macrophage Activation Syndrome (MAS) episode (8/8), intermittent inflammatory arthritis (3/7), persistent itchy rash (6/7), sJIA-LD (6/7), clubbing (4/7), and peak total IL-18 levels from 77,000 to >650,000 pg/mL. Two patients had MAS flares triggered by *S. aureus* infections. One patient with comorbid Trisomy 21, repaired congenital heart disease, and laryngomalacia developed respiratory failure and underwent tracheotomy due to sJIA-LD. All patients had received high-dose glucocorticoids (5/7 with regular IV pulses), IL-1 blockade, and at least one JAK inhibitor prior to aIL-1b/18 initiation.

Six of 7 patients remained on αIL-1β/18 at the time of data acquisition, with a duration of 0.9 to 3.6 years exposure. One patient stopped αIL-1β/18 after 4 months for lack of efficacy. Of the six patients remaining on αIL-1β/18, all have weaned off systemic glucocorticoids (save replacement-dose hydrocortisone, 2/6). Additionally, they all had a substantial reduction or complete discontinuation of other Still's treatments. These patients all showed stabilization or improvement of chest CT's, and they all showed clinically significant functional improvement (timed walk test, pulmonary function test, and/or ventilator settings as applicable/evaluable).

No infusion reactions were reported. One patient developed pseudomonal line infection and worsened cholangitis. Another patient was found to have *S. aureus* vertebral osteomyelitis 5 months after αIL-1β/18 initiation. Symptoms and inflammatory markers initially improved with antibiotics and holding αIL-1β/18, but MAS soon flared. Re-initiation of αIL-1β/18 in conjunction with antibiotics led to clinical improvement, but the infection has required long-term antibiotic treatment.

Conclusion: In this highly refractory cohort, αIL-1β/18 was overall well-tolerated, and 6/7 patients showed clinical improvement and significant reduction in glucocorticoid and other Still's therapies. These data strongly support prospective trials, with careful monitoring particularly for invasive bacterial infection, in this immunosuppressed population with life-threatening Still's disease.

Acknowledgments: All patients were provided αIL-1β/18 via a Managed Access Program. Novartis conducted a scientific accuracy and intellectual property review of this abstract, but has not otherwise instigated or influenced the content of this publication
Disclosure of Interest: None declared

Identifier: O41

PHOSPHOMEVALONATE KINASE DEFICIENCY: UNCOVERING NEW DIMENSIONS OF THE DISEASE PHENOTYPE

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Introduction: Phosphomevalonate kinase (PMVK) deficiency is a recently identified autoinflammatory disease.
Objectives: To outline the clinical features of PMVK deficiency by analyzing the presented and published cases.
Methods: Genome sequencing was performed in the two affected sisters and their parents at the *National Institutes of Health* Intramural Sequencing Center. The identified variant was confirmed by Sanger sequencing. In-silico thermodynamic protein stability predictions were made based on the predicted 3D structure of PMVK by using INPS-3D, DynaMut2, and PremPS (ΔG threshold:0.5).
Results: The first patient is an 8.5-year-old girl born to consanguineous parents. She had severe diarrhea and fever lasting for one week when she was eight months old. She had fever, arthritis, thrombocytopenia, and elevated acute phase reactants (APRs) lasting for one month when she was 14 months old. She was diagnosed with systemic juvenile idiopathic arthritis (JIA) and treated with glucocorticoids and methotrexate. At 20 months of age, her disease flared with polyarthritis. There was a good response to tocilizumab, but she developed anaphylaxis. APRs remain elevated despite several lines of biological treatment (anakinra, canakinumab, etanercept, tofacitinib). The best clinical response has been achieved with canakinumab. She also has recurrent abdominal pain attacks lasting for 1 day every 2-3 months. She has short stature, probably due to chronic inflammation.

Her elder sister is ten years old. She has had recurrent fever attacks with abdominal pain, diarrhea, and arthritis lasting for 3-4 days since she was 2.5 years old. She was diagnosed with oligoarticular JIA when she was eight and treated with glucocorticoids and methotrexate. Her disease flared with chronic arthritis 2 years later, and etanercept has recently been started. Despite clinical remission, APRs remain elevated. Both sisters were anemic during follow-up.

Both patients were homozygous for the p.Val106Met variant in *PMVK*, while unaffected parents were heterozygotes. The in-silico scores suggest that this variant is pathogenic (CADD 24.8; REVEL 0.43; α-missense 0.53) and destabilizes the PMVK enzyme (Dynamut2=-0.73;PremPS=1.84;INPS-3D=-1.66). Mevalonic aciduria was detected in one patient.

In the literature, there are only three cases with PMVK deficiency (Table 1). Parental consanguinity and recurrent fever attacks were present in all. The predominant phenotype was chronic arthritis and cytopenia. The previous diagnosis was JIA in four patients. Abdominal pain, diarrhea, and arthritis were the main attack symptoms. Although the best clinical response was obtained with anti-IL-1 treatment, APRs remain elevated under treatment in two patients.

Reference	**Age, yrs**	**Sex**	**Age at onset**	**Chronic arthritis**	**Cytopenia**	**Previous diagnosis**	**Mevalonic aciduria**	***PMVK* variants**
Yildiz et al., 2022 (n=1)	14	M	6 yrs	+	Anemia	FMF, JIA	+	V106M/R110G
Berner et al., 2023 (n=1)	5	F	9 mos	+	Anemia	AID	+	V131A/V131A

					Platelet↓ Granulocyte ↓			
Jairaman et al., 2023 (n=1)	11	M	2.5 yrs	+	Anemia	JIA	NI	A133V/A133V
Presented case 1	8.5	F	8 mos	+	Anemia Platelet↓	JIA	-	V106M/V106M
Presented case 2	10	F	2.5 yrs	+	Anemia	FMF, JIA	+	V106M/V106M

(AID, autoinflammatory disease; FMF, familial Mediterranean fever; NI, not indicated)

Conclusion: The predominance of chronic refractory arthritis in the phenotype of PMVK deficiency misdirects clinicians to the diagnosis of JIA. Our analysis shows that JIA patients with recurrent fever flares and cytopenia should be tested for PMVK deficiency, especially in the presence of family history or parental consanguinity.
Disclosure of Interest: None declared

Identifier: O42

CHARACTERISTICS AND PROBLEMS OF JAPANESE PATIENTS WITH UBA1 VARIANT-NEGATIVE VEXAS SYNDROME-LIKE AUTOINFLAMMATORY DISEASE

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Introduction: With the accumulation of cases, the clinical features of VEXAS syndrome (VS) have been clarified. However, the management of *UBA1* variant-negative VS-like autoinflammatory disease (VLAD) patients remains unsolved.
Objectives: To identify the similarities and differences with VS, examine the clinical features, and clarify the problems related to the clinical management of VLAD patients.
Methods: Japanese patients suspected of VS were registered from October 2023 to November 2024. All patients underwent whole-exome sequencing of the *UBA1* gene. Patients' age, sex, related symptoms, comorbidities, the recently proposed disease activity index for VS called VEXAS current activity form (CAF), and treatments, were collected through the primary physicians. This clinical information was compared between VS and VLAD.
Results: We enrolled 83 patients and 48.2% (n=40) were negative for *UBA1* variant. The *UBA1* variant negative (VLAD) patients consisted of 34 males and 6 females, with a mean age of 70.9 ± 11.3 years (range: 43-88 years) at the time of genetic testing. Most of the patients in this group had hematopoietic abnormalities such as myelodysplastic syndrome or macrocytic anemia. Additional findings included trisomy 8 in 6 cases, chronic myelomonocytic leukemia in 2 cases, diffuse large B-cell lymphoma in 1 case, and T-cell lymphoma in 1 case. All patients had one or more clinical symptoms typical of VS, such as fever, rash, pulmonary infiltration, chondritis, and joint symptoms. All forty-three patients with VS were male, and the mean age at genetic testing was 75.6 ± 6.8 years, higher than in VLAD patients (p=0.02). The mean VEXASCAF was 3.05 in the VS group and 2.32 in the VLAD group, with no significant difference between the two groups (p=0.127).
Conclusion: Our findings highlight the existence of VLAD, but it remains unclear whether these cases share the similar pathophysiology as VS or whether they represent an independent disease category. Given that most patients are elderly and experience persistent inflammation, further research of pathogenesis and the development of appropriate treatment strategies for VLAD is needed.
Disclosure of Interest: None declared

Identifier: O43

TARGETING THE DYSREGULATED TYPE I IFN RESPONSE IN ADENOSINE DEAMINASE 2 DEFICIENCY EFFECTIVELY MITIGATES INFLAMMATION VIA PATHWAY INHIBITION AND GENE THERAPY

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Introduction: Deficiency of Adenosine Deaminase 2 (DADA2) is a rare autoinflammatory disorder characterized by systemic inflammatory manifestations, including vasculopathy, cytopenias, and recurrent fevers. A hallmark of DADA2 is the heightened type I interferon (IFN) signature, driven by elevated IFN-β and interferon-stimulated gene (ISG) expression, which contributes to its pathogenesis. Understanding the mechanisms behind this hyperinflammatory state is critical for developing targeted therapies.

Objectives: This study investigated the mechanisms responsible for the increased type I IFN signature in DADA2, evaluated the therapeutic potential of targeting the cGAS-STING and JAK-STAT pathways, and explored gene therapy as a curative strategy to correct the inflammatory phenotype in DADA2.

Methods: Peripheral blood mononuclear cells (PBMCs) from DADA2 patients were analyzed for type I IFN and ISG expression. A human monocytic U937 cell line with ADA2 knockout (KO), generated using CRISPR-Cas9, served as an *in vitro* disease model. Pharmacological inhibitors of the cGAS-STING and JAK-STAT pathways were employed to modulate IFN signaling, and a zebrafish model of DADA2 was used to validate findings *in vivo*. Lentiviral transduction of ADA2-deficient macrophages with a vector encoding ADA2 assessed the potential of gene therapy in restoring normal IFN responses.

Results: PBMCs from DADA2 patients exhibited a markedly elevated type I IFN signature, with increased expression of IFN-β and ISGs, such as *ISG15*, *IFIT1*, and *RSAD2*. In ADA2 KO U937 cells, stimulation with the synthetic dsDNA analogue poly(dA:dT) recapitulated the heightened IFN response. Inhibition of the cGAS-STING pathway with Ru521 or H151 significantly reduced IFN-β levels and normalized the IFN response. Similarly, blocking the JAK-STAT pathway using ruxolitinib or an anti-IFNAR antibody restored IFN-β and ISG expression to baseline levels. The zebrafish model confirmed the heightened type I IFN response observed in human studies, and pharmacological inhibitors effectively mitigated the inflammatory response *in vivo*, supporting these pathways as viable therapeutic targets. Finally, gene therapy restored ADA2 expression in ADA2-deficient macrophages and normalized the type I IFN response. Lentiviral transduction fully reversed the hyperactive IFN response, demonstrating the potential of gene therapy as a curative approach for DADA2.

Conclusion: Our study identifies the cGAS-STING and JAK-STAT pathways as central drivers of the heightened type I IFN response in DADA2, providing strong evidence for pharmacological inhibition as a viable strategy to mitigate inflammation. Additionally, the successful restoration of ADA2 function and normalisation of the IFN response through gene therapy underscores its potential as a long-term curative strategy. These findings offer a roadmap for both immediate and future therapeutic interventions aimed at reducing the inflammatory burden in DADA2 patients.

Disclosure of Interest: None declared

Identifier: O44

FIRST GLOBAL SERIES OF VEXAS SYNDROME IN WOMEN: A COMPARATIVE ANALYSIS OF 14 FEMALE AND 274 MALE CASES

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Introduction: VEXAS syndrome is a monogenic autoinflammatory disease associated with somatic mutations in the *UBA1* gene explaining the male predominance of the disease. Indeed, as *UBA1* is not subject to X chromosome inactivation and is pseudoautosomal in women, the second allele theoretically protects women against the deficiency of the mutated one. However, VEXAS syndrome has been reported in women in cases of constitutional or acquired X monosomy.
Objectives: The aim of our study was to describe the cohort of female patients with VEXAS syndrome with a cohort of males.
Methods: We conducted an international multicenter retrospective study between November 2020 and October 2024. Women with VEXAS syndrome were included through a worldwide call for observation to colleagues engaged in VEXAS research, and men cases were collected from the French VEXAS cohort. All cases of VEXAS syndrome were confirmed by the identification of a *UBA1* pathogenic mutation among patients displaying compatible features of VEXAS including inflammatory and/or blood disorders.
Results: We included 14 women respectively from France (n=8), Mexico (n=3) and United-States (n=3). and compared them with 274 men. The mean age on diagnosis did not differ between women (72.9 ±9.6 years) and men (72.9 ±8.5 years, p=0.56). Women presented respectively the following features: neutrophilic dermatosis (n=7), fever (n=7), weight loss (n=6), arthralgia or arthritis (n=5), pulmonary infiltrates (n=3), chondritis (=2), aortitis and thromboembolic events (n=1 each) . The comparison of clinical features between men and women did not show any difference. One woman of 14 (7,1%) died during the follow-up period versus 37 men (13,5%) (p=0.70).

Biologically, all women were anemic and 10/14 (71.4%) presented a macrocytosis. Compared to men, women had lower hemoglobin level at diagnosis: 8.55 ±2.06 g/dl versus 10.86 g/dl± 8.32 in men (p=0.005), and a non-significant trend to a higher mean corpuscular volume: 104.5 ±8.6 fl in women versus 100.98 ±8.6 in men (p=0.60). The CRP level at diagnosis did not significantly differ between women and men (95.4 ±14.7 mg/l versus 78.49 ±72.7 mg/l, respectively, p=0.60).

Bone marrow aspirates were available in 10 women and showed vacuoles (n=5) and myelodysplasia (n=4) including isolated del(5q) (n=2), dysplasia of a single lineage (n=1) and ring siberoblast (n=1). Bone marrow karyotype revealed X monosomy in 8 cases. Additional mutations were identified by high-throughput sequencing (performed in 7 women): TET 2 (n=3), DNMT3A (n=1), ASXL1 (n=1), RUNX1 (n=1), TP53 (n=1), U2AF1 (n=1), and SRSF2 (n=1).

Women displayed the following *UBA1* mutations: p.M41V (n=5), p.M41T (n=4), p.M41L (n=3), c.118-1G>C (n=1), andc.118-2A>G (n=1). The frequencies of each mutation did not differ with men. The mean variant allele frequency (VAF) in blood similar between women and men: respectively 37% ±25 (n=13) and 42% ±24 (assessed in 63/274 men, p=0.48).

Conclusion: VEXAS features seem not to differ between male and female, except for more pronounced anemia in women that may be related to a longer diagnosis delay. Consequently, the presence of suggestive clinical signs associated with macrocytic anemia and biological inflammation should prompt the clinicians to perform *UBA1* sequencing in women, as for men.

Disclosure of Interest: None declared

Identifier: PT01

VEXAS SYNDROME IN FRANCE: A MULTICENTER CASE-SERIES OF 318 CASES FROM THE FRENCH VEXAS STUDY GROUP (FRENVEX).

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Introduction: VEXAS syndrome is a monogenic somatic autoinflammatory syndrome associated with *UBA1* mutations that was firstly described in 2020 by Beck et al. The clinical picture is heterogeneous and the disease seems to be not so rare among men >50 years old.

Objectives: To describe clinical characteristics, laboratory findings, main treatments and outcomes of VEXAS syndrome in a large French cohort.

Methods: All patients with a genetically proven VEXAS syndrome with a pathogenic *UBA1* mutation were collected in a redcap e-CRF in France between December 2020 and December 2024. Ethical agreements were obtained from Cochin ethic committee. Statistics were performed thru easymedstat® software.

Results: Among 318 patients, 308 (96,9%) were males with median age at diagnosis of 74.3 years old [min 51 -max 96,3].

The main clinical features were skin lesions (77%), mainly sweet syndrome and erythematous papules but also vasculitis lesions 21.2%, livedo 13% and urticaria 9%; followed by alteration of general status with weight loss (56,7%), fever (57,3%) lung involvement (49.6%), mostly pulmonary infiltrates; thrombosis (47%) was frequent, almost always veinous. Ocular inflammatory involvement was present in 46.2%, mainly conjonctivitis (n=18), orbital mass (n=16) uveitis (n=15) episcleritis (n=14) and scleritis (n=10). The other main features were respectively relapsing chondritis in 35,5%; arthralgia (36.8%), adenopathies in 23.9%; nervous system (23.6%) with mainly aseptic meningitidis (60%); gastrointestinal involvement (18.6%), splenomegaly in 14.6%, followed by hepatomegaly in 8.5%, kidney involvement in 8%, heart involvement in 5,3%. AA amyloidosis was present in only 2 cases.

Median hemoglobin rate was 9,9 g/dL [6-10,5] and median globular volume (MGV) 101,2 [82-122]; median platelets were 189000 [5-196000]. Median CRP levels were at 60 [0,5-335] mg/l; median ferritin was 860 [1-977]. *UBA1* sequencing was mostly performed by NGS panel (53.4%) and sanger (45,9%) and showed as most frequent mutations: p.M41T (40,7%), p.M41V (27,1%), p.M41L (20,3%), and other (11%). The mean VAF was 50.8%. Other myeloid somatic mutations were detected by panel in 70 cases (34,8%) mostly *DNMTA3* and *TET2*.

Hematological disease was present myelodysplastic syndrome (MD; 40%), mostly MDS with single lineage dysplasia (14.2%) or multiple (13.3%); monoclonal gammapathy of unknown significance was detected in (n=43, 21.3%). Karyotype had been performed in 175 cases and normal in 64.6%.

When researched (patients underwent bone marrow aspiration in 268 cases (95.4%), vacuoles were present in 70,5%.

Most patients received steroids (88,5%); JAK inhibitors were used in 62 patients (26,4%), IL-6 inhibitors in 53 cases (22.5%) , mostly tocilizumab; azacytidine and IL1 blockers: each in 39 patients (16.7%). Previous immunosuppressive therapies

were methotrexate (18.1%), TNF blockers (12.2%), cyclophosphamide (5.5%), MMF (4.7%), rituximab (3.8%). Only 3 patients underwent stem cell allograft; 15 patients had recurrent red blood cells transfusions

Fourty eight patients died (15%) at a median age of 77.2 years old [min 55- max 78.6, mostly from infections (31%); Other's etiologies were neoplasia, cardiovascular and VEXAS, each 14.6%. No patients progressed to acute leukemia

Conclusion: To date this is the largest cohort of VEXAS syndrome patients showing the heterogeneity of clinical presentation with mainly biological inflammation and systemic features such as alteration of general status and predominance of various cutaneous features with elevated MGV. Vacuoles are not always present; Recurrent chondritis and myelodysplastic syndrome are not mandatory.

Acknowledgments: All French investigators

Disclosure of Interest: None declared

Identifier: PT02

PROGRESSIVE GLOMERULONEPHRITIS IN PEDIATRIC SAVI PROVIDES INSIGHTS INTO PATHOGENESIS AND THE ROLE OF TYPE I IFN IN RENAL OUTCOMES

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Introduction: STING-associated vasculopathy with onset in infancy (SAVI) is an IFNopathy caused by gain-of-function mutations in *STING1*. Rarely, SAVI can manifest with kidney disease including p-ANCA positive glomerulonephritis (GN). A pediatric SAVI case with positive p-ANCA and progressive GN highlights pathogenetic insights and treatment challenges.

Objectives: To investigate the pathogenesis of GN in a pediatric SAVI patient and assess the impact of Type I IFN blockade on renal and systemic outcomes.

Methods: Patient is enrolled in NCT02974595 protocol. We conducted immunophenotyping, genetic analysis, kidney biopsy (including electron microscopy), and longitudinal biomarker assessment (IFN score, autoantibodies, cell-free nuclear and mitochondrial DNA). Outcomes were tracked before and after anifrolumab (IFNAR blockade).

Results: A 6-year-old girl with SAVI presented with livedo reticularis, anemia (Hb 7 mg/dL), stunted growth, and hematuria/proteinuria. A kidney biopsy revealed pauci-immune crescentic GN with extensive tubular fibrosis and endothelial damage. WES/WGS identified a pathogenic *STING1* mutation (p.R281Q) but no kidney disease variants. Despite initial treatment with steroids, cyclophosphamide, and rituximab, kidney function worsened to CKD stage 4. Anifrolumab therapy normalized IFN score, ESR, and cfDNA levels, improved systemic inflammation, and stabilized kidney function temporarily. However, fibrosis progression necessitated kidney transplantation. The patient is 211 days from transplant. Post-transplant, the patient maintained inflammatory remission and a suppressed IFN score with continued anifrolumab infusions.

Conclusion: Early detection of SAVI and intervention with IFN-blocking therapies may stabilize renal outcomes and prevent irreversible damage. This case highlights the need for genetic testing in progressive GN and emphasizes the potential of innovative treatments in IFNopathies. Sustained IFN suppression pre- and post-transplant may improve prognosis.

Acknowledgments: This work was supported by the Intramural Research Program, NIAID, NIH.

Disclosure of Interest: None declared

Identifier: PT04

PREGNANCY OUTCOMES IN WOMEN WITH FAMILIAL MEDITERRANEAN FEVER TREATED WITH ANAKINRA: A RETROSPECTIVE STUDY

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Introduction: Familial Mediterranean Fever (FMF) is an autoinflammatory disease mainly treated with colchicine. Anakinra, an interleukin-1 receptor antagonist, is used for colchicine-resistant cases. However, data on the safety of Anakinra during pregnancy is limited.
Objectives: This study aims to evaluate pregnancy outcomes of FMF patients who received at least one dose of Anakinra during pregnancy.
Methods: A retrospective single-center study was conducted to analyze clinical data and pregnancy outcomes of FMF patients who received Anakinra during pregnancy.
Results: This study included data from 27 pregnancies involving 19 mothers. The average maternal age at pregnancy was 31.5 ± 3.95 years. The most common genotype among mothers was homozygous M694V, observed in %72.2 (13/18) of cases. Amyloidosis was present in %15.8 (3/19) of mothers. In %51.9 (14/27) of the pregnancies, mothers were on Anakinra treatment prior to pregnancy, while in the remaining pregnancies Anakinra treatment was started during pregnancy.

Out of the 27 pregnancies, 26 resulted in delivery, and one is still ongoing at 15 weeks of gestation. Among the terminated pregnancies, 26 babies were born, one of whom was stillborn. The frequency of C-section was %80.8 (21/26) and the rate of preterm birth was %34.6 (9/26). Assisted reproduction techniques were utilized in %30.4 (7/23) of the pregnancies.

The most common maternal complication during pregnancy was preeclampsia (5/23) followed by bleeding (2/23), hypertension (2/23), gestational diabetes (1/23), and cerebrovascular event (1/23).

Intrauterine growth restriction was reported in %18.5 (5/27) of the pregnancies. The rate of neonatal ICU hospitalization was %16.7 (4/24) among babies. It was reported that %34.8 (8/23) of the babies were small for gestational age. Mean weight, length, and head circumference of the babies were 2.8 ± 0.76 kg, 46.5 ± 6.2 cm, and 33.8 ± 3.8 cm, respectively. The average Apgar scores at first and fifth minutes were 7.8 ± 1.4 and 9.0 ± 1.1, respectively.

The average current age of the children is 75.3 ± 45.9 months, with a mean weight of 26.7 ± 11.4 kg and mean height of 116.4 ± 22.8 cm. Among these children, the most common chronic condition was allergic conditions (4/9), followed by growth hormone deficiency (1/9), PFAPA (1/9), torticollis (1/9), and a heart murmur (1/9).

Parameter	**Value**
Maternal age, mean ± SD, years	31.5 ± 3.95
M694V homozygous	%72.2 (13)
Amyloidosis	%15.8 (3)
Live births	%96.2 (25)
Stillborn	%3.8 (1)
Preeclampsia	%21.7 (5)
IUGR	%18.5 (5)
Birth weight, mean ± SD, kg	2.8 ± 0.76

Birth length, mean ± SD, cm	46.5 ± 6.2 cm

Conclusion: Despite complications like preeclampsia and intrauterine growth restriction, the majority of pregnancies resulted in live births with favorable outcomes. Anakinra appears to be safe during pregnancy, with no major teratogenic effects observed. However, long-term follow-up is necessary to assess the full spectrum of outcomes

Disclosure of Interest: None declared

Identifier: PT05

IMMUNOLOGICAL INSIGHTS INTO H SYNDROME: A FRENCH NATIONAL COHORT STUDY OF 33 PATIENTS HIGHLIGHTING AUTO-INFLAMMATORY MANIFESTATIONS

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Introduction: H syndrome is a rare genetic disorder caused by biallelic loss-of-function variants in the *SLC29A3* gene. It is increasingly recognized as an auto-inflammatory disease within the group of histiocytosis, characterized by multisystem involvement.

Objectives: This study aims to expand the clinical and immunopathological spectrum of H syndrome by analyzing a large national patient cohort. It evaluates the disease's long-term progression and describes the use of emerging therapies.

Methods: This retrospective and prospective study reviewed clinical and genetic data from patients diagnosed with *SLC29A3* mutations between 2012 and 2024. Patients were identified through multidisciplinary rare disease networks across France, including pediatric immunologists, rheumatologists and haematologists. Referring physicians and principal investigator contributed anonymized data via the secured database “Histiobase”. This registry is conducted in accordance with current legislation and regulations. The CCTIRS approval number is 096191, and the CNIL registration number is 909027.

Results: On December 2024, data were collected from 33 patients spanning 28 families, with a median age of 23 years (range: 0.5–66) and a sex ratio of 1.29 M/F.

Key findings include:

- **Histiocytic infiltrations** (71%) leading to retroperitoneal or mediastinal fibrosis, compressive masses located in heart or kidney leading to upper urinary tract dilatation and renal failure.
- **Sensorineural hearing loss** (70%)
- **Hepatosplenomegaly and lymphadenopathies** (69%).
- **Dermatological features** (65%), including hyperpigmentation, thickening and hypertrichosis.
- **Musculoskeletal involvement** in over half the patients, with joint contractures, tenosynovitis, myositis, and arthritis.
- **Ophthalmologic manifestations** (44%) such as anterior granulomatous uveitis.
- **Hematological abnormalities** (20%), including pure red cell anemia, autoimmune cytopenia, and hemophagocytic lymphohistiocytosis.

Biological findings revealed elevated inflammatory markers in 87% and hypergammaglobulinemia in 70%. A small number of adult patients (n=3) presented with a monoclonal peak, while another had hypogammaglobulinemia associated with severe respiratory infections requiring immunoglobulin supplementation. Memory B-cell deficiency was observed in 6 of 7 tested patients.

Autoimmunity was detected in 25% of the cohort, with both specific and non-specific autoantibodies, such as those associated with diabetes mellitus or anti-SSA antibodies, leading to sicca syndrome. Additionally, anti-MPO antibodies were found, mimicking ANCA vasculitis.

Genetic analysis confirmed biallelic *SLC29A3* mutations in all patients. Somatic mutations in the MAP kinase pathway, such as *MAP2K1* and *NRAS*, were identified in biopsies from 3 patients.

Many patients were initially misdiagnosed with various rheumatologic and immunologic conditions, highlighting the significant diagnostic challenges associated with the syndrome.

Regarding the therapeutic insights**,** IL-6 antagonists proved effective in inflammatory symptoms, including fever, arthritis, and skin hyperpigmentation, in 16 patients. However, MEK inhibitors, such as Cobimetinib, demonstrated good results in addressing organ infiltration and proliferative lesions in a smaller group of patients (n=5), achieving complete responses in cases (n=2) where IL-6 antagonists provided only partial relief or where symptoms reappeared after prolonged treatment.

Conclusion: This study expands the clinical spectrum of H syndrome, underscoring its classification as both a genetic histiocytosis and a multisystem inflammatory disorder. It highlights autoimmune features, potential immunodeficiency, and a predisposition to fibrosis, which contribute to significant morbidity and mortality. Promising therapeutic options, including MEK inhibitors and IL-6 antagonists, offer hope for better disease management and improved patient outcomes.

Disclosure of Interest: None declared

Identifier: PT06

EFFECTS OF CANAKINUMAB DOSE ADJUSTMENTS ON DISEASE CONTROL OF AUTOINFLAMMATORY PERIODIC FEVER SYNDROMES – INTERIM RESULTS OF THE RELIANCE NON-INTERVENTIONAL STUDY

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Introduction: Treatment of autoinflammatory periodic fever syndromes (PFS)with the interleukin-1β inhibitor canakinumab (CAN) has been shown to be safe and effective in controlled clinical trials and real-world setting.
Objectives: The RELIANCE non-interventional study investigates the long-term safety and effect on control of disease activity of CAN in patients with cryopyrin-associated periodic syndromes (CAPS), familial Mediterranean fever (FMF), hyper-IgD syndrome/mevalonate kinase deficiency (HIDS/MKD) and tumor necrosis factor receptor-associated periodic syndrome (TRAPS) in routine clinical practice. This interim analysis examines dose adjustments of CAN in achieving disease control with regards to a treat-to-target strategy.
Methods: RELIANCE is a prospective, non-interventional observational study in Germany, which enrolled pediatric (age ≥2 years) and adult patients with a clinically confirmed diagnosis of PFS, who routinely receive CAN. Effectiveness and safety parameters were recorded at baseline and assessed at 6-month intervals. The recommended starting dose (SD) of canakinumab was dependent on the age, body weight and indication as described in the Product information. Less than SD (<SD) was defined as <87.5% of SD and greater than SD (>SD) was defined as >112.5% of SD.
Results: In the present interim analysis, data from N=268 patients with PFS enrolled in the RELIANCE registry between September 2017 and December 2023 were included. The median age of the total study cohort was 19.5 years (2–80

years [45.1% < 18 years]; N=137 female patients [51.5%]) and the median duration of CAN treatment before study entry was 2 years (0−15 years).Over the course of the study, the proportion of patients receiving higher than the recommended SD (>SD) increased from 33.6% at baseline to 54.8% at month 30 and 80.0% at month 60 (**Table 1**). Furthermore, 18.7% of the study participants had at least one injection with more than twice the recommended SD (> 200% of SD). Effectiveness as indicated by control of disease activity was comparable across all three dosing categories over the course of the study. More than 90% of patients had no or mild/moderate disease activity in all dose categories at baseline and month 30 as assessed by investigators (PGA) (data for month 60 not yet available). In addition, patients' assessment of disease activity (VAS score 0-10) was similarly low with median VAS scores between 1.0 and 3.0 across all dose categories at baseline, month 30 and month 60.

The percentage of patients in the >SD dosing group experiencing non-serious adverse drug reactions (nsADR) was higher than in the <SD or SD dosing group (44.2% of patients in >SD compared to 24.6% and 20.5% of patients in the <SD and SD dosing groups, respectively). While no patients in the SD dosing group experienced serious adverse drug reactions (SADR), 7.2% and 8.4% of patients in the <SD and >SD dosing groups experienced SADR, with no statistically significant difference between SADR rates in the two dosing groups (<SD and >SD) (p=0.783; chi-square test).

Conclusion: The present interim analysis of the RELIANCE study confirms the overall safety and effectiveness of long-term treatment with canakinumab. An increasing proportion of patients received dose adjustments towards higher doses over the course of the study, reflecting the increased implementation of a treat-to-target strategy.
Disclosure of Interest: J. Kümmerle-Deschner Conflict with: Jasmin B. Kuemmerle-Deschner: has received grant/research support and speaker fees from Novartis and Sobi; and is a consultant of Novartis and Sobi., J. Henes Conflict with: Joerg Henes has received grant/research support from Novartis, Roche, Sobi; is a consultant of Novartis; and has contributed to speakers bureaus with AbbVie, AstraZeneca, BMS, Boehringer-Ingelheim, Chugai, Janssen, Novartis, Pfizer, GSK, Sobi, Roche, UCB., A. Pankow Conflict with: Anne Pankow has received study support from Novartis., T. Kallinich Conflict with: Tilmann Kallinich has received research support from Novartis., B. Kortus-Goetze Consultant for: Birgit Kortus-Goetze is a consultant of Novartis., P. T. Oommen Conflict with: Prasad T. Oommen has received study support from Novartis., T. Krickau Conflict with: Tobias Krickau has received study support, speaker fees and consultancy fees from Novartis., C. Schuetz Conflict with: Catharina Schuetz has received study support from Novartis., A. Janda Conflict with: Ales Janda has received study support from Novartis., I. Foeldvari Consultant for: Ivan Foeldvari is a consultant of and has received study support from Novartis., G. Horneff Conflict with: Gerd Horneff has received grant/research support from AbbVie, Chugai, Merck Sharp & Dohme, Novartis, Pfizer and Roche; and contributed to speakers bureaus with AbbVie, Bayer, Chugai, Merck Sharp & Dohme, Novartis, Pfizer and Roche., J. Rech Conflict with: Juergen Rech: has received grants from Novartis and Sobi; speaker fees from AbbVie, Biogen, BMS, Chugai, GSK, Janssen, Lilly, MSD, Mylan, Novartis, Roche, Sanofi, Sobi and UCB; and consultancy for AbbVie, Biogen, BMS, Chugai, GSK, Janssen, Lilly, MSD, Mylan, Novartis, Roche, Sanofi, Sobi and UCB., F. Weller-Heinemann Conflict with: Frank Weller-Heinemann has received study support from Novartis., M. Hufnagel Grant /Research support from: Markus Hufnagel has received study support from Novartis., T. Kümpfel Conflict with: Tania Kümpfel has received study support from Novartis., F. Meier Conflict with: Florian Meier has received honoraria from Novartis., F. Dressler Conflict with: Frank Dressler has received study support from Novartis and is a consultant of AbbVie, Mylan, Novartis and Pfizer., D. Windschall Conflict with: Daniel Windschall has received study support from Novartis., I. Andreica Conflict with: Ioana Andreica has contributed to

speakers bureaus with AbbVie, Chugai, Novartis, UCB, MSD, Lilly, Sobi, AstraZeneca, Amgen, Pfizer and Gilead; received consultant fees from AstraZeneca and UCB; is a consultant for AbbVie, Chugai, Novartis, UCB, Galapagos, Takeda, AstraZeneca, Lilly, Boehringer Ingelheim, Amgen and Sobi., M. Borte Conflict with: Michael Borte has received grant/research support from Pfizer, Shire, and Novartis., M. Krusche Conflict with: Martin Krusche has received study support from Novartis., M. Fiene Conflict with: Michael Fiene has received study support from Novartis., N. Blank Conflict with: Norbert Blank has received grant/research support from Novartis and Sobi; and is a consultant of Novartis, Sobi, Lilly, Pfizer, AbbVie, BMS, MSD, Actelion, UCB, Boehringer-Ingelheim and Roche.

Identifier: PT07

IMPACT OF AUTOINFLAMMATORY DISEASES: INSIGHTS FROM AN INTERIM ANALYSIS OF THE PRO-AID STUDY

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Introduction: Uncontrolled disease activity in autoinflammatory diseases (AID) can cause substantial morbidity, mortality and reduced health-related quality of life. Today, AIDs such as Familial Mediterranean Fever (FMF), NOD-like receptor protein 3 (NLRP3)-AID, Tumor Necrosis Factor Receptor-Associated Periodic Syndrome (TRAPS) and Mevalonate Kinase Deficiency (MKD) are effectively treatable and treatment recommendations are available. A cornerstone in AID management is the treat-to-target (T2T) strategy, which aims to achieve no or minimal disease activity and plays a crucial role in reducing the disease burden. The disease burden extends beyond physical symptoms and organ damage, encompassing significant psychosocial challenges and impaired social participation.

Objectives: To explore the burden of illness in children and adolescents with FMF, NLRP3-AID, TRAPS and MKD.

Methods: Children and adolescents (≤18 years) diagnosed with FMF, NLRP3-AID, TRAPS, or MKD were enrolled in the multicenter, prospective PRO-AID cohort study within the National Pediatric Rheumatological Database. At enrollment, demographic data and Parents/Patients Global Assessment of current disease activity (PPGA), overall well-being, fatigue, and pain (each on a numeric rating scale of 0 to 10) as well as the number of missed days from kindergarten/school/work in the past 12 months were gathered from parents. In addition, the treating physicians provided information on diagnosis, treatment and disease activity measured with the Physician Global Assessment (PGA). Adolescents (≥12 years) were screened for mental health issues using the Patient Health Questionnaire-9 (PHQ-9) and the Generalized Anxiety Disorder Scale-7 (GAD-7).

Results: A total of 124 patients (45% female) with an average disease duration of 7.4±4.1 years were included. Diagnoses were as follows: FMF (n=95; 76%), NLRP3-AID (n=18; 15%), MKD (n=6; 5%), and TRAPS (n=5; 4%). The mean age at symptom onset was 2.8±3.1 years, with an average diagnostic delay of 16.9±16.1 months. Most patients (93%) received treatment, either with biological drugs (30%), colchicine (78%) or both.

The mean PGA was 1.2±1.8, highest in NLRP3-AID (1.4±2.2), followed by FMF (1.2±1.8). The mean PPGA was 2.2±2.8, with FMF showing the highest values (2.3±2.6). Across all AID, PPGA values exceeded PGA values. Fatigue was reported by more than half of the patients, with the highest scores in NLRP3-AID (3.2±3.7) and FMF (2.3±2.8). Coping difficulties were noted in 38% of all patients, predominantly in NLRP3-AID patients. Adolescents experienced more pain, fatigue, and coping challenges compared to younger children. Notably, one in four adolescents with an AID (up to 32% in FMF) reported moderate to severe depressive or anxiety symptoms (PHQ-9 or GAD-7 scores ≥10). In addition, more than 60%

of patients missed school/kindergarten due to AID-related illness, with an average of 17.7±15.2 days per year. Absenteeism was highest in NLRP3-AID (29.2±18.8 days).

Conclusion: FMF, TRAPS, NLRP3-AID and MKD impose subjective disease burden, particularly in adolescence, with fatigue, psychological stress, and limited social participation impacting quality of life. A multidimensional approach in disease monitoring, including mental health and social participation, is essential to improve patient-centered care.

Acknowledgments: Stiftung “Kindness for Kids”, which financially supports the project.

Disclosure of Interest: T. Welzel Conflict with: invited talks for Novartis (no personal honoraria), J. B. Kuemmerle-Deschner Conflict with: received honoraria and study funding from Novartis and SOBI, K. Tenbrock: None declared, G. Horneff: None declared, D. Föll: None declared, J. Klotsche: None declared, M. Niewerth: None declared, Ö. Satirer: None declared, R. Berendes: None declared, H. Lausmann: None declared, P. Oommen Conflict with: received honoraria from Novartis, M. Lieber: None declared, T. Krickau Conflict with: received honoraria from Novartis and Pfizer, F. Dressler Conflict with: received honoraria from Abbvie, Novartis and Pfizer; Adboards from Fresenius, Mylan and Novartis, N. Brück: None declared, D. Windschall: None declared, M. Hufnagel Conflict with: received study funding from Novartis, T. Kallinich: None declared, K. Minden Conflict with: received honoraria from Amgen, Biogen, medac, and Novartis

Identifier: PT08

PREDICTION OF THE COLCHICINE RESPONSE ACCORDING TO FAMILIAL MEDITERRANEAN FEVER (FMF) 50 SCORE IN PEDIATRIC PATIENTS: ACUTE PHASE REACTANTS OR EXISTING SCORING SYSTEMS?

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Introduction: Familial Mediterranean Fever (FMF) is the most prevalent monogenic autoinflammatory disorder, characterized by recurrent episodes of fever, polyserositis, and arthritis. The Auto Inflammatory Diseases Activity Index (AIDAI), Pras, Mor scores and the International Familial Mediterranean Fever Severity Scoring System (ISSF) are utilized to evaluate disease activity, while the FMF50 scoring system assesses treatment response.
Objectives: This study aimed to assess and analyze the disease activity and treatment response of FMF patients utilizing the AIDAI, Pras, Mor, ISSF and FMF50 scoring systems.
Methods: The investigation encompassed FMF patients that met the Eurofever/PRINTO classification criteria and had been undergoing colchicine treatment for a minimum of 6 months. The data were obtained from medical records and analyzed within the framework of AIDAI, Pras, Mor, and ISSF scores. Patients without a mutation in Exon 10 on Mediterranean fever (*MEFV)* gene and those with insufficient drug adherence were excluded from the study. The FMF50 score was employed to evaluate treatment response. Patients were stratified into two groups based on their FMF50 responses at 6 months as responsive and non-responsive. These groups were subsequently compared, and statistically significant variables were incorporated into a logistic regression model to identify independent predictors.
Results: There were 134 eligible patients; however, 17 were excluded due to protocol non-adherence during their follow-up. (44.4% female, n=52). The number of patients achieving an FMF50 score at 3 months was 73 (62.39%), whilst at 6 months, it increased to 84 (71.79%). The median ages for symptom onset and diagnosis were 48 (4-186) months and 72 (18-198) months, respectively. In univariate analysis, high C-reactive protein (CRP) levels (OR 1.035, 95% CI 1.002–1.070, $p<0.05$), ISSF scores (OR 1.703, 95% CI 1.135–2.557, $p<0.05$), and AIDAI scores (OR 1.253, 95% CI 1.053–1.491, $p<0.05$) at the third month were determined as predictive for failure to achieve an FMF50 response at the sixth month. In multivariate analysis, ISSF score and AIDAI were evaluated separately, and high ISSF score (OR 1.745, 95% CI 1.129–2.698, $p<0.05$) and high AIDAI (OR 5.045, 95% CI 1.067–23.846, $p<0.05$) were identified as independent predictors for failure to achieve an FMF50 response.
Conclusion: Among acute-phase reactants, CRP, and among routinely utilised scoring systems, ISSF and AIDAI, have demonstrated predictive value in determining the FMF50 response in patients with FMF. These findings will be valuable for informing treatment decisions in pediatric FMF cases.
Disclosure of Interest: None declared

Identifier: PT09

TREATMENT OUTCOMES IN VEXAS SYNDROME: A RETROSPECTIVE STUDY FROM THE UK VEXAS INTEREST GROUP (VEXNET-UK)

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Introduction: VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) syndrome represents a recently described disorder caused by somatic UBA1 mutations. Limited evidence exists regarding optimal therapeutic strategies. While high-dose glucocorticoids are often effective initially, patients frequently develop steroid-dependence and associated toxicity, highlighting the urgent need for effective steroid-sparing agents.

Objectives: To evaluate outcomes of targeted therapies in the largest UK VEXAS cohort to date and identify clinical predictors of treatment response.

Methods: Retrospective analysis of 71 targeted therapies in 59 genetically-confirmed VEXAS patients across UK centres. Complete response (CR) required clinical remission, CRP ≤10 mg/L, and prednisolone ≤10 mg/day. Partial response (PR) required improvement in clinical features and 50% reduction in both CRP and corticosteroid dose from baseline. Outcomes and biochemical paramaters were assessed at 3, 6, and 12 months. Univariate logistic regression identified factors associated with response.

Results: Among 59 patients (98% male, median age 70 years), treatments included tocilizumab (n=19), anakinra (n=13), azacitidine (n=13), baricitinib (n=11) and prednisolone alone (n=10). MDS was present in 46%. At 6 months, in those maintaining therapy, response rates were: azacitidine 91% (36% CR), tocilizumab 64% (36% CR), anakinra 100% (33% CR), and baricitinib 40% (0% CR). Treatment discontinuation occurred in 41% by 12 months, most commonly due to adverse events (17%) and death (13%). Anakinra showed high discontinuation (62%) mostly due to injection site reactions (n=5). Serious infections were frequent with azacitidine (62%) and tocilizumab (47%).

Compared to other therapies, azacitidine associated with improved response at 6 months (OR 6.7, p=0.010) and tocilizumab at 12 months (OR 3.2, p=0.047). Absence of fever (OR 7.9, p=0.010) or thromboembolism (OR 14.1, p=0.013) predicted better outcomes. By 6 months, tocilizumab and anakinra achieved marked CRP improvement (median 4 and 2 mg/L respectively), whilst azacitidine showed best haemoglobin response (102 to 119 g/L).

Conclusion: In UK practice, azacitidine and tocilizumab showed superior efficacy in VEXAS syndrome, though with notable infection risks. Treatment selection should consider individual risk factors and tolerability. The absence of fever or thromboembolism at diagnosis predicts better outcomes. Prospective studies are needed to confirm optimal treatment sequencing and develop standardised protocols.

Acknowledgments: Supported by Kennedy Trust, MRC (129855), and NIHR Leeds BRC. We thank the patients and their families for their participation in this research. We acknowledge the support of the VEXNET-UK consortium and all contributing clinical teams across the UK centres.

Disclosure of Interest: None declared

Identifier: PT10

INFECTION BURDEN IN PATIENTS WITH GENETIC INTERFERONOPATHIES: A MONOCENTRIC RETROSPECTIVE COHORT STUDY

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Introduction: Type I interferonopathies constitute a group of rare and severe Mendelian multisystemic autoinflammatory disorders caused by the constitutional activation of the type I interferon axis (IFN-I).
The immunological consequences of chronic and unregulated IFN-I signaling remain poorly understood. Recently, severe and atypical infectious events have been incidentally observed in small interferonopathy cohorts. However, the hypothesis of an associated intrinsic immunodeficiency has not been clinically evaluated in the scientific literature.
Objectives: The present study aims to assess the infectious burden of patients with type I interferonopathies and look for potential intrinsic or extrinsic determinants. Ultimately the objective is to investigate a potential immunodeficiency associated with type I interferonopathies, evaluate the impact of immunosuppressant therapies within this context and formulate of immunological hypotheses.
Methods: Here, we report the results of a retrospective, monocentric cohort study including 59 patients with genetic type I interferonopathies and followed at Necker Hospital for Sick Children. Significative infectious events (SIEs) requiring hospitalisation were collected as well as various clinical and immunological parameters.
Results: SIE prevalence in the cohort was 34% and the global SIE incidence rate (IR) was 5.1 per 100 patient-years (p-y), well above epidemiological values in general population. SAVI patients presented the highest IR with a high frequency of fungal SIEs. SIEs IR tended to be higher under immunosuppression although this association was not statistically significant except for AGS patient under JAK inhibition. However, severe and unusual infections were also observed in patients naive of any immunosuppressant.

We were unable to evaluate other potential determinants with multivariate analysis due to small sample sizes and cohort heterogeneity.

Conclusion: This preliminary work provides new data to further characterise interferonopathy-associated immune dysregulation and type I IFN axis implication in pathology. Prospective and well- designed clinical studies are required to gain a deeper understanding of the interlink between immunodeficiency and type I interferonopathies.
Disclosure of Interest: None declared

Identifier: PT11

DISCONTINUATION OF COLCHICINE TREATMENT IN PATIENTS WITH FAMILIAL MEDITERRANEAN FEVER

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Introduction: Familial Mediterranean fever (FMF) is a hereditary autoinflammatory disease characterized by self-limited recurrent attacks of fever, polyserositis, and arthritis. Colchicine is the mainstay of treatment to suppress flares and prevent complications of FMF.
Objectives: The present study aims to evaluate the clinical and genetic characteristics, as well as the long-term outcomes, of FMF patients who discontinue colchicine in comparison with patients on continuous colchicine treatment.
Methods: Patients with at least one MEFV mutation, meeting Tel-Hashomer or Eurofever/PRINTO classification criteria, and receiving colchicine for at least six months were enrolled in the study. Patients were divided into three groups: those who were not restarted colchicine after discontinuation (group 1), those who were restarted colchicine after discontinuation (group 2), and a control group who continued colchicine without discontinuation (group 3). Demographic, clinical, genetic data and disease severity scores were compared between groups
Results: The total cohort consisted of 153 (58.8%) males. The median age at discontinuation of colchicine in groups 1 and 2 was 11.26 (min-max: 2.82-20.62) years and the median follow-up time after discontinuation of colchicine was 5.24 (IQR: 2.25-7.56) years. The most common clinical features at presentation in all three groups were abdominal pain, fever, and arthritis. Chest pain, erysipelas-like erythema, arthralgia, and fever were significantly higher in group 3 compared to groups 1 and 2. The E148Q variant in the MEFV gene was significantly more frequent in group 1 than in group 3. The association of the M694V/exon 10 variant was significantly higher in group 3 than in groups 1 and 2. The frequency of patients meeting only the Tel-Hashomer criteria was similar in groups 1 and 2, and higher than in group 3. The frequency of patients meeting the Eurofever/PRINTO classification criteria was similar in groups 2 and 3, and higher than in group 1.
Conclusion: These findings suggest that it might be possible to discontinue colchicine in carefully selected FMF patients with specific genetic and clinical profiles. Severity scoring and genotype analysis may play a crucial role in identifying patients for discontinuation.
Disclosure of Interest: None declared

Identifier: PT12

HUMAN ADA2 DEFICIENCY IS CHARACTERIZED BY THE ABSENCE OF AN INTRACELLULAR HYPOGLYCOSYLATED FORM OF ADENOSINE DEAMINASE 2

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Introduction: Human deficiency of adenosine deaminase 2 (DADA2) is a rare autoinflammatory disease with a complex clinical phenotype of recurrent fever, vasculitis and stroke as well as immunodeficiency and bone marrow failure. It is caused by pathogenic variants in *ADA2* that lead to impaired ADA2 protein secretion and reduced deaminase activity. Next to its role in the regulation of extracellular adenosine levels, ADA2 has recently been shown to mediate lysosomal nucleic acid sensing. However, ADA2 has primarily been established as a secretory protein and an intracellular form has not yet been characterized.

Objectives: The aim of this study was to analyze the processing and trafficking of wild-type (WT) and mutant ADA2, and thereby explore the cellular mechanisms driving DADA2.

Methods: We differentiated human monocyte-derived macrophages (HMDM) from 12 healthy controls (HC) and 10 DADA2 patients. Eleven pathogenic *ADA2* variants were overexpressed in HEK293T cells or transduced into *ADA2*$^{-/-}$ U-937 cells. ADA2 protein expression and molecular weight in these cells were assessed by western blot after sequentially inhibiting enzymes involved in N-glycan processing in the endoplasmic reticulum (ER), Golgi apparatus and lysosome or protein trafficking via the secretory pathway. Glycan removal was performed by PNGase F, Endo H and alpha-mannosidase. Localisation of ADA2 glycoforms was determined by subcellular fractionation.

Results: We identified a low-molecular-weight (LMW) form of ADA2 expressed exclusively intracellularly in HC HMDM and cell lines expressing WT ADA2. This LMW-ADA2 was subjected to glycan trimming by alpha-mannosidases after transfer to the Golgi and was distinct from secreted high-molecular-weight (HMW) ADA2. Cells expressing pathogenic *ADA2* variants including DADA2 patients' HMDM lacked LMW-ADA2. Mutant ADA2 was retained in the ER and did not undergo glycan processing in the Golgi apparatus. We confirmed the absence of LMW-ADA2 upon overexpression of pathogenic *ADA2* variants in HEK293T cells and monocytic U-937 cells as a feature shared by all examined DADA2-associated variants. By subcellular fractionation, we further showed that LMW-ADA2 localizes to the lysosomal compartment.

Conclusion: We describe a previously unreported intracellular hypoglycosylated form of ADA2 and establish the absence of this LMW-ADA2 as a cellular characteristic of DADA2. Thereby, we introduce a protein correlate of the recently described lysosomal form of ADA2 and highlight its absence in ADA2-deficient cells.

Acknowledgments: We thank Jaak Jaeken, Daisy Rymen and Eva Morava-Kozicz for sharing their expertise and insight on protein glycosylation. We thank Lotte Bral for her assistance in the production of the knock-out cell lines. Above all, we would like to express our gratitude to our patients and their parents for their willingness to participate in our study and to their treating physicians and nurses for their efforts in the collection of research samples.

This project has received funding from the European Research Council (ERC) under the European Union's Horizon 2020 research and innovation program. IM is a Senior Clinical Investigator at the Research Foundation–Flanders, and is

supported by a KU Leuven C1 Grant; by the Research Foundation-Flanders (FWO); and by the Jeffrey Modell Foundation. This work was supported by ERN-RITA. LE is supported by a PhD Fellowship from the Research Foundation – Flanders (FWO). SD is supported by a PhD Fellowship from the Research Foundation – Flanders (FWO). RS is a FWO senior clinical investigator fellow. PA is supported by grants from the Flemish Research Foundation, the KU Leuven C14/21/095 InterAction consortium, the EOS MetaNiche consortium, the iBOF/21/053 ATLANTIS network and by the EOS DECODE consortium.

Disclosure of Interest: None declared

Identifier: PT13

PYRIN INFLAMMASOME ACTIVATION LEADS TO IL-18 SECRETION AND PERPETUATES IFN-GAMMA SECRETION IN A NOVEL CULTURE-BASED MEVALONATE KINASE DEFICIENCY MODEL

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Introduction: Mevalonate Kinase Deficiency (MKD) is a rare metabolic autoinflammatory disease that arises from loss-of-function mutations in the mevalonate kinase gene (*MVK*). The pyrin inflammasome, an intracellular danger receptor for pathogens, is activated as an indirect result of decreased mevalonate kinase enzyme activity. In MKD patients, the overactive pyrin inflammasome results in the hypersecretion of interleukin-1β (IL-1β) which contributes to recurrent fever episodes.
Objectives: To date, cellular and molecular aspects that contribute to MKD pathogenesis are incompletely understood. This study set out to develop an improved *in vitro* model of MKD, and examine metabolic and inflammatory MKD phenotypes.
Methods: We employed CRISPR/cas9 base editing to introduce the I268T (894T>C) *MVK* mutation into THP1 cells. Wildtype and mutated cells were subjected to untargeted metabolomic analysis and *in vitro* activation assays.
Results: We show that $MVK^{I268T/I268T}$ THP1 cells mimic the metabolic phenotype associated with MKD, including the accumulation of mevalonic acid and a shift in energy metabolism. Upon stimulation of the pyrin inflammasome with etiocholanolone, $MVK^{I268T/I268T}$ THP1 cells increase IL-1β secretion, ASC-speck formation and pyroptosis which could be rescued through geranylgeranyl pyrophosphate supplementation. Etiocholanolone stimulation of $MVK^{I268T/I268T}$ THP1 cells also induced interleukin-18 (IL-18) secretion, which enhanced interferon gamma (IFNγ) levels in co-culture with phytohaemagglutinin-stimulated peripheral blood mononuclear cells.
Conclusion: These findings highlight IL-18-mediated IFNγ release as a potential mediator of MKD pathogenesis.
Disclosure of Interest: None declared

Identifier: PT14

AUTOINFLAMMATORY PATIENTS WITH GOLGI-TRAPPED CDC42 EXHIBIT INTRACELLULAR TRAFFICKING DEFECTS LEADING TO STING HYPERACTIVATION AND ER STRESS

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Introduction: Most autoinflammatory diseases arise from mutations in innate immunity genes. Recently, four CDC42 variants were linked to neonatal-onset syndromes with cytopenia, auto-inflammation (e.g., hemophagocytic lymphohistiocytosis), and rash. The mechanisms behind these phenotypes remain elusive.

Objectives: This study investigates how CDC42 variants contribute to autoinflammatory disorders.

Methods: We used a combination of microscopy techniques and transcriptomic profiling to analyze the cellular effects of CDC42 variants. Specifically, we investigated protein trafficking dynamics between the endoplasmic reticulum and the Golgi apparatus, ER stress, activation of the **STING** pathway, and type I interferon responses in patient-derived cells harboring CDC42 mutations and THP-1 monocytic cells expressing CDC42 variants.

Results: The recurrent p.R186C variant, trapped in the Golgi, disrupts ER-Golgi protein trafficking, causing ER stress, a hallmark of immune dysregulation. This variant leads to STING accumulation in the Golgi via COPI-mediated transport, activating STING and inducing Interferon-stimulated genes (ISG) transcription. Similarly, the p.192C24 variant shows Golgi retention, causing similar defects. In contrast, p.Y64C and p.C188Y, which do not accumulate in the Golgi, fail to trigger significant STING activation or ISG expression. Thus, p.R186C and p.192C24 variants uniquely induce ER stress, STING overactivation, and increased type I IFN responses. Patients with Golgi-trapped variants display elevated IFNα, a marker of STING activation, correlating with disease severity and suggesting STING hyperactivation as a key driver.

Conclusion: Our study uncovers novel mechanistic insights into the effects of **Golgi-trapped CDC42** variants. These variants disrupt normal protein trafficking and induce **ER stress**, which leads to the overactivation of the **STING** pathway. The associated increase in **IFNα** levels provides a rationale for exploring **combination therapies**, targeting both the underlying trafficking defects and the hyperactive immune response. These findings offer a potential co-therapeutic approach for patients with severe autoinflammatory syndromes linked to CDC42 mutations, underscoring the importance of targeting innate immune pathways like **STING** in managing these complex diseases.

Disclosure of Interest: None declared

Identifier: PT15

GAIN-OF-FUNCTION HUMAN UNC93B1 VARIANTS AS A NOVEL CAUSE OF TYPE I INTERFERONOPATHY VIA ENHANCED TLR7 AND TLR8 SIGNALLING

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Introduction: UNC93B1 is a highly conserved protein expressed in the endoplasmic reticulum, that acts as a chaperone for nucleic-acid sensing Toll-like receptors (TLRs). UNC93B1 deficiency in humans causes susceptibility to herpes simplex encephalitis. In mice, specific *Unc93b1* missense mutations result in severe autoimmunity via distinct mechanisms.
Objectives: We looked for UNC93B1 variants in our cohort and functionally confirmed the effect of the mutations in vitro and in patients cells.
Methods: We searched for very rare variants in the exome sequence data of 63 kindreds (81 patients) with a molecularly uncharacterized diagnosis of either systemic lupus erythematosus (SLE) or chilblain lupus (CBL). We analyzed responses to stimulation with TLR ligands in patient peripheral blood cells, a HEK293T reporter system expressing UNC93B1 variants and TLRs, and THP-1 cells expressing mutant UNC93B1. We also studied UNC93B1-TLR interactions using proximity ligation assay (PLA) and co-immunoprecipitation (co-IP).
Results: We have identified five unrelated patients harbouring distinct rare missense substitutions in *UNC93B1* in the heterozygous (G325C, L330R, R466S and R525P) or homozygous (I317M) state. The patients with the I317M and the G325C variants presented with SLE with auto-immune haemolytic anemia. The patient carrying the G325C variant also had pulmonary hypertension. The probands carrying the other variants (L330R, R466S and R525P) were all displaying CBL. In all cases, the disease started during childhood. A persistent upregulation of interferon stimulated gene expression was present in the blood of all patients sampled. We therefore set out to study the link between these mutations in UNC93B1 and enhanced type I interferon signalling. We recorded a gain of TLR7 and, to a lesser extent, TLR8 activity with the I317M (in vitro) and G325C (in vitro and ex vivo) variants in the context of SLE. Contrastingly, in three families segregating CBL, the L330R, R466S, and R525P variants were isomorphic with respect to TLR7 activity in vitro and, for R525P, ex vivo. Rather, these variants demonstrated a gain of TLR8 activity. PLA analysis and co-IP suggests enhanced interaction between UNC93B1 mutants and TLR8 at baseline or upon stimulation, which could explain the gain in TLR8 activation.

From a therapeutic point of view, thanks to the identification of these mutations and their implication in the type I interferon signalling pathway, two patients have benefited from a JAK inhibitor and one patient with CBL is now on anifrolumab with clinical improvement.

Conclusion: Our work highlights and expands the phenotype of an emerging monogenic cause of a type I interferonopathy state encompassing lupus and chilblain lupus that informs the understanding of the specific role of UNC93B1, TLR7 and TLR8 in nucleic-acid immunity. In addition, the discovery of these new diseases may prompt physicians to use targeted therapies such as TLR7/8 inhibitors in the future.
Disclosure of Interest: None declared

Identifier: PT16

PERSISTENT IFN SIGNATURE IN PATIENTS WITH PAPA SYNDROME AND ITS REGULATION BY JAK INHIBITION

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Introduction: Pyogenic arthritis, pyoderma gangrenosum, and acne (PAPA) syndrome is a debilitating hereditary disorder. Disease-causing mutations in PSTPIP1 ectopically activate the pyrin inflammasome under sterile conditions. We previously reported that the elevated IL-18 in PAPA patients induces IFN-γ production and subsequently pyrin expression, forming a reinforcing loop of pathogenesis. Janus kinase (JAK) inhibitor treatment significantly improved the clinical condition of PAPA patients. However, it has been unclear which cell types or signaling pathways are regulated by the JAK inhibition.
Objectives: In this study, we aimed to investigate single-cell transcriptomic landscapes of peripheral blood immune cells from patients with PAPA syndrome before and after JAK inhibitor treatment.
Methods: We recruited three PAPA syndrome patients with gender and age-matched healthy donors. Fresh PBMCs were collected from patients before and after JAK inhibitor treatment and from healthy donors and analyzed by droplet-based single-cell RNA sequencing (scRNA-seq).
Results: scRNA-seq analysis revealed aberrant activation of TNF and IFN-γ signaling pathways in patients with PAPA syndrome who exhibited persistent symptoms despite IL-1β blocker treatment. These dysregulated inflammatory signatures were most prominent in the expanded monocyte population, specifically in a pathogenic subpopulation of classical monocytes. This subpopulation displayed elevated expression of CCL3 and CCL4, alongside TNF- and IFN-γ-related gene set signatures. Further analyses revealed that these monocytes exhibited increased expression of *IL18* as well as *IL1B* genes, with *IL18* upregulation specifically being associated with IFN-γ production from NK and T cells. This interaction explains a reinforcing inflammatory loop formed by inflammasome-driven IL-18 production from activated monocytes, IL-18-induced IFN-γ production from NK and T cells, and IFN-γ-induced activation of monocytes, perpetuating systemic inflammation. Treatment with a JAK inhibitor, which was implemented to disrupt this IL-18 – IFN-γ loop, successfully reduced IFN-γ-induced aberrant activation of monocytes, although IL-18-induced IFN-γ production from NK and T cells was only partially reduced.
Conclusion: Our findings highlight the critical role of an inflammatory loop between IL-18 produced by activated monocytes and IFN-γ produced by NK and T cells in the pathogenesis of PAPA syndrome, suggesting a strategy to target complex cytokine signaling networks for the treatment of patients with refractory PAPA syndrome.
Disclosure of Interest: None declared

Identifier: PT17

SOMATIC GAIN-OF-FUNCTION MUTATION IN TLR7 CAUSES EARLY-ONSET SYSTEMIC LUPUS ERYTHEMATOSUS

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Introduction: Early-onset systemic lupus erythematosus (SLE) cases have been linked to high-impact genetic variants in several genes, defining the concept of monogenic lupus. Several germline gain-of-function (GOF) mutations in TLR7 have been reported to cause human SLE.
Objectives: We identified a case of early-onset SLE characterized by acute immune thrombocytopenia, recurrent fever, pneumonia, myocardial damage, thyroid dysfunction, lymphadenopathy, hepatosplenomegaly, and cerebral calcification. Our objective was to investigate the genetic and molecular mechanisms underlying the disease.
Methods: Whole-exome sequencing and targeted sequencing were performed and a somatic mutation in *TLR7* was identified. RNA sequencing, quantitative PCR (qPCR), intracellular cytokine staining, and phospho-flow cytometry were performed to characterize inflammatory signatures. In addition, NF-kB dual-luciferase reporter assays, qPCR, and RNA pull-down assays were performed to assess the functional impact of the TLR7 mutation on immune signaling.
Results: We identified a novel somatic TLR7 mutation (p.Phe506Ser), which is likely to arise during early embryonic development. This mutation led to transcriptional upregulation of pro-inflammatory cytokines and interferon-stimulated genes (ISGs), such as *TNF* and *IFI27*, with significant increases in intracellular cytokine expression, including TNF, following stimulation with the ligand ssRNA and the agonist R848 in patient PBMCs. In addition, functional analysis in HEK293T cells demonstrated that the mutant TLR7 exhibited increased binding affinity for ssRNA and enhanced responsiveness to agonists, resulting in hyperactivation of TLR7-mediated signaling.
Conclusion: We report the first case of early-onset SLE caused by a somatic TLR7 gain-of-function mutation. Our findings demonstrate that the TLR7 F506S mutation drives excessive pro-inflammatory signaling in the patient's PBMCs, contributing to disease pathogenesis.
Disclosure of Interest: None declared

Identifier: PT18

ASSESSMENT OF ADA2 ACTIVITY LEVELS: REPORT FROM THE ITALIAN STUDY GROUP ON DADA2

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Introduction: Adenosine Deaminase 2 deficiency (DADA2) is a rare monogenic autoinflammatory disease resulting from loss-of-function mutations in ADA2. Functional assays are crucial for early diagnosis. In 2021, we introduced a liquid chromatography-tandem mass spectrometry (LC-MS/MS) method to assess ADA2 activity from dried plasma spot (DPS).
Objectives: To define cut-offs of ADA2 activity in the normal population and to assess the test's utility in a large multicentre real-life cohort of patients with suspected DADA2.
Methods: In this prospective study, we included all patients who underwent the ADA2 functional assay by LC-MS/MS as a preliminary screening test in presence of a clinical picture potentially consistent with the diagnosis of DADA2 (group 1) or as a confirmatory functional test in subjects with previously detected biallelic or heterozygous ADA2 mutations (group 2).

We used the preliminary cut-off values for ADA2 enzymatic activity provided by our previous pilot study [1].

Moreover, to better define the cut-off levels, the enzymatic test was performed in healthy donors.

Receiver Operating Curves (ROC) analysis evaluated the diagnostic performance of ADA2 activity in DPS. Spearman correlation coefficients were employed to investigate the relations between ADA2 activity in DPS and age. Significance was determined at a threshold of $P<0.05$ for all analyses, with two-tailed tests utilized.

Results: A total of 219 symptomatic subjects were enrolled: 198 in group 1 and 21 in group 2.

5 subjects in group 1 exhibited a pathological ADA2 activity: all of them were confirmed to have biallelic pathogenic mutations in the *ADA2* gene. 6 patients had intermediate activity levels: 1 was found to have biallelic variants in the *ADA2* gene, while 5 did not have any mutations.

In 11 out of 15 patients of group 2 with biallelic ADA2 mutations, 11 presented a pathological ADA2 activity, 3 an intermediate activity wihile in 1 patient the activity was normal. Among 6 patients with heterozygous mutations, ADA2 activity was intermediate in 4 and normal in 2.

To better define the cut-off levels of ADA2 enzymatic activity we considered the data of the 219 patients included in this study, 17 previously reported patients with biallelic *ADA2* mutations [1], 22 asymptomatic carriers and 133 healthy donors.

The enzymatic test effectively discriminated between patients with biallelic *ADA2* mutations and carriers (AUC=0.951, $P<0.001$), between carriers and healthy donors (AUC=0.888, $P<0.001$), and between subjects with biallelic *ADA2* mutations and healthy donors (AUC=0.993, $P<0.001$), with high sensitivity and specificity.

Between the 133 healthy donors, a significant inverse correlation was found between ADA2 activity in DPS and age ($P<0.0001$).

The ADA2 activity cut-off values in DPS were identified as follows: ≤ 0.09 mU/mL for patients with DADA2, 0.10 – 0.39 mU/mL for carriers, and ≥ 0.40 mU/mL for subjects with normal levels. All patients with two pathogenic variants in the ADA2 gene exhibited ADA2 activity ≤ 0.09 mU/mL. For three patients, with a mild phenotype, exhibiting a pathogenic variant along with a VUS in the ADA2 gene, carrier-like ADA2 activity was observed, while 1 patient, carrying two VUS, the ADA2 activity was normal.

An overlap in ADA2 activity levels was observed between carriers and healthy subjects.

Conclusion: The LC-MS/MS ADA2 enzymatic test from DPS demonstrated to be easy to perform, quick and with high sensibility and specificity.

The presence of a pathological enzymatic activity should guide to further genetic tests, in case of a non-confirmatory genotype, while in patients with a non-confirmatory genotype a normal ADA2 activity can be of help to rule out the diagnosis of DADA2.

[1] A Novel LC – MS / MS-Based Method for the Diagnosis of ADA2 Deficiency from Dried Plasma Spot Molecules. 2021 21;26(18):5707.

Acknowledgments: This study was funded by the Italian Ministry of Health through the RF-2019-12370600 project grant.
Disclosure of Interest: None declared

Identifier: PT19

NOVEL CDC42 MUTATION REVEALS A MECHANISM OF PYRIN INFLAMMASOME ACTIVATION.

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Introduction: Genetic changes in the gene encoding the cell division control protein 42 homolog (CDC42), a member of the RHO GTPase family, can lead to heterogeneous disease phenotypes, including growth dysregulation, facial dysmorphism, neurodevelopmental abnormalities, and hematological and immunological aberrations. Specific gene variants in CDC42 can cause autoinflammatory disease, such as NOCARH syndrome. For instance, the $CDC42^{R186C}$ variant accumulates in the Golgi apparatus and results in overactivation of innate immune signaling pathways, including the Pyrin inflammasome. Pyrin is an intracellular pattern recognition receptor that detects cytoskeleton disruptions, such as RhoA inhibition by the bacterial toxin TcdB. Upon activation, Pyrin interacts with the adaptor protein ASC to form the inflammasome complex, which induces cell death and inflammation.

Objectives: We identified a heterozygous missense variant, $CDC42^{M45L}$ from patients experiencing periodic fevers with violaceous rash, arthralgia, and splenomegaly. In this study, we aim to investigate whether $CDC42^{M45L}$ is pathogenic via activation of the inflammasome.

Methods: To analyze how $CDC42^{M45L}$ contributes to inflammasome activation, we reconstituted wild-type or $CDC42^{M45L}$in the CDC42-deficient human myeloid cell line THP-1 and stimulated the cells with different inflammasome activators. To visualize the subcellular location of CDC42 variants, we overexpressed these variants in HeLa cells and examined cells using confocal microscopy. To investigate the interaction partners of CDC42 responsible for promoting inflammasome activation, we performed immunoprecipitation in HEK293T cells overexpressing CDC42 variants and Pyrin, with or without ASC, and analyzed the results using mass spectrometry or immunoblotting.

Results: We found that $CDC42^{M45L}$ promoted Pyrin inflammasome activation in response to the Pyrin activator TcdB. Our results showed that $CDC42^{M45L}$ distributes evenly in the cytoplasm, suggesting an inflammasome-activating mechanism that is different from $CDC42^{R186C}$. Proteomic analysis further revealed that $CDC42^{M45L}$interacts with a distinct spectrum of effector proteins compared to other CDC42 variants. Notably, we found that $CDC42^{M45L}$ exhibited increased affinity for binding Pyrin in the absence of ASC and promoted Pyrin activation in the presence of ASC.

Conclusion: Our results indicate that variants in CDC42 can promote an interaction with and activation of the Pyrin inflammasome. In agreement with this, patients with the $CDC42^{M45L}$ variant experienced significant benefit from therapy targeting the inflammasome cytokine IL-1.

Acknowledgments: The authors acknowledge the facilities and the technical assistance of the flow cytometry laboratory at Walter and Eliza Hall Institute of Medical Research, FlowCore and Monash Micro Imaging at the Monash Health Translation Precinct. The work was supported by the European Joint Programme on Rare Diseases (S.L.M, ODINO project, EJP RD JTC2022) and the NHMRC (S.L.M, GNT2008699). S.F. was supported by the Jack Brockhoff Foundation (JBF Grant number 5252).

Disclosure of Interest: S. Feng: None declared, T. Reygaerts: None declared, M. C. Wierzbowski: None declared, S. Ojaimi: None declared, S. L. Masters Consultant for: S.L.M. is the scientific advisor for Odyssey Therapeutics, Employee of: S.L.M. is the vice president of discovery biology of NRG Therapeutics

Identifier: PT21

EVIDENCE FOR DYSREGULATED ERYTHROPOIESIS IN MICE AND HUMANS WITH MEVALONATE KINASE DEFICIENCY

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Introduction: Mevalonate kinase deficiency (MKD) is a rare autoinflammatory disorder caused by bi-allelic loss-of-function mutations in *MVK*, encoding an enzyme of the mevalonate pathway. Lack of mevalonate kinase leads to loss of synthesis of isoprenoid lipids necessary for the post-translational prenylation of small GTPase proteins, resulting in their accumulation in a mislocalised, unprenylated form. Individuals with MKD present with a spectrum of symptoms depending on the severity of the mutations, from periodic flares of systemic inflammation to a more severe and potentially fatal disease. Anaemia, a common feature in MKD, is thought to be secondary to chronic inflammation. However, how defects in the mevalonate pathway cause inflammatory disease is still poorly understood, largely due to lack of genetic animal models that recapitulate the human disease. Using CRISPR/Cas9 gene editing, we developed a variety of genetic mouse models of MKD, with different mutation combinations in *Mvk* resulting in mevalonate kinase residual enzyme activities ranging from 20-2%. These mice, kept under specific pathogen-free housing conditions, recapitulate the mild-to-severe biochemical spectrum of MKD with no evidence of inflammation in the steady state.
Objectives: To better understand the mechanisms underpinning the pathophysiology of anaemia in MKD.
Methods: We performed complete blood measurements in mice and MKD patients with a haematology analyser; H&E staining of blood and bone marrow smears and spleen sections; flow cytometric analysis to identify and quantitate erythrocyte populations in blood, bone marrow and spleen; and high-parameter immune cell profiling with the Akoya/phenocycler antibody panel to assess the haematopoietic structures in mouse spleen.
Results: We found that *Mvk* mutant mice, like MKD patients, are anaemic with decreased haemoglobin and red blood cell (RBC) number. RBC distribution width (RDW), a measure of the variability in RBC size, was significantly increased in all *Mvk* mutant mice genotypes compared to wildtype and heterozygous controls, was very consistent regardless of age and sex, and inversely proportional to residual mevalonate kinase activity. Furthermore, circulating RBC from *Mvk* mice displayed altered shapes and sizes, and showed greater variation in forward scatter (FSC/size) measured by flow cytometry. Importantly, like in *Mvk* mutant mice, RDW values were also significantly elevated in all 9 MKD patients assessed (mean 15.2%, range 13.6-18.7% *vs* normal range 10.5-13.0).
RBC maturation in mice is defined by loss of CD45, upregulation of Ter119, and changes in cell size and CD71 expression. We found a significantly higher frequency of large (FSC high) erythroid cells (CD45-Ter119^{+}) with variable expression of CD71 in *Mvk* mutant bone marrow (~60% *Mvk* vs 40% control) and spleen (~20% vs <1%). *Mvk* spleens were bigger, with larger red pulp containing Ter119+CD71+ cells, and smaller B and T cell zones. Finally, we confirmed that the anaemia and all other features of the erythrocyte compartment present in *Mvk* mutant blood, bone marrow and spleen were recapitulated upon bone marrow transplantation from *Mvk* mutant donors into wildtype mice. This included accumulation of large erythroid cells and altered shape and size of circulating RBC, suggesting that anaemia and anisocytosis (RBCs of variable size) in MKD may not be solely the result of chronic inflammation.
Conclusion: These findings reveal that *Mvk* mutant mice have underlying anaemia and anisocytosis, and signs of dysregulated erythropoiesis in the absence of overt inflammatory disease. Our results suggest that the increase in RDW in humans with MKD may be the result of a defect in erythropoiesis caused by lack of protein prenylation, and not solely secondary to inflammation.
Disclosure of Interest: None declared

Identifier: PT22

COMPARISON OF IMMUNOLOGICAL BIOMARKERS AND LUNG HISTOLOGY IN PATIENTS WITH ELEVATED IL18 - PULMONARY ALVEOLAR PROTEINOSIS AND RECURRENT MACROPHAGE ACTIVATION SYNDROME (IL-18PAP-MAS) AND OTHER INFLAMMATORY LUNG DISEASES

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Introduction: Recently, pulmonary alveolar proteinosis (PAP) and recurrent macrophage activation syndrome (MAS) have been reported in rare patients (pts) with systemic juvenile idiopathic arthritis (SJIA) like disease. The pathomechanisms of lung disease remain elusive.

Objectives: We aimed to characterize genetic and immunological biomarkers of IL-18PAP-MAS pts. We sought to understand pathophysiology by comparison of blood and lung biopsy markers to other inflammatory diseases.

Methods: Eight patients with IL-18PAP-MAS were enrolled in an IRB approved protocol (NCT02974595). Serum (n=8), whole blood RNA (n=8) bronchoalveolar lavage (BAL, n=2) samples and lung biopsies (n=3) from IL-18PAP-MAS pts were compared to samples from pts with NLRC4-MAS (n=4), Interferon (IFN) mediated disease (n=10) including pts with STING associated vasculopathy with onset in infancy (SAVI, n=7), neonatal onset multisystem inflammatory disease (NOMID, n=4), sarcoidosis (n=10) and healthy controls (HC, n=3). Cytokines were measured by Luminex assay in serum and BAL, *CXCL9* and *CXCL10* transcript levels were measure by Nanostring. Immunoregulatory proteins expression was assessed in the lung tissue biopsies (IL18PAP-MAS, n=1 and SAVI, n=2) using a Co-Detection by Indexing (CODEX) platform. Lung biopsies scored for inflammatory features, (cell infiltrate, lymphoid aggregates, type 2 pneumocyte hyperplasia, hyaline matrix, cholesterol crystals, mucus plugging, transudate/exudate) and damage (emphysema, consolidation, vascular damage, fibrosis, neovascularization, thrombosis. Radiographs were scored by one radiologist.

Results: Of 8 pts with IL-18PAP-MAS and nail clubbing, 2 pts (25%) met the ILAR SJIA criteria. All patients had high elevation of serum IL-18 levels similar to patients with NLRC4-MAS. *CXCL9* and *CXCL9*/*CXCL10* ratio (IFN gamma response markers) were higher in IL-18PAP-MAS compared to interferonopathy and controls. BAL fluid from IL-18PAP-MAS pts had higher expression of IL-18 and free IL-18, which were solely detected in IL-18PAP-MAS in contrast to SAVI and sarcoidosis. Histologic features showed innate immune cells including high expression of neutrophils, histiocytes and alveolar macrophages with fewer lymphocytes and B cell infiltrates compared to SAVI, and low numbers of parenchymal and peribronchial lymphoid aggregates. Cholesterol clefts and mucous plugging were cardinal features in IL-18PAP-MAS. Distinctive radiological features suggestive of active inflammation included consolidation most prominent in the lower lobes, intralobular septal thickening, and pulmonary nodules, with higher inflammatory vs damage score in contrast to SAVI. Analysis of 48 CODEX biomarkers displayed distinct findings with evidence of epithelial-endothelial detachment, significant expression of IFN gamma, CD38, CD163, and MPO in IL-18PAP-MAS compared to SAVI.

Conclusion: IL-18PAP-MAS is a newly recognized, not yet genetically defined clinical syndrome. Histological pulmonary features of IL-18PAP-MAS differ from lung manifestations of SAVI and sarcoidosis, which includes recruitment of innate immune cells, predominantly neutrophils and alveolar macrophages. BAL fluid shows high expression of total and free IL-18 compartmentalized in the lung of IL-18PAP-MAS but not in SAVI and sarcoidosis suggesting a potential role of free IL-18 in the distinct pathogenesis of PAP in IL-18PAP-MAS.

Disclosure of Interest: None declared

Identifier: PT23

INVESTIGATING NK CELL DEFICIENCY AND DYSFUNCTION IN FAMILIAL MEDITERRANEAN FEVER WITHIN THE IMMUNAID COHORT: A MULTI-OMICS PERSPECTIVE

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Introduction: Familial Mediterranean Fever (FMF), traditionally linked to MEFV mutations and pyrin-dependent inflammasome activation, is increasingly recognized as a disorder involving broader immune dysregulation. Multi-omics analyses reveal impaired NK cell function, altered cytokine profiles, and disruptions in both innate and adaptive immune pathways. Additionally, metabolic reprogramming in immune cells and potential non-canonical inflammasome activation suggest more complex inflammatory mechanisms beyond pyrin. Despite this, the mechanisms triggering the disease remain incompletely understood, necessitating further research to elucidate the interplay between genetic mutations, immune dysregulation, and systemic inflammation in FMF.

Objectives: This study aims to investigate the broader immunometabolic perturbations in FMF pathophysiology by leveraging a multi-omics approach to identify key cellular interactions, immune processes, and metabolic pathways that underlie immune dysregulation.

Methods: We analyzed PBMCs, plasma, and urine from FMF patients in the ImmunAID cohort using bulk and single-cell RNA sequencing, microRNA sequencing, flow cytometry, proteomics, lipidomics, and other in-vitro validation approaches. Multi-omics integration was performed using gene co-expression networks, multi-omics correlation structures, intercellular communication mapping, metabolic flux analysis, and developmental trajectory inference to uncover immune and metabolic abnormalities.

Results: FMF patients exhibited a selective reduction in $CD16^+$ NK cells, critical for cytotoxicity and IFN-γ production. This dysfunction disrupted NK cell-mediated communication with memory B cells, cDC2, and $CD4^+$ T cells, altering their developmental trajectories and highlighting interdependent immune dysregulation.

Cell-type-specific analysis revealed disrupted mitochondrial pathways, particularly in NK cells, with deficits in tRNA processing and altered lipid metabolism. Reduced LXR/RXR activation in macrophages and dendritic cells, along with changes in immune soluble factors and inflammation-associated lipid mediators, further impaired immune activation and communication.

Pathway enrichment analysis revealed shared immune processes, including complement cascade and immunoregulatory interactions between lymphoid and non-lymphoid cells at both gene and protein levels. Interestingly, IL-10 signaling was significantly increased, suggesting compensatory mechanisms that appear insufficient to counteract systemic immune dysregulation potentially driven by NK cell dysfunction.

Together, these findings underscore NK cell dysfunction as a central feature of FMF pathophysiology, driving altered cell-to-cell communication, metabolic perturbations, and developmental abnormalities in B cells, T cells, and dendritic cells. These systemic immune imbalances occur despite compensatory activation of regulatory pathways in FMF patients.

Conclusion: These findings challenge the traditional inflammasome-centric view of FMF, emphasizing NK cell dysfunction as a central driver of immune dysregulation. The disruption of NK cell-mediated interactions with other immune subsets, coupled with systemic metabolic perturbations, highlights the complexity of FMF pathogenesis. This study provides novel insights using a multi-omics approach, offering a basis for targeted therapeutic strategies that address both immune and metabolic abnormalities, broadening our understanding of the disease.

Keywords:

Familial Mediterranean Fever (FMF), Natural Killer cells, pathway enrichment analysis, MEFV mutation, multi-omics, metabolic perturbation, inflammation

Acknowledgments: We acknowledge the ImmunAID consortium for providing patient samples and data used in this study. We also thank all internal and external collaborators and institutions that supported the project execution.
Disclosure of Interest: None declared

Identifier: PT24

GENERATION OF PATIENT-DERIVED IPSCS FOR HYPERIMMUNOGLOBULIN D SYNDROME

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Introduction: Hyperimmunoglobulin D Syndrome is an autoinflammatory disease comprising one of the phenotypic manifestations of Mevalonate Kinase Deficiency (MKD). Model systems for HIDS research comprise primary cells, immortalized cell lines, and mouse models. Available models may have disadvantages in terms of easy access, availability, cost, and accuracy in disease mechanisms. iPSC models provide an opportunity for infinitely expandable cells that are disease- and patient-specific.

Objectives: This study aims to create new iPSC lines containing HIDS-causing *MVK* mutations. The goal is to establish an infinitely expandable, disease- and patient-specific model of HIDS for drug research and functional studies.

Methods: Primary fibroblast cultures of 3 HIDS patients one homozygous for the V377I mutation and the other two homozygous for the M300V mutation were derived from skin punch biopsy samples. Cells were transfected with plasmids featuring Yamanaka factors and cultured in TeSR-E7 Reprogramming Medium. iPSC colonies formed by reprogrammed cells were further expanded in mTeSR1 medium. Patient-derived iPSC lines were characterized with qRT-PCR and immunofluorescence (IF) staining for pluripotency factors expression. Then pluripotency capacity of the colonies was demonstrated by *in vitro* Trilineage Differentiation Assay and validated with qRT-PCR and IF staining. The cell lines were sequenced and shown to contain the pathogenic *MVK* mutations, the same as the primary fibroblasts from which they originated. For quality control of iPSC colonies; PCR for possible plasmid integration, STR analysis for their compatibility with primary fibroblasts and karyotype analysis for possible chromosomal abnormality, were performed.

Results: Ten colonies were isolated from reprogrammed cells and of those at least 3 colonies from each patients' cells were appropriate as a result of quality control experiments. iPSC lines for each patient that were capable of differentiation into three germ layers containing pathogenic *MVK* mutations were generated.

Conclusion: This is the first example of an iPSC model specific for HIDS. The generation of a new model system for this disease allows for easier access to HIDS cells for researchers, opening the way for novel research into disease mechanisms and therapies.

Acknowledgments: This project was supported by the Scientific and Technological Research Council of Türkiye (Grant number: 122S379) and the Scientific Research Projects Coordination Unit of Hacettepe University (Grant number: THD-2024-21311).

Disclosure of Interest: None declared

Identifier: PT25

COMPOUND HETEROZYGOUS VARIANTS IN PIGO LEADING TO A NOVEL COMPLEMENT-MEDIATED AUTOINFLAMMATORY DISEASE

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Introduction: We present here a term male infant presenting with recurrent fevers, skin rash, and persistently elevated C-reactive protein, along with a background of urogenital anomalies, developmental delay, dystonia and hyperphosphatemia. His disease was only partially controlled with anakinra and systemic corticosteroids. Genetic and laboratory investigations were performed to uncover the cause of his presentation.
Objectives: Presentation of the first reported case of PIGO-related autoinflammatory disease.
Methods: The patient underwent genome wide sequencing to identify contributory variants to his presentation. Flow cytometry was performed to assess for deficiency of glycophophatidylinositol (GPI)-anchored proteins at the cell surface. Serum soluble C5b-9 (sC5b-9) was measured by enzyme-linked immunosorbent assay to detect excess activation of the complement pathway.
Results: Genome wide sequencing revealed previously undescribed compound heterozygous variants of uncertain significance, c.2647G>C (p.Gly883Arg) and c.95G>T (p.Arg32Leu), in *PIGO*, each inherited separately from the patient's healthy parents. PIGO is an enzyme in the GPI-anchor biosynthesis pathway. Consistent with defective PIGO activity, the patient demonstrated decreased surface expression of GPI-anchored proteins compared to his parents. Deficiency of PIGO has previously been associated with Mabry syndrome, a condition that shares many features with our patient, including hyperphosphatemia, urogenital anomalies, and developmental delay, but not previously demonstrated to manifest with autoinflammation. However, deficiency of PIGT, a separate downstream enzyme in the GPI-anchor biosynthesis pathway, has been shown to cause complement-mediated inflammation. Given clinical similarities between our patient and descriptions of PIGT-related autoinflammatory disease and the known importance of GPI-anchored proteins in inhibiting complement activation, we measured sC5b-9 in the patient's serum and detected elevated levels that were consistent with constitutive overactivation of the complement system, which was further confirmed when the patient developed atypical hemolytic-uremic syndrome (aHUS) at the age of 2.5 years old. He was started on complement blockade using eculizumab with full response of aHUS, as well as complete and sustained remission of his clinical and laboratory features of autoinflammation.
Conclusion: To our knowledge, our patient represents the first reported case of PIGO-related autoinflammation, a condition associated with complement overactivation and complete responsiveness to eculizumab. This report underscores the utility of genome wide sequencing and functional analysis of inflammatory pathways to arrive at novel diagnoses and treatment options for patients with rare monogenic diseases.
Disclosure of Interest: E. Itzkovitz: None declared, M. Batthish: None declared, V. Belostotsky,: None declared, R. Laxer Consultant for: Akros Pharma, Eli Lilly, Sobi, Novartis, Sanofi, Conflict with: Royalties: UpToDate, D. Dissanayake: None declared

Identifier: PT27

THE GENETIC LANDSCAPE OF PRIMARY IMMUNE REGULATORY DISORDERS IN POLAND

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Introduction: Primary immune regulation disorders (PIRDs) are a subset of inborn errors of immunity with a heterogeneous phenotype characterized by autoimmunity and hyperinflammation, mainly manifested by fever, lymphadenopathy, organomegaly, and lymphoproliferation. Treatment of PIRD is difficult due to overlapping features of other inborn errors of immunity (IEI) and often depends on accurate diagnosis, requiring genetic testing.
Objectives: The aim of the study was to analyze the spectrum of genetic background of autoinflammatory diseases and immune regulation disorders in Polish patients with suspected IEI who underwent genetic screening in 2016–2024.
Methods: The analysis included 470 patients with suspected IEI who presented with characteristic symptoms of PIRD. The criteria included at least 2 of the following: impaired immune tolerance, recurrent fever, rash, lymphadenopathy, organomegaly, vasculitis, colitis, arthritis, or sterile inflammation. We performed deep targeted Next Generation Sequencing (NGS) using a custom panel of over 500 genes associated with IEI and hematological disorders, supported with high-density SNP-array when needed. The following results describe the largest cohort of genetic variants associated with PIRD in Poland.
Results: Disease-causing variants were identified in 140 of 470 (29.78%) patients. Autoinflammatory and immunoregulatory disorders accounted for 60% of the results obtained. The most common were immune regulatory disorders (37%), with HLH being the most common subcategory (12%), while autoinflammatory disorders accounted for 24%, including inflammasome-related conditions (10%), non-inflammasome-related conditions (9%) and type 1 interferonopathies (5%). A significant number of patients had alterations in the AIRE (8%), CTLA4 (6%) and FAS (5%) genes and XLP-related genes (6%). The remaining 39% of positive results were other IEIs, with the largest share being the CVID phenotype (10%) and complement deficiencies (8%), which may influence the pathogenesis of SLE and other autoimmune diseases. In 3 unrelated patients, we found extremely rare MSN defects. Novel mutations accounted for more than 20% of all variants revealed.
Conclusion: The results show the spectrum of PIRD in Poland and emphasize the importance of genetic testing in making a final diagnosis. The use of deep NGS supported by SNP-arrays as a screening method has improved the diagnostic efficiency, providing the possibility of personalized treatment, which is of particular importance considering the increasing number of available targeted immune and gene therapies.
Disclosure of Interest: None declared

Identifier: PT28

ANALYSIS OF CLINICAL MANIFESTATIONS ACROSS THE SPECTRUM OF UBA1 MUTATION BURDEN

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Introduction: VEXAS is a progressive systemic autoinflammatory disorder caused by somatic variants in *UBA1*. Analysis of large biobanks have shown variable disease manifestations
Objectives: We sought to better understand the discordance in disease penetrance between cohorts and to assess the impact of age, sex, and variant allele frequency (VAF) on expressivity in VEXAS
Methods: Whole exome sequencing data from 194,346 participants from two biobanks, Geisinger MyCode Community Health Initiative and Mount Sinai Bio*Me* Biobank were analyzed for disease-causing variants in *UBA1*. Variant calling was performed using the GATK 4.2 Mutect2 pipeline. Laboratory results, ICD10 codes, and medications were analyzed longitudinally across *UBA1*-variant carriers. To control for change of VAF over time, sub-analyses were performed on data limited to within one year, before or after, the time of sample collection
Results: We identified 23 participants, ie "cases", with pathogenic/likely pathogenic (P/LP) somatic variants in *UBA1* across both cohorts, providing an estimated prevalence of 1 in 8,450. Cases were comprised of 9 unique *UBA1* variants, VAF ranged from 2.9%-79%, 70% were male. We define high VAF as cases with VAF >20% (8/23, 34.8%) and low VAF as VAF$\leq$20% (15/23, 65.2%). Of female cases, 5/7 (71.4%) had a VAF $\leq$10%, demonstrating that females were disproportionally present in low VAF cases ($p<0.01$). Twenty (86.9%) cases developed anemia (100% high VAF; 80% low VAF;$p=0.53$). Eleven (47.8%) cases developed macrocytic anemia (high VAF 87.5%, low VAF 26.7%;$p=0.03$).

VEXAS-associated ICD10 codes were seen in both VAF groups but more consistently in high VAF cases (overall 73.9%; high VAF 100%, low VAF 60% ;$p=0.58$). Six (26.1%) cases had no VEXAS-associated ICD10 codes; ages ranged from 24-72 years, 2 (33%) were female, all were low VAF cases. Of these 6, 4(66%) had anemia and 3 (50%) had thrombocytopenia. In sub-analysis limited within one year of sample collection 7/8 (87.5%) high VAF cases had macrocytic anemia, compared to 2/15(13.3%) low VAF cases($p=0.001$). Longitudinal analysis in cases with $\geq$10 years of data were analyzed to better understand disease progression. In 2 cases with high VAF, macrocytosis developed > 5 years prior to time of sample collection, followed by anemia either one year prior or at the time of sample collection. In a case with low VAF, macrocytic anemia did not develop until 5 years after time of sample collection, but did have 50 unique steroid prescriptions

Conclusion: We identified 23 participants with P/LP *UBA1* variants, of which 21 (91%) had markers of clinical disease. Consistent with our prior analysis, phenotype was highly penetrant, and carriers displayed a wide range of clinical manifestations. Although VAF level did not dictate disease penetrance entirely, our study indicates that there is a VAF threshold where hematologic manifestations of VEXAS become increasingly penetrant and clinical symptoms more severe. At VAF below 20%, disease still manifests, however penetrance is incomplete and the clinical spectrum more variable. Milder disease in lower VAF individuals may not require medical intervention or may present as common symptoms requiring recurrent steroid use.

Our access to longitudinal data enabled us to follow cases over time and demonstrated a dynamic disease that progresses over time, however without repeat sequencing it remains to be seen if disease progression is a result of rising VAF. Our study highlights that low VAF carriers are frequently symptomatic and should be monitored for disease progression which can occur over several years

Acknowledgments: Regeneron Genetics Center. VEXAS Foundation.The Intramural Research Program of the Division of Cancer Epidemiology and Genetics of the National Cancer Institute, Rockville MD
Disclosure of Interest: None declared

Identifier: PT29

A NOVEL REXO2 VARIANT IN A PATIENT WITH LIVEDO RETICULARIS, PALMOPLANTAR ERYTHEMA AND DENTAL DISEASE

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Introduction: A dominant negative variant in the mitochondrial exonuclease *REXO2* (c.394A>G, p.T132Ala) has been recently recognized to cause an interferonopathy characterized by skin inflammation, via accumulation of mitochondrial RNA in the cytoplasm and consequent activation of the MDA5-MAVS axis. Currently, only a single patient with REXO2-associated autoinflammatory disease has been reported.
Objectives: To describe the genetic and clinical features of a patient with a novel variant in *REXO2*.
Methods: DNA was extracted from peripheral blood leucocytes in the proband and from buccal cells in the unaffected relatives. Variants identified by whole exome sequencing (WES) in the proband were prioritized based on variant population allele frequencies and prediction tools. The identified *REXO2* variant was assessed by Sanger sequencing in the proband and in the unaffected parents and sisters.
Results: The proband was born after an uncomplicated pregnancy to non-consanguineous parents of European-admixed American ancestry. At birth she was noted to have three capillary malformations, which remained stable over time. Since the first month of life, she presented with persistent non-painful palmar and plantar erythema. By one year of age she had developed recurrent episodes of mucosal bleeding, subsequently explained by a diagnosis of von Willebrand disease type 1, and signs of dental decay, that later progressed to severe dental caries and abscesses despite adequate oral hygiene. In the first two years of life, the patient presented with recurrent fevers that were attributed to upper respiratory and gastrointestinal infections, but without stereotypical features, in the absence of daycare attendance. During her third year of life she started experiencing episodes of blue discoloration of her extremities, and developed livedo reticularis, more prominent on the legs than on the arms. In addition, she complained of leg pain ascribed to growing pains and occasional oral ulcers. Inflammatory markers and autoantibodies were negative. Her laboratory workup was only significant for iron deficiency anemia, presence of giant platelets with normal platelet count, and occasional mild neutropenia. A cardiac ultrasound and an eye exam performed at the age of 3 were normal. The patient was referred to our Center for genetic testing on the suspicion of deficiency of adenosine deaminase 2 (ADA2). Sanger sequencing of all *ADA2* coding exons did not detect any variant. WES revealed a heterozygous c.503A>T, p.Asp168Val variant in the exonuclease domain of *REXO2* absent from public databases and predicted to be deleterious (CADD score 32, REVEL score 0.767, AlphaMissense score 0.988). Residue 168 is highly conserved and had been previously reported to be critical for REXO2 nuclease activity. The variant occurred de novo, and was absent in the three unaffected sisters. The patient, currently 11-years-old, has never required immunomodulatory treatment; her height and weight are at the 30th and 21st percentile respectively, her neurodevelopment and her exercise tolerance are normal.
Conclusion: A novel *de novo REXO2* variant may explain livedo reticularis, palmoplantar erythema and dental disease in a 11-year-old girl. This case report supports a role for *REXO2* in human disease and expands the phenotypic spectrum associated with *REXO2* variants. Upon evaluation of the interferon signature and further clinical monitoring, treatment with a JAK-inhibitor will be considered.
Disclosure of Interest: None declared

Identifier: PT30

MEVALONATE PATHWAY IN AUTOINFLAMMATION: VISUALIZING THE BIOCHEMICAL IMPAIRMENTS OF MEVALONATE KINASE DEFICIENCY

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Introduction: Mevalonate kinase deficiency (MKD) is a monogenic autoinflammatory disorder characterized by pathogenic *MVK* variants that impair isoprenoid metabolism. During prenylation, nonsterol isoprenoids function as lipid anchors for protein cell membrane integration. MKD disrupts prenylation-directed localization, activating downstream inflammatory signaling. Emerging evidence suggests the severity of MKD prenylation deficits is inversely proportional to residual mevalonate kinase enzymatic activity. Therefore, we used protein folding software to categorize common structural enzymatic defects in known pathogenic *MVK* variants. These structural defects were used to train a scoring algorithm, wherein defects with lower reported enzymatic activity were assigned a higher score. This pipeline was then used to evaluate uncharacterized *MVK* variants. By using MKD as a model, this pipeline could rapidly evaluate metabolic defects within the pathway, expanding the spectrum of mevalonate metabolic autoinflammatory conditions.
Objectives: Visualize the mechanism of mevalonate kinase with the cofactors and mevalonate substrate; Use the structural defects of known *MVK* variants to develop a protein folding pipeline that evaluates unclassified *MVK* variants.

Methods: Wild type mevalonate kinase enzyme was visualized with experimentally determined structures from PDB databases or predicted with Alphafold3. Binding of cofactors and mevalonate was predicted with Webina docking software to detect functional residues. Known pathogenic variants were visualized, and a scoring algorithm was created to assess mevalonate kinase structural changes. To train the scoring criteria, structural defects with lower reported enzymatic activity were assigned a higher score. Variants were compared to pathogenicity scoring from AlphaMissense and the ACMG/AMP clinical guidelines (Richards et al. 2015). Unclassified variants were then run through the scoring algorithm to assess a genotype-phenotype correlation.

Results: Docking of ATP/magnesium cofactors and the mevalonate substrate to wild type mevalonate kinase identified several key functional amino acid residues: K13, H20, N55, S135, S146, Y149, E193, D204, and A334. We next identified 285 known *MVK* variants, 181 of which were pathogenic/likely pathogenic while 67 were unclassified. While AlphaMissense correctly predicted pathogenicity of some variants, it did not predict pathogenicity of the more common pathogenic variants, such as V377I and I268T. Therefore, we visualized known *MVK* variants to develop a scoring algorithm that incorporated the structural changes observed in these pathogenic variants: proximity to proposed functional residues, loss of catalytic domains, etc. Approximately 23 of the previously unclassified variants were identified as likely deleterious through this pipeline.
Conclusion: Currently, 25% of all known *MVK* variants remain unclassified. Classifying *MVK* pathogenic variants often requires specialized enzymatic activity assays that may be inaccessible to some clinical labs, hindering MKD diagnosis. Moreover, many known pathogenic *MVK* variants are not captured with current *in silico* modeling tools due to conversative amino acid substitutions and an incomplete understanding of functional residues. Herein, we visualize mevalonate kinase activity with ATP/magnesium cofactors and mevalonate binding. By visualizing mevalonate kinase activity, we provide a protein folding pipeline that captures known pathogenic *MVK* variants and evaluates unclassified variants. While enzymatic assays remain the final confirmatory test, this model streamlines detection. Through this

pipeline, evaluating variants of the mevalonate pathway genes may reveal a unified group of mevalonate metabolic autoinflammatory conditions characterized by deficits in isoprenoids and prenylation.
Disclosure of Interest: None declared

Identifier: PT31

PERFORMANCE OF TARGETED GENE PANEL FOR ROUTINE DIAGNOSIS OF AUTOINFLAMMATORY DISEASES AT THE NATIONAL AMYLOIDOSIS CENTRE

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Introduction: The National Amyloidosis Centre (NAC) is the UK's reference laboratory for diagnosing systemic autoinflammatory diseases (SAIDs) and amyloidosis. We provide next-generation sequencing (NGS)-based genetic testing to patients with suspected autoinflammatory diseases across the UK. As a highly specialised NHS England service provider, we ensure diagnostic accuracy through a robust bioinformatics workflow and strict adherence to variant interpretation guidelines. Essential to this process is our multidisciplinary team (MDT) meetings, where genetic findings are correlated with clinical data to facilitate accurate diagnosis and timely care.
Objectives: To assess the performance of our clinical NGS panel used for the routine diagnosis of patients with suspected monogenic systemic autoinflammatory diseases (SAIDs).
Methods: We developed and validated a targeted NGS panel of 25 genes (*ADA2, CARD14, IL1RN, IL36RN, LPIN2, MEFV, MVK, NLRC4, NLRP12, NLRP3, NOD2, OSMR, OTULIN, PLCG2, PSMB4, PSMB8, PSMB9, PSTPIP1, RBCK2, SH3BP2, SLC29A3, SAVI1, TNFAIP3, TNFRSF1A and UBA1*) for SAIDs with specificity and precision of 100%. DNA samples from 4,409 patients referred between April 2018 and November 2024 were analyzed. Libraries were prepared using Illumina TruSeq and AmpliSeq kits, and sequencing was conducted on a MiSeq platform. Rare variants (MAF <2%) were filtered and assessed for pathogenicity using the Infevers database, ClinVar, and ACMG guidelines.
Results: In 4,409 patients, 1,055 distinct variants were detected in 1,929 cases (43.8%). Of these, 102 (9.7%) were classified as pathogenic or likely pathogenic (Table 1), 54 (5.1%) were novel, and 899 (85.2%) were variants of unknown significance (VUS). Genetic diagnosis for a monogenic disease was made in 308 out of 4,409 (7%) patients tested over a 6-year period. Notably, 13 patients were diagnosed as mosaic for cryopyrin-associated periodic syndromes (CAPS) with variant allele frequency (VAF) ranging from 3% to 27%. Diagnosis of recessive disorders, such as MKD and DADA2, were supported by the detection of novel trans variants alongside known pathogenic variants, corroborated by abnormal enzyme activity assays.

Table 1: Pathogenic (P)/likely pathogenic (LP) variants identified in patients with SAID

Genes	SAID Diagnosis	Number of P/LP variants (n=102)	Variants Identified
MEFV	FMF/ *Possibly dominant FMF	12	*V726A, A744S, *R761H, *M694V, *M694I, *M694del, *M680I, F479L, L682VfsTer16, I692del, G294V, E167D *Single MEFV variant in exon10

	Pyrin-associated autoinflammatory disease (PAAND)	3	S208T, S242R, R354W
MVK	MKD	12	V377I, V310M, N301T, H380R, W210Ter, I268T, Y116H, G202R, N205D E19K, D366AfsTer110, C.78+1G>A
NLRP3	CAPS/Mosaic CAPS	22	CAPS: T193M, R260W, D303N, E304K, E311K, I334V, T348M, A439V, F523C, Y536C, S547C, L632F, V890E Mosaic CAPS (13 patients): E304D, E307S, A352T, K355N, Y563S, G569V, E567Q, E567K, Y570C
TNFRSF1A	TRAPS	15	C59Y, C84Y, Y49C, Y67C, N70del, C72R, T79M, C81G, S86_E93del, G87V, S88P, R121W, V124M, H95L, V202D
ADA2	DADA2	10	H112Y, R34W, G47V, G47R, R169Q, Y227C, P251L, N370K, N423K, S479P
TNFAIP3	HA20	11	M112T, S548DfsTer129, L147QfsTer7, G251S, F637ETer2, E661NfsTer36 R136QfsTer3, R283Ter, E374D, L626VfsTer45, T604RfsTer93
UBA1	VEXAS	4	M41T, M41V, M41L, c.118-1G>C
Other genes with low occurrence of diagnosis	Various (Psoriasis, SAVI, HA20, H syndrome, PSORS14, NOD 2-associated granulomatous disease,	13	*NOD2*: R334W, R334Q, M513T, Q809K *CARD14*: G882AfsTer5 *NLRC4*: G172S, V341L *IL36RN*: L27P, P76L

			STING1: V155M, N154S *SLC29A3*: M1L, T449R

Conclusion: Targeted NGS continues to be an effective routine diagnostic tool for SAIDs, despite the high prevalence of VUSs. It is particularly valuable for the detection of low-level mosaic mutations. Expanding the availability of functional assays for more of the targeted genes could help with understanding the consequences of novel variants and VUSs.
Disclosure of Interest: None declared

Identifier: PT32

STILL'S DISEASE ASSOCIATED LUNG DISEASE: DATA FROM THE EUROPEAN REGISTRY

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Introduction: Lung disease (LD) is a new emerging severe life-threatening complication of Still's Disease (SD). Patients with SD complicated by LD are increasing and available data coming from North American patients. Frequency and features of SD-LD in Europe have never been reported.

Objectives: To evaluate the burden of SD associated LD in Europe.

Methods: Patients with diagnosis of SD-LD, followed in European paediatric rheumatology centres were identified through a survey sent to the members of the MAS/SJIA Working Party.

Results: Data from 61 SD-LD patients, diagnosed in 21 European paediatric rheumatology centres between 2007 and 2024, were collected. 59 patients were White-Caucasian and 2 African American; 38 were female. The median age at SD onset was 7.2 years and LD occurred after a median time of 3 years. Only 3 patients (5%) had trisomy 21. 85% (51) of the patients had at least one episode of MAS, 22 (44%) of whom had MAS at SD onset and 30 (59%) at time of LD diagnosis; 36 (71%) patients had >1 MAS episode. IL-18 levels, measured in 22 (36%) patients, were markedly elevated at time of SD onset and of LD diagnosis (media of 121451 and 138947 pg/ml respectively). 27 (44%) patients experienced drug adverse reaction to a cytokine inhibitor: 17 to tocilizumab,10 to anakinra and 2 to both. To note, 12 patients (19%) did not receive IL-1 or IL-6 inhibitor before LD diagnosis. Eosinophils count was measured in 55 (90%) patients totally, with values ranging from 0 to 4,000 cell/mmc at time of SD onset and from 0 to 15,000 cell/mmc at time of LD diagnosis. The HLA-DRB1 analysis was done in almost half of the patients (48%), and the HLA-DRB1*15 allele was positive in 22/29 (76%) patients. After LD diagnosis 54 (88%) patients received intravenous or oral glucocorticoids and additional treatments were very heterogeneous across the entire cohort. 7 patients underwent to hematopoietic stem cell transplantation. LD worsened in 14 patients and 21 developed complications 12 hypoxia, 6 O2 supplementation and 8 pulmonary hypertension. 29 patients (47%) required ICU admission and 11 (18%) died.

Conclusion: SD-LD, patients are also present in Europe. Prompt recognition is crucial and new therapeutic strategies are needed to reduce the risk and improve the outcome of this complication.
Disclosure of Interest: None declared

Identifier: PT33

EXTRA-OCULAR INVOLVEMENT IN CHILDREN WITH A PHENOTYPE SUGGESTIVE OF OCULAR SARCOIDOSIS

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Introduction: Paediatric sarcoidosis is a rare, idiopathic, multiorgan granulomatous disease manifesting in diverse phenotypes, including ocular inflammation in over half of cases. The diagnosis of ocular sarcoidosis (OS) in children is challenging due to a lack of paediatric-specific diagnostic criteria and difficulty in obtaining tissue biopsies. Extra-ocular involvement (EOI) may facilitate diagnosis and guide treatment, particularly in complex cases. This study retrospectively evaluates EOIs in children with suspected ocular OS, applying revised International Workshop on Ocular Sarcoidosis (IWOS) criteria to explore diagnostic applicability in paediatric populations.

Objectives: This study aimed:

to describe EOIs in children with suspected OS,

to evaluate whether they help classify patients using the revised International Workshop on Ocular Sarcoidosis (IWOS) criteria,

to explore associations between EOIs and clinical outcomes and treatment responses.

Methods: Medical records of 52 children diagnosed with or suspected of OS at Great Ormond Street Hospital for children NHS Trust between 2005 and 2020 were retrospectively reviewed. Patients were categorised based on IWOS criteria into definite, presumed, probable, and unclassified OS. Demographic, clinical, laboratory, imaging, and therapeutic data were collected. EOIs were defined as systemic manifestations, assessed by clinical and laboratory evaluation. Univariate logistic regression and hierarchical cluster analysis were used to explore associations.

Results: The cohort (48.1% female) had a median age of 7.8 years at uveitis onset. Black (32.7%) and Asian (30.8%) ethnicities predominated. Most cases (94.2%) involved bilateral uveitis, with panuveitis being the most common subtype (48.1%).

EOIs were present in 65.4% of children with presumed OS, with peripheral lymphadenopathy (26.9%), arthritis (26.9%), liver (25%), and renal (23.1%) involvement being the most frequent. Children fulfilling IWOS criteria were significantly more likely to exhibit EOIs (80% vs. 52%, $p=0.033$), particularly lymphadenopathy ($p<0.001$) and skin manifestation ($p=0.022$). Skin involvement was associated with worse systemic outcomes (OR=0.14; 95% CI: 0.03–0.81; $p=0.028$).

Two distinct phenotypes were identified through cluster analysis. The first, observed in younger children (<8 years), was characterised by milder anterior uveitis, minimal EOI, and poorer treatment response. The second, prevalent among Black African children >8 years, displayed severe panuveitis, more EOIs, and a favourable response to early Disease Modifying Antirheumatic Drugs (DMARDs).

Conclusion: Paediatric OS often presents with EOIs that may support a diagnosis of sarcoidosis leading to early treatment and influence treatment outcomes. Black African children with severe phenotypes benefited from early DMARD initiation especially MMF. Skin involvement emerged as a predictor of systemic severity, underscoring the need for prompt skin biopsy in suspected cases so treatment can be tailored. The revised IWOS criteria may require adaptation for paediatric populations adding biomarkers and imaging to enhance diagnostic accuracy. Early initiation of treatment with DMARDs favours a better disease outcome.

Acknowledgments: We would like to express our gratitude to Emily Kalms for her invaluable contributions to this study.

Disclosure of Interest: None declared

Identifier: PT34

ADULT-ONSET STILL'S DISEASE: A SINGLE-CENTER REVIEW OF CLINICAL FEATURES, TREATMENT, AND OUTCOMES

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Introduction: Adult-onset Still's disease (AOSD) is a rare systemic inflammatory disorder of unknown etiology, characterized by arthritis, fever, and a maculopapular rash, often accompanied by hyperferritinemia. Diagnostic methods and comprehensive data on the disease remain limited.
Objectives: This study aims to present demographic data, clinical features, lab values, management strategies, and outcomes of 93 patients with AOSD followed in a tertiary clinical center.
Methods: Data regarding the clinical features, treatment modalities, and survival outcomes were retrospectively collected from patient files that met Yamaguchi's Criteria.
Results: We included 93 patients with AOSD who were regularly followed up at our tertiary center, with mean age at onset of 33.60 ± 14.42 years. Of whom 64.5% (60/93) were female.

Common clinical manifestations included fever (93.4%, 85/91), rash (65.6%, 59/90), arthritis (57.8%, 52/90), arthralgia (82.2%, 74/90), pharyngitis (%55.6, 50/90) and myalgia (%51.7, 46/89). Less frequent features were pleuritis (10.0%, 9/90), pericarditis (10.0%, 9/90), hepatomegaly (15.6%, 14/90), splenomegaly (23.3%, 21/90), and abdominal pain (17.0%, 15/88). Other symptoms included odynophagia in 40.7% of patients (33/81), hypertriglyceridemia in 32.8% (22/67), proteinuria in 22.7% (20/88), and lymphadenopathy (LAP) in 39.8% (35/88).

Comorbid conditions were present in 77.6% of patients (59/76), while macrophage activation syndrome/hemophagocytic lymphohistiocytosis (MAS/HLH) was identified in 14.1% of cases (13/92). Malignancy was present in 3.9% of patients (3/76). The survival rate was 94.0% (79/84) at the time of follow-up.

Laboratory findings showed changes in the median values of several parameters between the first and last visits, reflecting the effects of treatment. Ferritin levels decreased from a median of 520.7 µg/L to 72.3 µg/L. ESR declined from a median of 50.0 mm/h (n=90) to 13.5 mm/h. CRP levels dropped from a median of 45.6 mg/L to 3.5 mg/L. Similarly, WBC counts reduced from a median of 10,050/mm³ to 7,620/mm³, and neutrophil counts decreased from a median of 6,000/mm³ to 4,205/mm³ (n=84). Hemoglobin levels increased from a median of 12.2 g/dL (n=88) to 12.95 g/dL (n=83).

Treatment approaches varied, with glucocorticoids being the most commonly used (93.3%, 84/90), followed by methotrexate (72.4%, 63/87), and anakinra (45.3%, 39/86). Biological agents such as tocilizumab (26.5%, 22/83) and canakinumab (15.5%, 13/84) were also employed. Additional treatments included hydroxychloroquine (HCQ) in 38.6% of patients (34/88), azathioprine (AZA) in 3.5% (3/86), cyclosporine A (CyA) in 3.5% (3/86), and Janus kinase inhibitors (JAKi) in 2.3% (2/86). The median highest glucocorticoid dose was 20.0 mg/day, with a lowest dose of 2.5 mg/day.

Parameter	Value
Gender (Female)	%64,5 (60/93)
Age of onset, mean ± SD, years	33,60 ± 14,42

Fever	%93,4 (85/91)
Rash	%65,6 (59/90)
Arthritis	%57,8 (52/90)
HLH/MAS	%14,1 (13/92)
Ferritin at first visit, median (IQR, 25-75)	520.7 (172.4-1989.5)
Ferritin at last visit, median (IQR, 25-75)	72,3 (29,8-176,0)
Survival (Alive)	%94,0 (79/84)

Conclusion: The diverse clinical presentations of AOSD make the diagnosis challenging. The variability in treatment approaches highlights the need for individualized management. Effective use of immunosuppressive treatments led to significant reductions in inflammatory markers and favorable outcomes in this cohort.

Disclosure of Interest: None declared

Identifier: PT35

ANAKINRA DERIVED AMYLOIDOSIS DETECTED IN TWO PATIENTS, REPORT FROM THE UK NATIONAL AMYLOIDOSIS CENTRE

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Introduction: Amyloidosis is a rare protein misfolding disorder caused by different precursor proteins resulting in amyloid formation and deposition in various tissues and organs. To date, 42 amyloidogenic proteins were reported, of these four are iatrogenic, caused by frequent subcutaneous injection of a protein drug (insulin, enfuvirtide, glucagon-like peptide-1 analog, and IL-1RA protein). Except for AIL1RAP (IL-1Ra protein) amyloidosis the remaining iatrogenic amyloid types are localized and confined to the injection site.

Objectives: Here we describe two patients who, as a result of treatment with interleukin-1 (IL-1)–blocking agent anakinra, developed AIL1RAP (IL-1Ra protein) amyloidosis.

Methods: Both patients underwent detailed clinical and laboratory investigations including histological and laser micro dissection (LMD) liquid chromatography and tandem mass spectrometry (MS) on Congo red–positive tissue. We also examined 25 gene panel associated with hereditary systemic autoinflammatory diseases using the next generation sequencing (NGS) technology, specifically looking for low frequency alleles in the *NLRP3* gene, which are well documented in the literature as a cause of mosaic CAPS.

Results: Patient 1 presented at the age of 15 years with a dramatic onset of a Still's like disease accompanied by fever, arthralgia, pharyngitis and salmon pink rash, which appeared to be worse over the affected joints. She was refractory to anti pyrectics, antibiotics and DMARDS. While treated with tocilizumab she developed a rapid macrophage activation syndrome and was switched to anakinra 100 mg alternative days with a sustained excellent response. She first noticed small lumps in the subcutaneous tissue at the site of injections on her right thigh 7 years after starting the treatment and when switched to the left thigh there was a rapid progression in both the number and size of lumps. The patient has since switched to canakinumab, 150 mg every 6 weeks, with complete response.

Patient 2 presented with symptoms of CINCA/NOMID shortly after birth with urticarial rash, fever, lymphadenopathy, frontal bossing, saddle nose, recurrent episcleritis and elevated inflammatory markers. She has no family history of CAPS. She started treatment with anakinra at the age of 2 and half years with a very good clinical response and remained on 100 mg bd until at the age of 20 years when she noticed nodular infiltration on both her thighs at the anakinra injection site. She was switched to canakinumab 300 mg every 4 weeks.

In both patients a skin biopsy was obtained for histological evaluation. It showed the presence of amyloid was demonstrated by staining of amorphous material with Congo red dye that displayed a characteristics apple-green birefringence under cross polarised light. Subsequently a LC-MS/MS performed on Congo red–positive amyloid deposits demonstrated the presence of AIL1RAP (IL-1Ra protein) amyloidosis. The amino acid sequence of the fibrillar protein detected in amyloid deposits lacked the N-terminal 24 amino acid sequence, corresponding to recombinant IL-1Ra.

In both patients analysis of our hereditary systemic autoinflammatory disease NGS panel did not detect causative pathogenic variant. We had not found a low frequency allele in the *NLRP3* gene.

Conclusion: While anakinra derived amyloidosis is rare, it can occur, in patients with high dose subcutaneous injections administered over prolonged time. To date, four patients with CINCA/NOMID were reported with AIL1RAP (IL-1Ra protein) amyloidosis; two of them developed systemic amyloidosis with nephrotic syndrome. We describe here two further patients with a skin biopsy confirmed amyloid deposition derived from exogenous, recombinant IL-1RA. We

performed an SAP scintigraphy to assess if amyloid was present in other organs and confirmed there was no visceral amyloid deposition. Interestingly, Patient 1 is the 1st case with anakinra derived amyloidosis who does not have CINCA/NOMID (was diagnosed with Still's disease) and had not been on a very high dose of anakinra administered over 7 years.

Disclosure of Interest: None declared

Identifier: PT36

UNRAVELING THE GENETIC AND TRANSCRIPTOMIC DRIVERS OF MONOGENIC AUTOINFLAMMATORY DISEASES IN CHILE: BRIDGING GAPS IN DIAGNOSIS AND TARGETED THERAPY

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Introduction: Inborn errors of immunity (IEI) are rare genetic disorders that disrupt immune function, leading to infections, autoimmunity, autoinflammation, and cancer. Among IEIs, monogenic systemic autoinflammatory diseases (SAID) are characterized by recurrent fevers and chronic inflammation, with variants identified in over 60 genes. Despite advances in genomic technologies like genome and exome sequencing (ES) over 60% of cases remain undiagnosed.Transcriptomic approaches offer an unbiased strategy to identify dysregulated pathways for targeted treatments. In Chile, SAID prevalence is unknown, and limited access to ES and RNA-seq hampers diagnosis and discovery. We developed a research pipeline to study SAID patients in Chile.

Objectives: Identify genetic and transcriptomic drivers of SAID to uncover novel disease-causing genes and pathways for targeted therapeutic approaches.

Methods: Chilean SAID patients, either known or unknown genetic causes, were referred to our study by their physicians. Blood samples for DNA, serum and peripheral blood mononuclear cells were collected. For undiagnosed patients, parental EDTA samples were collected for trio ES. Multiparametric immune phenotyping assessed T and B cells, monocytes, NK/T cell functionality by flow cytometry. Inflammatory cytokines, including free IL-18, CXCL9, and CXCL10 were measured by ELISA. Type I interferon signature was assessed by RT-qPCR. Bulk RNA sequencing was performed on whole blood. Differential expression analysis with DESeq2 compared healthy donors to genetically known or unknown SAID patients. Differentially expressed genes were grouped into biological processes using Blood Transcriptomic Modules (BTM) to identify immune pathway enrichment.

Results: A total of 98 patients with heterogenous SAID manifestations were enrolled (53% female, 47% male). 22% had a known genetic diagnosis, including pathogenic or likely pathogenic variants in *NLRP3, ADA2, NFKB, MVK, TNFAIP3, XLPDR.* Four patients had Variants of Unknown Significance in *NLRC4*(1), *STAT1*(1) and *CTLA4*(2), for which our functional studies suggest pathogenicity. The rest remains undiagnosed, with ES analysis ongoing. The most prevalent clinical manifestations were mucocutaneous involvement (77%), gastrointestinal symptoms (65%), and recurrent fever (62%). Onset occurred in early childhood for 72% of patients. Immunophenotyping revealed heterogenous dysregulation of T, B and monocyte compartments. Patients with inflammasomeopathies had the highest free IL-18 levels, followed by patients with interferonopathies and immune dysregulation. CXCL9 and CXCL10 were elevated in immune dysregulation patients. All patients with a genetic diagnosis of interferonopathy had an increased interferon score. Transcriptomic analysis of BTM showed enrichment or depletion in modules related to monocytes, dendritic and B cells, associated with flow cytometry findings. In interferonopathy patients, BTM results revealed enrichment in type I interferon pathways, as expected. In undiagnosed patients, enriched modules varied, but they may correspond to known mechanisms like inflammasome activation, type I interferon upregulation, and NF-κB dysregulation, which could inform therapeutic strategies.

Conclusion: Our study provides a systematic platform to evaluate SAID patients. Ongoing studies in this cohort will probably lead to genetic and mechanistic discoveries to guide therapeutic interventions.

Acknowledgments: We would like to thank all the patients and their families for participating in this study. This work was funded by Jeffrey Modell Foundation and FONDECYT Project No. 1221802, ANID, Chile.

Disclosure of Interest: None declared

Identifier: PT37

SITRAME SYNDROME: INSIGHTS FROM 46 PATIENTS: THE LARGEST COHORT STUDY OF A NOVEL SYSTEMIC AUTOINFLAMMATORY DISEASE

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Introduction: SITRAME (systemic inflammatory troncular recurrent acute macular eruption) syndrome is a newly identified systemic autoinflammatory disease (USAID) described in 2023. It is characterized by recurrent erythematomacular eruptions on the trunk, with systemic inflammation evidenced by elevated C-reactive protein (CRP) during flares. The initial report described 16 patients, and diagnostic criteria were published in 2024.
Objectives: The aim of this study is to describe the characteristics of the largest cohort of patients with SITRAME syndrome to date.
Methods: The cohort included patients followed up at the French National Reference Center for Adult Autoinflammatory Diseases, all fulfilling the diagnostic criteria for SITRAME syndrome.
Results: A total of 46 patients were reported with a median SITRAME score of 7; all adults of Caucasian descent, with 27 women (58.7%). The median age at inclusion was 56.3 years, ranging from 27 to 77 years. The median age at symptom onset was 34 years, and at diagnosis, it was 53.5 years, with a median diagnostic delay of 19.9 years. Flares of SITRAME syndrome lasted a median of 3 days, with annual recurrences ranging from 1 to 20 times. During flares, CRP levels were elevated to a median of 26.5 mg/L, normalizing in between. All patients met the major diagnostic criteria, and the most frequent minor criteria included triggering factors like infections, vaccinations, and intense physical activity (73.9%).

During flares, all patients displayed an erythematous rash affecting the trunk, which was macular in 93.5% and pruritic in 10.9%. The rash extended beyond the trunk, reaching the arms in 26%, the thighs roots in20%, the legs in 11% and face in 9%. The rash covered between 10% and 50% of the body surface in 67.4% of patients. Symptoms associated with the rash included fever (50%), asthenia (47.8%), arthromyalgia (28.3%), headache (17.4%), and abdominal pain (13%). The most common triggers were ENT infections (63%), vaccinations (26%), physical activity (10.9%), and medications (17.4%). Regarding severity, 39.1% of patients had more than 50% of their body surface affected by the rash. Severe asthenia, affecting daily activities, was observed in 28.3% of cases. 8.7% of patients experienced at least one flare per month.

Histological analysis of skin biopsies from 16 patients revealed no vasculitis or isolated neutrophilic infiltrates, but a mixed neutrophilic and eosinophilic infiltrate in 6 cases, and an eosinophilic infiltrate in 3 cases. Genetic analysis of 15 patients showed inconclusive results.

Therapeutic interventions included colchicine for 19 patients (43.2%) at 1 mg/d: for 7 patients it decreased the intensity and length of flares; corticosteroids, which were ineffective in 3 patients; one patient received anakinra during a crisis, which was able to improve the symptoms; anti-IgE treatment (300 mg/month) were ineffective for two patients.

Seven patients were followed for at least 12 months, and two for 24 months. No serious complications, such as inflammatory amyloidosis or death, were observed.

Conclusion: SITRAME syndrome is an individualized entity within USAID, affecting adults sporadically. This study confirms the original description ~~It~~ suggesting that the syndrome is more common than previously thought, with already 46 French patients affected. Despite the frequent recurrence of attacks associated with asthenia and elevated CRP, no

serious inflammatory complications are reported so far Further research is needed to understand the pathophysiology, improve therapeutic management and prevention.
Acknowledgments: Ref 1: Soria et al, *J Eur Acad Dermatol Venereol*. 2023 Apr;37(4):e538-e542.

Ref 2: Soria et al, *J Eur Acad Dermatol Venereol*. 2025 Jan;39(1):e87-e90.

Disclosure of Interest: None declared

Identifier: PT38

THE PREVALENCE AND SPECTRUM OF DAMAGE IN PATIENTS WITH UNDIFFERENTIATED SYSTEMIC AUTOINFLAMMATORY DISEASE

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Introduction: Undifferentiated Systemic Autoinflammatory Disease (uSAID) encompasses a group of systemic autoinflammatory disorders that do not fit into any specific, recognized category. Patients with uSAID typically present with symptoms such as recurrent fevers, serositis, skin rashes, arthralgia, and myalgia, yet lack a confirmed genetic diagnosis. It is a diagnosis of exclusion, applied when clinical features and test results do not align with any recognized autoinflammatory condition. The prognosis of uSAID has not been systematically studied before and based on some publications in the literature, it is thought that there may be a misconception that this group of diseases has a benign course.
Objectives: To determine the prevalence and spectrum of damage in patients with uSAID.
Methods: Electronic medical records of uSAID patients were reviewed for demographic and clinical characteristics, including disease onset, organ involvement, treatments used, and details of organ damage. Patients with concomitant chronic diseases were excluded. Damage was defined as irreversible tissue degeneration with clinically significant functional impairment from inflammation. Potentially fatal damage was defined as any condition posing a risk to life. Descriptive statistics were applied to assess the prevalence and spectrum of damage, and parameters associated with damage were analyzed.
Results: A total of 182 patients were analyzed, with a median age of 30 years (range: 3–74) and 58% female. The median age at disease onset was 9 years (range: 0–63). The most common disease symptoms/manifestations were fever, constitutional symptoms and arthralgia/arthritis. Patients reported intermittent flares, while 15 individuals reported chronic symptoms. Damage was identified in 72 patients (39.5%), with potentially fatal damages/complications (such as cardiomyopathy, portal hypertension, interstitial lung disease, venous thrombosis, and neutropenia) observed in 28 patients (15.4%). The spectrum of damage was highly variable and included more domains than those captured by the Autoinflammatory Disease Damage Index (ADDI), which was developed for four common monogenic autoinflammatory diseases: FMF, MVK, TRAPS, and CAPS. The presence of eye, ear, and neurologic involvement was significantly associated with damage.

Affected Organs/Systems by Damages	**n (%)**
Neurologic (stroke, epilepsy, cranial neuropathy)	13 (7.1)
Ocular (glaucoma, retinopathy, keratopathy, cataract, vision loss)	12 (6.6)
Liver (fibrosis, portal hypertension)	3 (1.6)

Renal (proteinuria, amyloidosis, kidney stones)	11 (6.0)
Musculoskeletal (joint restriction, myopathy, bone deformity, avascular necrosis)	16 (8.8)
Skin (fibrosis, disfigurement, alopecia, non-healing wounds, etc.)	12 (6.6)
Hematologic (profound anemia, myelodysplasia, thrombosis, etc.)	32 (17.6)
Endocrine (growth delay, diabetes, malnutrition, adrenal failure, etc.)	21 (11.5)
Reproductive/Genitourinary (amenorrhea, infertility, miscarriage, IUGR, etc.)	6 (3.3)

Conclusion: Despite the potential ascertainment bias stemming from the inclusion of patients with severe disease referred to the NIH, the spectrum of damage in individuals with uSAID is both diverse and affects a significant proportion of cases. The complexity of this damage extends beyond what is captured by ADDI, highlighting the critical importance of clinicians employing advanced clinical acumen to determine the necessity and scope of further evaluations. Moreover, certain clinical characteristics are strongly associated with damage, underscoring the need for vigilant monitoring and personalized management strategies to mitigate long-term complications effectively.

Disclosure of Interest: None declared

Identifier: PT39

RELEVANCE OF PATTERN RECOGNITION RECEPTOR SIGNALING IN CONTEXT OF MULTI-MEDIATOR INFLAMMATION – TOWARDS UNDERSTANDING A ROLE OF TLR4-DEPENDENT DAMAGE ASSOCIATED MOLECULAR PATTERN SIGNALING IN AUTOINFLAMMATION

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Introduction: Damage-associated molecular patterns (DAMPs) are self-derived molecules that are considered to drive and perpetuate inflammatory conditions via pattern recognition receptors. In such lines S100A8/A9 and A12 proteins, which can be quantified at high levels in sera of some systemic mono- or polygenic IL-1 driven autoinflammatory diseases, have been reported to signal through toll-like-receptor 4 (TLR4). While such mechanistic conclusions are largely derived from *in vitro* experiments, an *in vivo* relevance of TLR4-dependent DAMP-signaling is largely unclear, particularly in settings with already ongoing inflammation and multiple cytokine and chemokine signalling happening simultaneously.
Objectives: To better understand the relevance of remnant TLR4-signaling in a model of multi-mediator inflammation.
Methods: We generated a human blood inflammatory matrix by stimulation of healthy donor (HD) whole blood with LPS and ATP, which was profiled for inflammatory mediator expression using proximity elongation (Olink 96 inflammation panel) and multiplexed bead array assay (Luminex). HD whole blood was stimulated directly with LPS or treated with freshly prepared cell-free blood inflammatory matrix, with or without TLR4 antagonist (LPS-RS), anti-IL-1β/IL-18 bispecific antibody (MAS825), JAK-STAT (Tofacitinib, Ruxolitinib; JAKi) or PI3K-inhibition. Following 4h of stimulation, gene expression in blood cells was assessed by 67-gene NanoString panel.
Results: Blood inflammatory matrix profiling revealed elevation in a total number of 50 markers compared to non-stimulated whole blood cells. When transferring cell-free blood inflammatory matrix to fresh whole blood preparations (n=6 independent experiments), we observed 23 genes with elevated expression, while direct stimulation of whole blood cells with LPS prompted expression increase in 33 genes. Both LPS-stimulation and treatment of whole blood cells with inflammatory matrix resulted in an overlapping top-5 gene signature with maximum expression (LPS-stimulation: *IL6>IL1A>IL1B>PTX3>CCL20*; blood inflammatory matrix: *IL1A>IL6>CXCL10>IL1B>IL1RN*) at comparable magnitude (80-900fold). In contrast, LPS-stimulation of whole blood cells induced a type I interferon-related gene signature, which was completely absent from inflammatory matrix stimulated blood cells. Importantly, treatment of LPS-stimulated blood cells with the TLR4-antagonist LPS-RS resulted in significant downregulation of almost all overexpressed genes (26/33). In contrast, TLR4-antagonism in inflammatory matrix stimulated blood cells resulted in non-significant expression decrease of only 10 out of 23 genes. When testing the efficacy of other inhibitors and drugs in our model, we observed the bi-specific anti-IL-1β/anti-IL-18 antibody MAS825 to result in a significant decrease of *IFNG*, *CXCL9* and *CXCL10* expression. Treatment of blood inflammatory matrix stimulated cells with JAKi resulted in complete abrogation of *CXCL9* and *CXCL10* transcription and some but significant decrease in *IL1RN* and *PTX3* expression. Finally, treatment with PI3Ki prompted pronounced reduction of most blood inflammatory matrix induced gene expression, but revealed no effect on *IFNG* and *IL8* expression, while increasing *CTIIA* transcription.
Conclusion: In our whole blood model of IL-1-driven multi-parameter inflammation, we observed little impact of TLR4-inhibition on blood cell gene expression. This may question the relevance of at least TLR4-dependent DAMP-signaling in driving inflammation, when this occurs in concert with other potent inflammatory mediators. In contrast, targeting IL-18, JAK-STAT or PI3K-signaling axis in multimediator inflammation demonstrated a pronounced and in part highly selective impact.
Disclosure of Interest: None declared

Identifier: PT40

PHENOTYPIC AND FUNCTIONAL CHARACTERIZATION OF INNATE LYMPHOID CELLS IN SYSTEMIC JUVENILE IDIOPATHIC ARTHRITIS PATIENTS

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Introduction: Systemic Juvenile Idiopathic Arthritis (sJIA) is an autoinflammatory disease characterized by fever, rash, lymphadenopathy, hepatosplenomegaly and serositis. Macrophage activation syndrome (MAS) is a potentially lifethreatening complication of sJIA. Innate immune mechanisms and overproduction of inflammatory cytokines, including interleukin-1 (IL-1), IL-6, and IL-18, play a central role in the pathogenesis of sJIA. Likewise, the expansion and prolonged activation of macrophages and CD8+ T cells, along with excessive interferon-gamma (IFN-γ) production, are the main drivers of MAS manifestations.

Objectives: Innate Lymphoid Cells (ILCs), comprising Natural Killer (NK) cells and helper-ILCs (hILCs), represent the innate cellular source of IFN-γ. Peripheral blood hILCs encompass ILC1s, ILC2s, and ILCPs, with ILC1s producing IFN-γ and ILC2s producing IL-13. This study aimed to understand the potential role of these cells in sJIA pathogenesis/progression through phenotypic and functional characterization of ILCs in sJIA patients.

Methods: Peripheral ILCs from children with inactive sJIA under IL-1 inhibitors treatment (n=34) were analyzed by flow cytometry and compared to those of 23 healthy children.

Results: : In inactive sJIA patients, circulating NK cells were significantly reduced, with a higher proportion of CD56bright cells, compared to healthy controls. The frequency and number of hILCs was comparable between the two groups, with hILCs correlating with therapy duration. In sJIA patients, the composition of hILC subsets showed increased ILC1 frequency and decreased ILC2 and ILCP frequencies compared to controls. While the frequency of ILC1 positively correlated ($p<0.05$, $r=0.4$), the frequency of ILC2 negatively correlated ($p=0.01$, $r=0.45$) with IL-18 plasma levels, indicating a shift in hILC subset proportions associated with a disease activity marker related to the FN-γ pathway. To assess the functional capacity of NK cells and hILCs, peripheral blood mononuclear cells were stimulated with PMA/ionomycin or with IL-18/IL-12, and intracellular IFN-γ levels were measured by flow cytometry. While NK cells from sJIA patients exhibited comparable IFN-γ production to controls under various stimulations, hILCs displayed lower IFN-γ production, indicative of intrinsic functional impairment. Notably, IL-13 levels remained unaffected, suggesting a specific defect in IFN-γ production by hILCs in inactive sJIA patients.

Conclusion: Inactive sJIA patients display a lower frequency of NK cells, and an increased frequency of ILC1s as compared to healthy donors. Despite this alteration, hILCs have an intrinsic defect in IFN-γ production. Altogether, these findings suggest an alteration in group 1 ILC subset composition and function in sJIA patients, despite the absence of clinical disease activity.

Disclosure of Interest: None declared

Identifier: PT41

TACKLING THE DIAGNOSIS OF HA20 IN CHILDREN: CHALLENGES OF A HIGHLY VARIABLE CLINICAL AND GENETIC SPECTRUM

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Introduction: Heterozygous pathogenic mutations in the ***TNFAIP3*** gene lead to haploinsufficiency of the A20(HA20) protein,which is associated with a complex inflammatory disorder at the intersection of auto inflammation and autoimmunity.To date there is very little data available regarding paediatric presentation.

Objectives: This observational study aims to enhance the understanding of HA20 in paediatric patients by describing the phenotype,the disease course and the treatment strategies.

Methods: We conducted a retrospective analysis of patients diagnosed with HA20 in France,utilizing both the SOFREMIP(Francophone Society of Paediatric Rheumatology and Inflammatory Medicine)mailing list and data from the referent genetics laboratory.Inclusion criteria were disease onset before the age of 18 years,the presence of a *TNFAIP3* mutation classified as pathogenic,likely pathogenic,or a variant of uncertain significance(VUS),and the reasonable exclusion of other similar conditions.Data on demographics,clinical features,laboratory findings,imaging,disease progression and treatment efficacy were analysed and compared to previous reports in literature.

Results: We included 19 patients(47%Female,89%Caucasian)from 12 non-consanguineous families,carrying 11 distinct ***TNFAIP3*** mutations,two of which were newly identified.The median age at disease onset was 4 years(range:1 month–17 years).Age at onset was significantly lower in boys compared to girls(2.5 years vs 6 years,p = 0.004).Disease flares had a median duration of 3 days and occurred approximately every 35 days.Clinical presentations varied widely among patients and even among family members with the same mutation.

At disease onset,63.2% of patients presented with oral ulcers and 21.1% with genital ulcers(Table 1).Over the disease course, these proportions increased to 82% and 63.2%, respectively.Other frequent features during the disease course included fever(70.6%)and gastrointestinal manifestations,such as abdominal pain(61.1%),diarrhoea(42.1%),and colitis(22.2%).Arthralgia was significantly more common in children with disease onset before 5 years of age(p = 0.015).Acute-phase reactants were moderately elevated during flares(median CRP 93 mg/L vs 7 mg/L out of flares).None

of the patients exhibited features of a definitive autoimmune rheumatic disease,although 6/15 (40%)patients had positive ANA titers, 1/7 (14.3%)tested positive for rheumatoid factor.Colchicine monotherapy was effective in 16.7% of patients.Among biological DMARDs,infliximab was the most effective,with a 100% response rate(4/4 patients).

At onset	(N)	(%)	**During disease Course**	(N)	(%)		(N)	(%)
Oral ulcers	12	63.2	Oral ulcers	16	84.2	Lymphadeno pathy	6	31.6
Fever	10	52.9	Fever	14	73.7	Headache	5	26.3
Abdominal pain	6	31.6	Genital ulcers	12	63.2	Colitis	4	22.2
Arthralgias	5	26.3	Abdominal pain	11	61.1	HSMG	2	11.8
Genital ulcers	4	21.1	Arthralgias	10	52.6	Uveitis	2	10.5
Skin rash	4	21.1	Diarrhea	8	42.1			
Fatigue	2	10.5	Skin rash	7	36.8			
Arthritis	2	10.5	Arthritis	7	36.8			
Uveitis	1	5.3	Fatigue	6	31.6			

Conclusion:

This study highlights the wide phenotypic variability of HA20 syndrome,even among siblings carrying the same mutation.Our study revealed that oral and genital ulcers may be absent,both at disease onset and throughout its course.Additionally,we highlight key distinctions between HA20 and pediatric Behçet's disease(BD),notably the median age of onset(4years vs 11years in BD),the predominance of GI involvement,which may be severe,and the peculiar aspect

of mucosal ulcerations which are deeper and distinct from common cankers sores.Despite providing new insights,the limited sample size of our study precludes definitive conclusions regarding phenotype-genotype correlations.Further studies involving larger cohorts are essential to clarify the phenotype-genotype correlation as well as to achieve a deeper understanding of the factors influencing clinical expression and disease progression of HA20 in paediatric patients.

Disclosure of Interest: None declared

Identifier: PT42

WHAT CAN WE LEARN FROM THE DRAWING OF CHILDREN WITH AUTOINFLAMMATORY DISEASES?

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Introduction: Systemic auto-inflammatory diseases (SAIDs) have a significant impact on patients and their families due to recurrent inflammatory flares and their consequences. Better assessment of the burden of disease in children could improve care and therefore quality of life and well-being. Young children express themselves more easily through drawing than through direct narration. Talking to an adult, sometimes a stranger, about their disease, their suffering and its consequences is not an easy task for a young child or a teenager. Drawing can facilitate this exchange.

Objectives: To Identify nonverbal representations of disease through drawings of patients with six SAIDs: Familial Mediterranean Fever (FMF), Mevalonate Kinase Deficiency (MKD), Tumor Necrosis Factor Receptor-Associated Periodic Syndrome (TRAPS), Cryopyrin-Associated Periodic Syndrome (CAPS), Periodic Fever, Aphthous Stomatitis, Pharyngitis and Cervical Adenitis Syndrome (PFAPA), and Still's Disease.

Methods: We conducted a multi-center qualitative study with a psychodynamic approach based on the collection of oriented drawings. Patients between the age of 6 and 17 were invited to draw what their disease meant to them, and to discuss their graphic production with the interviewer. The drawings were analyzed in three stages: a formal analysis focusing on the graphic aspects; a psychodynamic analysis focusing on the readability of the drawing; and an interview analysis to compare the patient's verbatims with data from the drawings. We looked for internal diversity in the sample (age, gender, type of illness/activity).

Results: 9 girls and 8 boys (4 FMF, 2 MKD, 1 TRAPS, 2 CAPS, 4 PFAPA, 4 Still) produced 18 drawings. They were 10 children (6 to 12 years old) and 7 teens (13 to 16). The drawings were centered, used the available space on the page and used a variety of colors. However, red was the predominant color used to indicate areas of pain, emblematic places or certain prohibitions. The hospital, treatments (syringe, pills) or physical symptoms (red marks, location of pain) were the most common drawings (11 drawings). But 3 expressed their fear through drawings of monsters and villains, and 2 their idea of a sacrifice to avoid flares (e.g. dietary restriction). Temporality and onset of pain were also emphasized by drawing a weekly schedule with the evolution of symptoms according to the treatment taken. Girls were keen to express their feelings and emotions through bubble comics (5/9), while boys were interested in depicting elements related to care (5/8). The disease was represented by concrete drawings in 10 patients, including 8 children's drawings, and by a more imaginary vision in the drawings of 4 teenagers. Patients easily added comments and useful information to their drawings. They expressed the feeling of being attacked by the disease, of having to fight it to prevent it from winning and taking over too much space.

Conclusion: Drawings provided valuable information about the burden and journey of the disease and the fears and feelings the children experience. This study identified a list of themes useful for constructing a drawing reading grid, giving caregivers a tool to support their exchanges with their pediatric patients.

Acknowledgments: APICIL Foundation for its financial support

Disclosure of Interest: None declared

Identifier: PT43

USING A T-CELL DIRECTED APPROACH IN THE TREATMENT OF DADA2-RELATED NEUTROPENIA RESULTS IN RECOVERY OF MYELOID CELL DEVELOPMENT PRE-TRANSPLANT AND SUCCESSFUL ENGRAFTMENT POST-TRANSPLANT

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Introduction: Deficiency of adenosine deaminase 2 (DADA2) is a genetic disease initially described with fevers, medium vessel vasculitis and recurrent, lacunar, ischemic strokes in children. Over the past decade the phenotype expanded to involve hematologic features such as various cytopenias including profound neutropenia. Administration of tumor necrosis factor inhibitors results in dramatic reduction in risk for ischemic strokes and decreased inflammatory burden of disease but little to no effect on neutropenia. Additionally, there have been multiple reports of graft failure in DADA2 patients undergoing transplant with neutropenia being their transplant indication.

Objectives: To better characterize and treat DADA2 patients with neutropenia.

Methods: Two patients with profound neutropenia underwent bone marrow biopsies to analyze cellular makeup. Post biopsy, cyclosporine was loaded at 5mg/kg/day for 6 days as well as a glucocorticoid taper of prednisone 30mg daily x 2days, 20mg x 2days, 10mg x 2days and then 5mg daily. Maintenance cyclosporine was approximately 2.5-3.5 mg/kg/day with levels followed closely.

Results: Patient 1 (R169Q/deletion in exon 7) is a 57 yo female with a 28 year history of neutropenia as well as arthalgias, rash, splenomegaly requiring splenectomy and fevers. Bone marrow biopsies completed in 1996 and 2023 revealed normal to hypercellular marrow (40-70%) with markedly decreased granulocytic precursors and extensive lymphocytic infiltrates and aggregates with antibody staining against CD3 identifying the majority of lymphocytes as T-cells. After DADA2 diagnosis, the patient was initially treated with subcutaneous immune globulin x 4 doses without improvement in neutropenia. Subsequently, she was initiated on cyclosporine and glucocorticoids with increasing ANC in 3 days from 200 to 800. She then was loaded with infliximab prior to switching to adalimumab. Within one week of cyclosporine initiation, ANC increased to 1600. Follow-up bone marrow biopsy performed 4 months after cyclosporine initiation showed normocellular marrow with progressive trilineage hematopoiesis and normal maturation of myeloid cells. Decreased, yet still present, T-cell lymphocytosis and multiple small T-cell lymphoid aggregates were observed. Five months post-cyclosporine initiation, ANC was 4560.

Patient 2 (R169Q/G47W) is a 17 yo male with a 2 year history of neutropenia and necrotizing, neutrophil rich, subcutaneous arteritis. At the time of DADA2 diagnosis, etanercept was initiated. Due to lack of hematologic response, he transferred to adalimumab. Despite resolution in skin rash and fevers, ANC remained 0. Bone marrow biopsy revealed normocellular marrow with a paucity of myeloid cells and significant lymphoid infiltration and lymphoid aggregates that were CD3 antibody positive for T-cells. One week after initiation of cyclosporine, ANC rose to 2900. The patient was maintained on this regimen for 9 months preceding transplant. Conditioning for transplant was T-cell directed including 3 days of pulse methylprednisolone and fludarabine. The patient had an uncomplicated post-transplant course with successful engraftment and remains disease free 5 years post-transplant.

Conclusion: DADA2-associated neutropenia has a strong T-cell infiltrate presented here on patient bone marrow biopsies. Expanding the treatment regimen in neutropenic DADA2 patients to include T-cell directed therapies has normalized ANCs in the pre-transplant period and sustained post-transplant engraftment. Notably, the infiltrate is less, albeit present, after adding the cyclosporine yet myeloid cells have become apparent. Additional studies utilizing alternative T-cell directed regimens are needed to further investigate this approach both for patients preparing for transplant and for those who are not transplant candidates.

Disclosure of Interest: None declared

Identifier: PT44

CLINICAL FEATURES AND EFFICACY OF DIFFERENT MODALITIES OF TREATMENT IN A PATIENT WITH NEMO DELETED EXON 5 AUTOINFLAMMATORY SYNDROME (NDAS)

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Introduction: NDAS is a recently described disease, resulting from certain variants of the *IKBKG* gene leading to expression of NEMO protein with skipped exon five. Clinical features of the disease include periodic fever, panniculitis, ectodermal dysplasia, hepatosplenomegaly with hepatitis and B-cell lymphopenia with hypogammaglobulinemia.
Objectives: To describe an effect of different treatment modalities in a patient with NDAS.
Methods: Genetic testing was done via whole-exome sequencing, segregation analysis was performed by long-range nested PCR and subsequent Sanger sequencing, Human Androgen Receptor Assay (HUMARA) based on quantitative fluorescent methylation-sensitive PCR for $(CAG)_n$ repeat in AR gene locus was used for X chromosome inactivation assay.
Results: Female patient of Yakut descent born to non-consanguineous parents presented at birth with multiple daily episodes of fever and panniculitis-like skin lesions. Shortly after birth, she developed ischemic brain frontal lobe stroke and hepatosplenomegaly. The patient was started on prednisone 1 mg/kg with partial effect: fever frequency was reduced to 1-2 times per day. Neonatal screening showed low TRECs (33 copies/10^5 cells) and moderate reduction in lymphocyte counts (CD3+ 917 cells/µl, naïve CD3+CD4+ 571 cells/µl, CD19+ 554 cells/µl). Serum immunoglobulin A and G levels were undetectable, IgM level was elevated to 1,3 g/l. Genetic testing revealed previously described de novo *IKBKG* c.671+2T>G variant leading to expression of NEMO with partially skipped exon five. X-chromosome inactivation skewed 75%:25% was demonstrated.

On admission to our Center, the patient had bilateral pneumonia, which was successfully treated with antibiotics and intravenous immunoglobulin (IVIG). Despite treatment with steroids, the patient had elevated inflammatory markers: high neutrophils and CRP 109 mg/l (reference 0-5 mg/l). We tested CD169 (SIGLEC1) expression on monocytes that was slightly elevated – 72,3 (reference 0-25). The patient was started on baricitinib 5 mg/m^2, adalimumab 2 mg/kg once in 2 weeks and continued prednisone 0,4 mg/kg. Such a combination was previously described to be effective in NDAS patients. She also continued antibiotic prophylaxis with azithromycin and immunoglobulin substitution. Panniculitis resolved, but the patient continued to have a fever every 3-7 days.

At the follow-up 4 months later (aged 9 months) the patient normalized her lymphocyte subsets CD3+ 3,04 cells/µl, CD3+CD4+ 2,02 cells/µl, naïve CD4+ T-cells 1090 cells/µl, CD19+ 1400 cells/µl, but showed elevated AST 649 IU/l (reference 0-56 IU/l) and ALT 532 IU/l (reference 0-58 UI/l). As treatment toxicity could not be ruled out baricitinib and adalimumab were discontinued, which led to progression of hepatitis, return of panniculitis and inflammatory markers, as well as development of autoimmune pancytopenia. A short course of high-dose steroids (15 mg/kg for 3 days) plus rituximab 375 mg/m2 weekly x4 led to resolution of cytopenia and hepatitis. The patient was started on anakinra 10 mg/kg daily, tofacitinib 15 mg/m2, and prednisone 0,5 mg/kg. One month later the patient has no fever, skin lesions and hepatitis.

Conclusion: Patients with NDAS remain a challenging group in terms of treatment. We report a patient, that failed to achieve complete response on treatment with baricitinib, adalimumab and low dose steroids that was previously described as effective in patients with NDAS. Combined therapy with high-dose anakinra, tofacitinib and low dose steroids showed promising results and allowed to achieve complete remission of disease manifestation in short follow-up.
Disclosure of Interest: None declared

Identifier: PT45

RENAL INVOLVEMENT IN AUTOINFLAMMATORY DISEASES: DATA FROM THE EUROFEVER REGISTRY (RIAID PROJECT)

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Introduction: Despite estimates of the rate of AA amyloidosis complicating autoinflammatory diseases (AID), its true incidence is not known. It is anticipated that kidney involvement manifesting as proteinuria can be the first detectable marker of organ amyloid A deposition.

Objectives: To assess the frequency of renal pathology in a large cohort of patients with AID reported to the Eurofever registry.

Methods: Clinical and genetic data were extracted from the Eurofever registry based on optional responses. Data from the registration forms submitted until July 2024 (n=6678) were analysed.

Results: Amyloidosis was confirmed in 56 patients (31 females, 55.4%), 4 of them were children (7.1%, 4 girls, mean age 8±3 years). Majority had Tumor Necrosis Factor Receptor-Associated Periodic Syndrome (TRAPS, n=20, 35.7%, 19% from 105 registered) and Familial Mediterranean Fever (FMF, n=20, 35.7%, 1.4% from 1466 registered) followed by cryopyrinopathy (CAPS, n=8, 14.2%, 6.1% from 131 registered), Mevalonate Kinase Deficiency (MKD, n=4, 7.1%, 4% from 100 registered), PAPA (n=2, 3.6%, 4.2% from 48 registered), Blau syndrome (n=1) and undefined AID (uAID, n=1). Paediatric patients had FMF and MKD (2 cases each). The mean AID diagnostic delay was 287±205 months. In 31 patients for whom the biopsy date or date of amyloidosis manifestation was available, the mean age of its onset was 39.7±18.2 years. Mean time of manifestation of amyloidosis since the onset of the primary AID was 24.3±18.1years. Abnormal proteinuria and/or albuminuria were reported in 231 patients (117 females, 50.6%, 163 children, 70.6%) with following diagnoses: FMF (n=76, 32.9%), uAID (n=40, 17.3%), CAPS (n=28, 12.1%), Syndrome of Undifferentiated Recurrent Fever (SURF) (n=24, 10.4%), MKD (n=15, 6.5%), Behcet´s disease (n=11, 4.8%), TRAPS (n=10, 4.3%), DADA2 (n=9, 3.9%), chronic nonbacterial osteomyelitis (n=5, 2.2%), PFAPA (n=5, 2.2%), 1 patient with each of PAPA syndrome, Blau syndrome, CANDLE, NLRP12-related disease, recurrent idiopathic pericarditis, SAVI, Still´s disease and TNFAIP3-associated autoinflammatory syndrome. 66.2% of patients with reported proteinuria/albuminuria had the last follow-up entered before 2019.

Conclusion: This is the first report on the prevalence of secondary amyloidosis and proteinuria among patients reported to the largest AID registry. Although the number of confirmed cases of amyloidosis in periodic fever syndromes does not exceed the expected rate, proteinuria has been reported more frequently. Outcome of these patients should be closely followed in order to assess potential evolution of amyloidosis in this cohort. Based on these preliminary results follow-up information has been requested from treating physicians that should enable analysis of amyloidosis risk factors.

Acknowledgments: Supported by the Czech Health Research Council (AZV CR) grant NU21-05-00522
Disclosure of Interest: Š. Fingerhutová Speaker bureau of: Sobi, H. Lachmann: None declared, E. Papadopoulou-Alataki: None declared, J. Frenkel: None declared, L. Cantarini: None declared, L. Obici: None declared, G. Fabio: None declared, I. Koné-Paut: None declared, G. Amaryan: None declared, W. Armbrust: None declared, E. Hoppenreijs: None declared, J. Kuemmerle-Deschner Grant /Research support from: Novartis, Sobi, Speaker bureau of: Novartis, Sobi, E. Moreno: None declared, M. Alessio: None declared, N. Ruperto: None declared, M. Gattorno Speaker bureau of: Novartis, Sobi, Fresenius-Kabi, P. Doležalová Speaker bureau of: Novartis, Sobi, Pfizer, Medac

Identifier: PT46

SURFING ON VUS: EXPERIENCE IN NORTH-EAST ITALY AND DESCRIPTION OF A COHORT OF ADULT AUTOINFLAMMATORY PATIENTS THROUGH A VALIDATED NEXT-GENERATION SEQUENCING PANEL OF GENES

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Introduction: The use of targeted gene panels for Next-Generation Sequencing (NGS) and Whole Exome Sequencing (WES) has become a cornerstone in confirming or supporting the diagnosis of various disorders, including systemic autoinflammatory diseases (sAIDs).

Objectives: This study aims to identify mutations and variants of unknown significance (VUS) to determine whether patients presenting with autoinflammatory clinical features can be categorised into specific sAID subgroups. Additionally, it explores whether VUS may correlate with distinct clinical phenotypes, transitioning from the unspecific "Systemic undifferentiated recurrent fevers (SURF)" paradigm toward new potential sAID subgroups.

Methods: Patients with clinical and biochemical inflammatory features, referred to the outpatient Clinic for Autoinflammatory Diseases of Padova University Hospital, were retrospectively reviewed from February 2023 to November 2024. NGS sequencing was performed using Custom "Fever & Autoinflammatory Disease" panel (SOPHIA Genetics) in Illumina MiSeq, which analyzes coding regions of 17 genes (*ADA2, CARD14, ELANE, IL10RB, IL10RB, IL1RN, LPIN2, MEFV, MKV, NLRP12, NLRP3, NLRP7, NOD2, PSMB8, PSTPIP1, TNFRSF11A, TNFRSF1A).* Variant calling and data analysis were performed by the Sophia-DDM-V6.5 bioinformatics analysis program.The interpretation of the variants was performed according to the 2015 ACMG standards and guidelines.

Results: Among 103 patients screened, 80 (77.7%) displayed at least one retained non-synonymous variant with a minor allele frequency (MAF) <= 0.05. Of these, 38 patients (47.5%) carried at least one VUS or pathogenic variant. Overall, 6 patients had pathogenic mutations which confirmed the clinical phenotype: two had *MEFV* mutations consistent with Familial Mediterranean Fever (FMF), two had *MVK* mutations indicative of Hyper-IgD syndrome, and one had a *TNFRSF1A* mutation compatible with Tumor Necrosis Factor Receptor-Associated Periodic Syndrome (TRAPS). VUS were detected in 31 subjects. Six patients exhibited compound heterozygous VUS. All individuals presented variable autoinflammatory symptoms, with partial or complete therapeutic response to colchicine and/or IL-1 inhibitors. Specifically, two clusters of patients were identified with *NOD2* variants: six carried the p.Arg702Trp variant (predominantly presenting with recurrent episodes of hyperpyrexia), while four the p.Leu1007Profs*2 variant (primarily exhibiting aphtosis and cutaneous rashes). One patient with the p.Ser402Phe variant developed granulomatous skin lesions. Furthermore, four patients with the p.F402L variant on *NRLP12* exhibited distinct symptoms and severity; three of them responded significantly to IL-1 inhibitors. Patients carrying two VUS across the same or different genes generally experienced a higher burden of inflammatory symptoms and 4 out of six had a complete response to colchicine or IL-1 inhibitors.

Conclusion: A validated gene panel for NGS is crucial for identifying mutations that confirm specific clinical phenotypes. Although patients with VUS remain classified as "SURF," emerging clusters of patients sharing the same VUS and clinical profiles suggest the possibility of "novel" gene-related pathologies. Further investigations, including WES or functional studies, are essential for enhancing the diagnostic framework for VUS carriers.

Disclosure of Interest: None declared

Identifier: PT47

PREGNANCY OUTCOMES AFTER MATERNAL AND PATERNAL ANTI-IL-1 TREATMENT EXPOSURE IN CRYOPYRIN ASSOCIATED PERIODIC SYNDROMES (CAPS)

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Introduction: Cryopyrin-Associated Periodic Syndromes (CAPS) are hereditary autoinflammatory disorders caused by *NLRP3* gain-of-function variants, leading to persistent inflammasome activation. IL-1 antagonists like anakinra and canakinumab effectively reduce inflammation, prevent organ damage, and improve quality of life. While anti-IL-1 therapies have enabled more CAPS patients to reach reproductive age, their use in pregnancy remains off-label, with limited safety data.

Objectives: To determine the effect of paternal and maternal anti-IL-1 treatment exposures on pregnancies and neonatal outcomes in Cryopyrin Associated Periodic Syndromes (CAPS).

Methods: A single-centre study of consecutive CAPS patients between 01/2012 and 07/2024 was performed. Patients who were exposed to anti-IL-1 treatment prior to conception and/or during pregnancy were included. Data included patient characteristics, disease activity before conception and during pregnancy, anti-IL-1 therapy, pregnancy complications, neonatal outcomes and child health trajectories. Primary outcome: a normal neonatal health status defined as the absence of congenital malformations, normal gestational age, and birth weight.

Results: A total of seven CAPS patients, including five women, were included; median age at conception 28.4 years. All had moderate CAPS; 43% experienced hearing loss. Eleven pregnancies were recorded including eight maternal and three paternal anti-IL-1 exposures. All patients had received canakinumab at conception; maternal exposures: anakinra in six pregnancies, canakinumab in one and anti-IL-1 switch in one. Pregnancy complications: miscarriage, preterm birth in one, respectively. These were associated with inadequate control of disease activity including worsened hearing loss. Neonatal outcomes: Mean gestational age 37+6 weeks, average birth weight 3028g, normal APGAR scores and no congenital malformations. Neonatal complications: sepsis, RSV infection in one, respectively. CAPS in 5/11 offsprings, effective control of disease activity early on, no hearing loss or amyloidosis in any child.

Conclusion: Maternal and paternal anti-IL-1 exposure during conception and pregnancy in CAPS patients was found to be safe. CAPS disease activity may have a significant impact on the development of pregnancy complications.

Disclosure of Interest: None declared

Identifier: PT48

INTERLEUKIN-18 AND INTERLEUKIN-1B BLOCKADE TO CONTROL INFLAMMATION IN PAMI SYNDROME BEFORE AND AFTER HSCT.

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Introduction: PSTPIP1-associated myeloid-related proteinemia inflammatory (PAMI) syndrome is a rare monogenic autoinflammatory disorder. Patients experience chronic systemic inflammation and multi-organ involvement, particularly affecting the skin, bones, and joints, which can be debilitating and require anti-inflammatory therapies. Neutropenia, unrelated to inflammation, is a constant feature. Hematopoietic stem cell transplantation (HSCT) has shown efficacy in some cases but is challenging due to systemic inflammation and organ damage, which increase risks of graft rejection, graft-versus-host disease (GVHD), and toxicities. Inflammatory flares post-HSCT may also contribute to rejection. Novel therapies are needed to control inflammation, ensuring safer HSCT or preventing complications in moderate disease.

Objectives: This study aimed to evaluate the safety and efficacy of a bispecific IL-1β/IL-18 monoclonal antibody, MAS825, in a patient with severe PAMI syndrome requiring HSCT, focusing on controlling inflammation during pre- and post-transplantation periods.

Methods: A female patient with genetically confirmed PAMI syndrome (p.Glu250Lys *PSTPIP1* mutation) received MAS825 through compassionate approval by ANSM (French National Agency for the Safety of Medicines and Health Products). The drug was provided by Novartis via a Managed Access Program. The goal was to reduce systemic inflammation and improve the patient's condition to facilitate safer transplantation.

Results: The patient presented with systemic inflammation from infancy, leading to chronic anemia, persistent neutropenia, and multi-organ involvement, including chronic hepatitis and recurrent painful skin ulcerations. Two episodes occurred on her hand, with one requiring a skin graft. By age 11, she developed a chronic, unremitting aseptic ulcer on her thigh suspected to involve neutrophil-driven inflammation. Corticosteroids initially controlled flares, but their efficacy waned, necessitating additional DMARDs, including canakinumab, which provided temporary stabilization. However, inflammation relapsed, worsening anemia and skin complications.

Given disease progression, cumulative organ damage, and treatment failure, HSCT was considered. MAS825 therapy was initiated 100 days before HSCT (eight doses) and continued until 55 days post-HSCT (four doses) to limit systemic autoinflammation, favor engraftment and decrease the risk or secondary graft rejection. While other bDMARD were withdrawn at MAS825 onset, it led to significant improvement before HSCT. The chronic thigh ulcer healed after three injections, and healing persisted during post-HSCT aplasia. Anemia resolved after the first infusion, eliminating the need for transfusions, while IL-18 levels steadily decreased, and corticosteroid doses were tapered. Neutropenia remained unchanged pre-HSCT but rapidly normalized post-transplant.

The patient underwent myeloablative conditioning followed by haploidentical HSCT with TCRαβ/CD19 depletion. The post-transplant period was uneventful, with MAS825 stopped at day +55 and corticosteroids at day +50. At one year post-HSCT, the patient's skin was fully healed, and IL-18 and zinc levels remained normal.

Conclusion: MAS825 was safely administered before and after HSCT, and was associated to significant clinical and biological improvement in a severe PAMI syndrome case. It appears to have mitigated HSCT-related complications in a context of autoinflammation and cumulative organ damage. However, whether these effects were due to IL-18, IL-1β

blockade, or their combination remains unclear. Further studies are needed to evaluate dual IL-1β and IL-18 blockade in autoinflammatory diseases, either as a bridge to HSCT or as long-term therapy.

Disclosure of Interest: B. Fournier Conflict with: FOURNIER Benjamin reports a relationship with Novartis Pharma SAS that includes: travel reimbursement. , L.-A. Eveillard: None declared, A. Escudier: None declared, G. Boursier: None declared, B. Neven: None declared, A. Welfringer: None declared, B. Bader-Meunier: None declared

Identifier: PT49

CLINICAL, GENETIC, AND IMAGING FEATURES OF AICARDI–GOUTIÈRES SYNDROME IN A LOCAL COHORT IN QATAR

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Introduction: Aicardi–Goutières syndrome (AGS) is a genetically determined encephalopathy caused by mutations that disrupt nucleic acid metabolism, characterized by calcification of the basal ganglia and white matter, demyelination, and chronic type I interferon activation. Clinically, AGS manifests with developmental regression, progressive microcephaly, spasticity and recurrent fevers. We examine the clinical, genetic, and imaging features of AGS in Qatar and evaluate our findings in relation to other cohorts.

Objectives: This study describes and emphasizes regional characteristics in the clinical presentation, genetic variants, imaging findings, and interferon signature in AGS patients seen at Sidra Medicine, the only tertiary pediatric hospital in Qatar, between 2018 and 2024.

Methods: This retrospective cohort study includes 11 AGS patients. All patients were monitored in the AGS multidisciplinary (MDT) clinic, staffed by a neurologist, rheumatologist, immunologist and rehabilitation specialist. Data collected included demographics, clinical features, genetic mutations identified via next-generation sequencing, interferon signature from serum and cerebrospinal fluid (CSF) and MRI findings. Imaging assessed hallmark AGS features, such as basal ganglia calcifications, cerebral atrophy, and leukoencephalopathy. Interferon signature results, where available, were compared pre- and post-treatment.

Results: Demographics: The eleven patients (7 males, 4 females) were aged 2 to 108 months (median 10 months, mean 23.5 months) at diagnosis and currently aged between 15 to 144 months. Nationalities included Qatari (6), Yemeni (3), Tunisian (1), and Syrian (1), with consanguinity reported in 36%.

Genetic Analysis: Homozygous TREX1 mutation was identified in 3 patients, Homozygous RNASEH2A mutation was identified in 3 patients, Homozygous RNASEH2B in 2 patients, compound heterozygous RNASEH2B in 2 patients and Homozygous RNASEH2C in 1 patient.

Clinical and Imaging Findings: Patients presented with classical AGS features, including recurrent fevers, developmental delays, motor deficits, and regression. MRI findings demonstrated hallmark abnormalities such as basal ganglia calcifications, leukoencephalopathy, and reduced white matter volume. These findings are detailed in Table 1. Interferon signature data, summarized in Figure 1, confirmed type I interferon activation.

Treatment: Seven of the eleven patients underwent treatment. Parents refused treatment in four patients. Six patients received Ruxolitinib and, one received Baricitinib. Two patients received reverse-transcriptase inhibitors in addition to Ruxolitinib.

Conclusion: This study highlights the classical clinical, genetic, and imaging features of AGS in a Qatari cohort. Mutations in TREX1, RNASEH2A, RNASEH2B, and RNASEH2C were identified, with compound heterozygous RNASEH2B variants comprising 18% of cases. The genetic distribution observed in this cohort is consistent with other described cohorts, where RNASEH2B and TREX1 mutations are the most frequently reported. However, the relatively higher prevalence of compound heterozygous RNASEH2B mutations in this cohort contrasts with the predominance of homozygous mutations typically seen in consanguineous populations, highlighting unique genetic variability in Qatar.

MRI findings are essential for diagnosis, and JAK inhibitors, particularly Ruxolitinib, control inflammation. Interferon signature analysis supports the diagnosis and underscores type I interferonopathy as central to the disease mechanism. These findings emphasize the importance of regional genetic studies and tailored therapeutic approaches to optimize outcomes in AGS, with implications for both local and global patient populations

Disclosure of Interest: None declared

Identifier: PT50

EFFECTS OF CANAKINUMAB TREATMENT ON COMMON LONG-TERM COMPLICATIONS IN AUTOINFLAMMATORY PERIODIC FEVER SYNDROMES – 60-MONTH DATA FROM THE RELIANCE NON-INTERVENTIONAL STUDY

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Introduction: Data from both clinical trials and real-world setting have confirmed safety and effectiveness of the interleukin-1β inhibitor canakinumab (CAN) for the treatment of autoinflammatory periodic fever syndromes (PFS).
Objectives: The RELIANCE non-interventional study investigates the long-term effectiveness and safety of CAN therapy of patients with clinically confirmed diagnosis of PFS including cryopyrin-associated periodic syndromes (CAPS), familial Mediterranean fever (FMF), hyper-IgD syndrome/mevalonate kinase deficiency (HIDS/MKD) and tumor necrosis factor receptor-associated periodic syndrome (TRAPS) in routine clinical practice. In this interim analysis of the RELIANCE registry, common long-term complications of PFS, laboratory parameters and safety were evaluated.
Methods: RELIANCE is a prospective, non-interventional, multi-center study in Germany that enrolls adult and pediatric patients (aged ≥2 years) diagnosed with autoinflammatory periodic fever syndrome and routinely treated with CAN. The study evaluates effectiveness and safety parameters collected at baseline and at 6-month intervals.
Results: Data analysis of the present interim analysis is based on N=268 patients with PFS enrolled in the RELIANCE registry between September 2017 and June 2023. The study cohort had a median age of 19.5 years at baseline (range: 2−80 years [45.1% < 18 years]; n=137 female patients [51.5%]) while the median duration of CAN treatment prior to study entry was 2 years (range: 0−15 years).

During the study, the neurocognitive status (measured, among other things, by the age-appropriateness of the current grade level at school in pediatric patients and by impairment of cognitive functions) did not reveal deteriorations or progression. The same applies to hearing impairment and sensorineural hearing loss – a common manifestation of CAPS.

Hearing loss based on current audiogram findings has been reported as unchanged for 85.7% of CAPS-patients at baseline, 78.6% at month 30 and 75.0% at month 60. In addition, relevant markers of inflammation including CRP, SAA, ESR, neutrophils, and S100A8 remained stable throughout the study.

At the analysis cut-off date (December 2023), a total of 1286 adverse events (AE) occurred in n=198 patients (73.9%). of which 135 events were classified serious AE (SAE) and 35 were considered serious adverse drug reactions (SADR). Overall, SAE and SADR were reported in n=50 (18.7%) and in n=14 (5.2%) of patients.

Conclusion: The interim analysis of the RELIANCE study affirms the long-term safety of canakinumab treatment as well as its effectiveness in controlling common long-term complications caused by autoinflammatory periodic fever syndromes. Thus, results from this study add to the available evidence for the safety and efficacy of long-term use of canakinumab.

Disclosure of Interest: M. Krusche Grant /Research support from: Novartis, Sobi, Consultant for: Novartis, Sobi, Paid instructor for: Novartis, Sobi, N. Blank Grant /Research support from: Novartis, Sobi, Consultant for: Novartis, Sobi, J. Henese Grant /Research support from: Novartis, Roche, Sobi;, Consultant for: Novartis, Speaker bureau of: AbbVie, AstraZeneca, BMS, Boehringer-Ingelheim, Chugai, Janssen, Novartis, Pfizer, GSK, Sobi, Roche, UCB., A. Pankow Grant /Research support from: Novartis, T. Kallinich Grant /Research support from: Novartis, B. Kortus-Goetze Grant /Research support from: Novartis, P. Oommen: None declared, T. Krickau Grant /Research support from: Novartis, Consultant for: Novartis, Speaker bureau of: Novartis, C. Schütz Grant /Research support from: Novartis, F. Ivan Grant /Research support from: Novartis, Consultant for: Novartis, G. Horneff Grant /Research support from: AbbVie, Chugai, Merck Sharp & Dohme, Novartis, Pfizer and Roche, Speaker bureau of: AbbVie, Bayer, Chugai, Merck Sharp & Dohme, Novartis, Pfizer and Roche., R. Jürgen Grant /Research support from: Novartis and Sobi, Consultant for: AbbVie, Biogen, BMS, Chugai, GSK, Janssen, Lilly, MSD, Mylan, Novartis, Roche, Sanofi, Sobi and UCB., Speaker bureau of: AbbVie, Biogen, BMS, Chugai, GSK, Janssen, Lilly, MSD, Mylan, Novartis, Roche, Sanofi, Sobi and UCB, F. Weller-Heinmann Grant /Research support from: Novartis, M. Hufnagel Grant /Research support from: Novartis, T. Kuempfel Grant /Research support from: Novartis, F. Meier Grant /Research support from: Novartis, F. Dressler Grant /Research support from: Novartis, Consultant for: AbbVie, Mylan, Novartis and Pfizer., D. Windschall Grant /Research support from: Novartis, I. Andreica Consultant for: AbbVie, Chugai, Novartis, UCB, Galapagos, Takeda, AstraZeneca, Lilly, Boehringer Ingelheim, Amgen and Sobi, Speaker bureau of: AbbVie, Chugai, Novartis, UCB, MSD, Lilly, Sobi, AstraZeneca, Amgen, Pfizer and Gilead, M. Borte Grant /Research support from: Pfizer, Shire, and Novartis, M. Fiene Grant /Research support from: Novartis, J. Kuemmerle-Deschner Grant /Research support from: Novartis and Sobi, Speaker bureau of: Novartis and Sobi

Identifier: PT51

AUTOINFLAMMATORY DISEASES IN THE NETHERLANDS: CLINICAL AND GENETIC INSIGHTS FROM THE EUROFEVER REGISTRY

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Introduction: The prevalence and clinical manifestation of autoinflammatory diseases varies per region and disease, even among patients with identical genetic mutations or within the same patient residing in a different country. These variations suggest that treatment might need to differ from other countries in the Netherlands. This is the first description of a cohort of patients with all autoinflammatory diseases in the Netherlands.
Objectives: This study aims to describe the patients with autoinflammatory diseases in the Netherlands. Additionally, this study aims to describe current treatment practices and associated outcomes.
Methods: Data from the Eurofever registry, which collects information on monogenic and complex autoinflammatory diseases, was analyzed. Three Dutch university medical centres began contributing in 2015, expanding to all eight centres in 2019. Data was extracted in June 2024, including patients residing in the Netherlands registered between 2015 and 2024. The analysis focused on the four most common monogenic diseases, as well as systemic undefined recurrent fever (SURF) and Periodic Fever Aphthous stomatitis Pharyngitis and cervical Adenitis syndrome (PFAPA). For these conditions, genetic characteristics, treatment practices, and outcomes were described.
Results: Data on 425 patients was recorded. Familial Mediterranean fever (FMF) was the most common diagnosis (113, 27%), followed by systemic undefined recurrent fever (SURF)(83, 20%). The most frequent mutations were Met694Val homozygosity in FMF (14, 21%), Val377Ile/Ile268Thr in Mevalonate Kinase Deficiency (MKD)(10, 18%), Trp414Leu in Cryopyrin associated periodic fever syndrome (CAPS)(4, 11%) and Arg92Gln in Tumor necrosis factor-receptor associated periodic syndrome (TRAPS)(5, 22%). Genetic testing was performed in 96% (221/230) of patients with monogenic diseases but was less frequent for SURF (18, 22%) and PFAPA (4, 19%), and if performed results were predominantly negative (SURF: 56, 67%, PFAPA: 16, 76%).

The most used first treatments varied: colchicine for FMF (99, 88%) and SURF (18, 22%), Anakinra for MKD (10,18%), CAPS (16, 43%), and TRAPS (5, 22%), and prednisone for PFAPA (6, 29%). Follow-up data (168 patients, 40%) showed variation in treatment use and remission rates (Table 1). In SURF, no medication was most commonly used (6, 24%) with remission in 2 patients (8%). For PFAPA, Anakinra was the most common treatment (2, 33%), achieving remission in 1 patient (17%).

Table 1. Treatment and disease status at last follow-up visit of the four most common monogenic diseases

	FMF (n=57)		**MKD (n=19)**				**TRAPS (n=10)**	
	Patients using	Patients in remission (28, 49%)	Patients using	Patients in remission (5, 26%)	Patients using	Patients in remission (16, 73%)	Patients using	Patients in remission (3, 30%)
Colchicine*	29 (51%)	11 (38%)	0	0	0	0	0	0
Canakinumab + Colchicine* (+Prednisone)*	10 (18%) (+1 (2%))	5 (50%) (+0)	1 (5%) (+0)	0 (+0)	0 (+0)	0 (+0)	0 (+0)	0 (+0)
no medication*	7 (12%)	5 (71%)	6 (32%)	2 (33%)	2 (9%)	2 (100%)	5 (50%)	3 (60%)
Canakinumab*	6 (11%)	6 (100%)	6 (32%)	1 (17%)	12 (55%)	10 (83%)	2 (20%)	0
Adalimumab* (+ Colchicine + Mycophenolate mofetil + Prednisolone)*	0 (+1 (2%))	0 (+1 (100%))	0 (+0)	0 (+0)	1 (5%) (+0)	1 (100%) (+0)	0 (+0)	0 (+0)
Anakinra* (+ Colchicine)*	0 (+1 (2%))	0 (+0)	4 (21%) (+0)	1 (25%) (+0)	2 (9%) (+0)	1 (50%) (+0)	3 (30%) (+0)	0 (+0)

Canakinumab + Prednisolone*	1 (2%)	0	0	0	0	0	0	0
Colchicine + Secukinumab*	1 (2%)	0	0	0	0	0	0	0

*number of patients and percentage (n (%))

Conclusion: This study provides the first nationwide description of 425 patients with autoinflammatory diseases in the Netherlands. FMF was the most prevalent diagnosis. Genetic testing was frequently performed in monogenic diseases, but findings were rare in SURF and PFAPA (15, 18%; 3, 14%). Only 168 patients (40%) had follow-up data, showing varied treatment outcomes. These results highlight the need for improved therapeutic strategies and follow-up care (and registration thereof) to improve outcomes.
Disclosure of Interest: None declared

Identifier: PT52

EULAR/PRES ENDORSED RECOMMENDATIONS FOR THE MANAGEMENT OF FAMILIAL MEDITERRANEAN FEVER (FMF): 2024 UPDATE

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Introduction: Familial Mediterranean fever (FMF) is the most common monogenic auto-inflammatory disease. However, many rheumatologists are not well acquainted with its management.

Objectives: These evidence-based recommendations update the ones issued in 2016 and aim to guide rheumatologists and other health professionals in the treatment and follow-up of patients with FMF.

Methods: A multidisciplinary panel was assembled, including rheumatologists, paediatricians, a nephrologist, an occupational therapist, a physiotherapist, two methodologists, and two patient representatives, all from the Eastern Mediterranean area and Europe. Several systematic reviews were performed on the pharmacological treatment of FMF and its complications. The previous recommendations were revised considering the updated evidence, and the new levels of evidence were incorporated. The agreement with the recommendations was obtained through a Delphi survey.

Results: The final set comprises 4 overarching principles and 12 recommendations, each presented with its degree of agreement (0-10), level of evidence, and rationale. The degree of agreement was greater than 9/10 in all instances, and the level of evidence improved in most updated statements. Improving adherence is emphasized as an important aspect in several statements. These new recommendations include a priority set, quality indicators, and other suggested implementation strategies.

Conclusion: This study presents a set of widely accepted recommendations for treating and monitoring FMF, supported by the best available evidence and expert opinion. These recommendations are valuable for guiding physicians in caring for patients with FMF.

Acknowledgments: EULAR provided financial support for organising the meetings and a research grant for the fellows (ES, TO) in the framework of the international Task Force QoC018 to update the recommendations for the management of FMF.

Disclosure of Interest: None declared

Identifier: PT53

A PATIENT WITH A NOVEL DOCK11 MUTATION MANAGED WITH COLCHICINE: A ROLE FOR PYRIN IN DOCK11-ASSOCIATED DISEASE?

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Introduction: An X-linked recessive inflammatory disease has been recently identified associated with *DOCK11* (dedicator of cytokinesis 11) mutations.
Objectives: To present a patient with DOCK11-associated disease, who is hemizygous for a novel *DOCK11* variant and treated with colchicine.
Methods: Genome sequencing was performed in the proband, his parents, and two unaffected half-sisters at the *National Institutes of Health* Intramural Sequencing Center. The identified variant was confirmed by Sanger sequencing. In-silico thermodynamic protein stability predictions were made based on the predicted 3D structure of DOCK11, by calculating the change in Gibbs free energy (ΔG) with INPS-3D, DynaMut2, and PremPS (ΔG threshold=0.5).
Results: Our patient is an 8-year-old boy, born to unrelated parents. He had a history of extended bleeding after circumcision, unexplained nosebleeds, and recurrent upper respiratory tract infections and otitis media. He has had recurrent fever attacks with abdominal pain, headache, arthralgia, and urticaria-like rash since he was nine months old. The attacks recurred twice every month and lasted for 3-5 days. Colchicine was started when he was seven. The attack frequency decreased, and the attacks were shorter (~1 day) under colchicine. He also has intermittent diarrhea and mild anemia. His platelet function tests were normal except extended closure times with ADP and epinephrin. He currently has one attack per 2 months under colchicine. His 47-year-old maternal uncle has a similar history, and we plan to get a DNA sample from him to check *DOCK11* variants.

The patient was hemizygous for the p.Arg1523Ser variant in *DOCK11*. His mother and maternal half-sister were heterozygotes, while the variant was absent in his father and paternal half-sister. This variant has not been reported before. Its very low frequency in GnomAD (0.000007) and high in-silico scores (CADD 25.3; REVEL 0.41; α-missense 0.99) suggest pathogenicity. Also, the variant is predicted to destabilize DOCK11 (Dynamut2=-1.37;PremPS=1.65;INPS-3D=-1.58).

Conclusion: There are only two recent studies in the literature reporting 12 patients with DOCK11-associated disease. The disease phenotype is diverse, with autoimmune features (autoimmune cytopenia, systemic lupus erythematosus) predominating in some patients and severe inflammatory phenotype in others (acute respiratory distress syndrome or systemic inflammatory response syndrome). Skin rash, digestive manifestations, and normocytic anemia were also present in some patients. Recurrent fever episodes, like those in our patient, have been reported in only one case. Our patient is unique since he has a novel mutation, and his disease is under control with colchicine. DOCK11 activates a small Rho GTPase called CDC42. CDC42 activity has been demonstrated to decrease in DOCK11-associated disease. CDC42 has a role in pyrin regulation but the exact nature of their interaction remains unknown. Its activation negatively regulates pyrin inflammasome activity by inducing pyrin phosphorylation. However, recent studies have shown that CDC42 is required for pyrin inflammasome activity independent of its GTPase activity. DOCK11-CDC42-pyrin interaction has not been investigated in depth in patients with DOCK11-associated disease. Considering the response to colchicine treatment and the phenotype with recurrent fever flares in our patient, we can hypothesize that the pyrin inflammasome has a role in disease pathogenesis. We plan functional studies to explore the DOCK11-CDC42-pyrin axis more, which could shed light on the unknown aspects of the disease pathogenesis.
Disclosure of Interest: E. D. Batu: None declared, D. L. Stone: None declared, J. J. Chae: None declared, C. Esperanzate: None declared, T. Romeo: None declared, H. Ercan Emreol: None declared, N. Deuitch: None declared, S. Ozen Consultant for: Novartis, Sobi, Speaker bureau of: Novartis, Sobi, D. L. Kastner: None declared

Identifier: PT54

BIOMARKER EVALUATION OF DISEASE ACTIVITY AND CARDIOVASCULAR RISK IN FAMILIAL MEDITERRANEAN FEVER

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Introduction: Familial Mediterranean Fever (FMF) is an autoinflammatory disease that is characterized by recurrent fevers and serositis. Persistent subclinical inflammation may contribute to the development of atherosclerosis and accelerated disease progression, which may potentially result in organ damage, including amyloidosis.
Objectives: This study examines the potential of specific serum biomarkers, including soluble urokinase plasminogen activator receptor (suPAR), soluble ST2 (sST2), oxidized low-density lipoprotein (oxLDL), trimethylamine N-oxide (TMAO), and NOD-like receptor protein 3 (NLRP3), for predicting cardiovascular risk and disease damage in FMF. The analysis examines the associations between these biomarkers and a range of clinical and laboratory parameters, disease activity-damage scores (ADDI and ISSF), and cardiovascular risk (SCORE2). It is hypothesized that these biomarkers will correlate with both disease activity and cardiovascular risk.
Methods: Consecutive patients diagnosed with FMF, aged ≥18 years, were enrolled at the Gazi University outpatient rheumatology clinic between January and September 2023. The following data were collected: demographic information, smoking history, family history, and laboratory findings. Patients were classified according to their clinical and laboratory characteristics, including colchicine resistance, defined as the persistence of FMF attacks (at least one attack per month) despite the regular and adequate use of colchicine at the maximum tolerated or recommended dosage for a minimum of six months. The SCORE2, ISSF, and ADDI scores were calculated, and the laboratory data were obtained from the hospital system. The relationships between variables were assessed using Kendall's tau.
Results: The study included 104 FMF patients and 46 controls. The FMF cohort was predominantly female (61.5%), mean age 38.9 ± 12.6 years; 24% had hypertension. Among FMF patients, 65 were colchicine-responsive and 39 were resistant. Median suPAR levels were significantly higher in the resistant group (1.58 ng/mL, IQR: 2.82) vs. responsive (0.85 ng/mL, IQR: 1.49) ($p=0.036$). The median ADDI score was 0 (IQR: 2). Significant positive correlations were found between ADDI scores and serum suPAR ($\tau=0.230$, $p=0.004$) and sST2 ($\tau=0.172$, $p=0.030$). The median ISSF score was 2 (IQR: 3). Patients with mild disease (ISSF ≤2) had significantly lower suPAR levels compared to those with moderate-severe disease (ISSF >2) ($p=0.026$). No significant correlations were observed between serum oxLDL or NLRP3 and creatinine, albuminuria, or proteinuria. However, significant positive correlations were found between suPAR and creatinine ($\tau=0.196$, $p=0.005$), albuminuria ($\tau=0.151$, $p=0.046$), and proteinuria ($\tau=0.166$, $p=0.020$). Similarly, sST2 levels showed positive correlations with albuminuria ($\tau=0.217$, $p=0.004$) and proteinuria ($\tau=0.191$, $p=0.007$), with a weak positive trend with creatinine ($\tau=0.127$, $p=0.065$). Stratification by SCORE2 risk showed a significant trend for increased suPAR ($p=0.01$) and sST2 ($p=0.003$) with increasing risk category.
Conclusion: Serum suPAR and sST2 levels correlate with albuminuria and proteinuria, indicating their potential for early identification of FMF patients at risk for renal complications, such as amyloidosis. Additionally, suPAR's association with ADDI and ISSF, and sST2's association with ISSF, along with their positive correlations with SCORE2, reinforce their relevance in disease monitoring and treatment personalization. Prospective studies are necessary to confirm these findings.

Disclosure of Interest: None declared

Identifier: PT55

CLINICAL PRACTICE STRATEGIES FOR THE USE OF BDMARDS IN COLCHICINE RESISTANT FAMILIAL MEDITERRANEAN FEVER ACROSS THE COUNTRIES; A CLIPS NETWORK INTERIM ANALYSIS

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Introduction: Familial Mediterranean Fever (FMF) is the most common AID. Affected patients require lifelong medication. In some situations, biologics may be indicated in FMF. Although evidence or consensus-based recommendations for treatment for colchicine resistant FMF (crFMF) exist, they are difficult to implement in a real-life setting due to the wide array of (country-specific) medical systems and financial capacities.

Objectives: We aimed to provide data reflecting the prescription habits of biological disease modifying antirheumatic drugs(bDMARDs) by physicians around the world to treat colchicine resistant FMF and to identify the strategies that doctors follow when using bDMARDs in clinical practice.

Methods: A global survey entitled 'Biologics in Monogenic Autoinflammatory Diseases', conducted as part of the COST-funded Clinical Implementation Strategies (CLiPS) initiative analyzed physicians' responses to 12 questions related to the indication and the management of (bDMARDs) in monogenic FMF. This publication is based upon work from COST Action CA21168 – Improving outcome of Juvenile Inflammatory Rheumatism via universally applicable clinical practice strategies (JIR-CliPS),supported by COST (European Cooperation in Science and Technology) - www.cost.eu ». We performed on May 2024 an interim analysis of the respondents of the bDMARDS in FMF questionnaire.

Results: Sixty-four participants responded on questions from block «Starting a bDMARD». Fifty-eight participants choose anti-IL1 for management of crFMF, 5 participants choose Anti-TNF and one participant choose anti-IL6. To assess how physician monitor patients with bDMARDS, we proposed several items based on clinical and biological targets. Sixty-two participants responded to the questions about targets.Among the participants, 26 selected a strict treatment target (0 attacks and CRP/SAA within the normal range), with the goal of achieving fewer than 1 flare over 6 months. Twenty-five participants favored a mild target, with 23 of them aiming for fewer than 2 flares or 50% flare reduction in 6 months and a normal CRP or SAA range. Nine participants accepted any reduction in attack severity, set as a goal 30 to 90% reduction of flares over 6 months, provided CRP remained within the normal range.

Regarding the frequency of monitoring of and routine laboratory, Thirty-seven participants monitor their patients under bDMARDS every 3 months. All of participants choose CRP for monitoring and 49 participants choose also ESR. Other laboratory markers included , SAA (N=17), S100 (N=5) and IL18(N=2). In the third part of the questionnaire, we inquired about modifying the treatment if the disease is not under control. Twenty- eight participants considered modifying biologics within 3 months if the disease is not controlled whereas, 25 participants choose to wait 6 months before modifying bDMARD. Regarding the number of episodes of elevated biomarkers, 31 participants allowed more than 2 episodes, while 28 allowed a maximum of 2 episodes.

Conclusion: Our interim analysis of this part of the questionnaire showed that in FMF, IL1 blocker seems indeed to be the first line treatment if a bDMARD is indicated . The most commonly prescribed biological marker was CRP. Interestingly, most of responder consider to modify biologics within 3 months if the disease is not controlled. The final analysis of the questionnaires will serve to elucidate the underlying causes of discrepancies between the observed results and international recommendations.

Disclosure of Interest: None declared

Identifier: PT56

COMPOUND HETEROZYGOSITY FOR MEFV I692DEL AND V726A PATHOGENIC VARIANTS IS ASSOCIATED WITH A SEVERE PHENOTYPE OF PYRIN-ASSOCIATED AUTOINFLAMMATORY DISEASE WITH ELEVATED INTERLEUKIN-18

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Introduction: Patients who are compound heterozygotes for the I692del and V726A *MEFV* pathogenic variants have a severe inflammatory disease with features that are atypical of familial Mediterranean fever (FMF).
Objectives: To describe the clinical findings, laboratory testing, and research studies of 53 patients who have at least one copy of the I692del variant. These patients were seen at NIH or identified through international collaboration.
Methods: We performed genotyping and laboratory testing, including IL-18, IL-18 BP, and free IL-18, on available samples. We also collected genotypes, clinical histories, laboratory values, and responses to treatment of patients followed by collaborators. We performed whole exome sequencing (WES) of 3 NIH patients to look for modifying alleles. The NanoString array tested for type I interferon (IFN) gene expression signature. Patients' whole blood samples were stimulated with IFNα, IFNγ, and IL-10 for pSTAT1 and pSTAT3 expressions. Liver biopsy tissue from the previously reported Japanese patient with autoimmune hepatitis was stained for inflammatory cytokines.

Results: All but one patient identified were of Egyptian, Lebanese, or Moroccan ancestry, suggesting a founder effect for the I692del *MEFV* variant in North Africa. Three patients were compound heterozygotes for I692del/M694I, 5 were homozygotes for I692del, and 45 were compound heterozygotes for I692del/V726A. Most also carried the E148Q common variant. One of the I692del homozygotes was the asymptomatic parent of several affected children. Three of the remaining four I692del homozygotes had mild disease.

Unusual clinical features included neutrophilic dermatoses, inflammatory bowel disease (IBD), arthritis, autoimmune hepatitis, aseptic meningitis, optic neuritis, severe anemia requiring transfusions, amyloidosis, and episodes of cytokine storm. Most patients had a poor response to colchicine and required therapy with anti-IL-1 medication, but treatment was limited by availability. Two patients followed at NIH required combination therapy with anti-IL1 and anti-TNF agents for IBD and skin abscesses.

Almost all (29/30) compound heterozygotes for I692del and V726A had high serum IL-18 and detectable free IL-18. Three NIH patients with the I692del/V726A genotype had persistent neutropenia and elevated zinc and aldolase even when their inflammation was well-controlled.

One Egyptian proband with the I692del/V726A genotype died during an episode of cytokine storm, as did three un-genotyped siblings from two other families. One proband with the I692del/V726A genotype survived a similar episode. One NIH patient with the I692del/V726A genotype experienced a life-threatening hyperinflammatory episode but recovered after treatment with high-dose steroids and anakinra.

Immunostaining the liver biopsy from the child with autoimmune hepatitis revealed a high expression of IL-18, IL-1b, and TNF cytokines localized to CD68+ tissue macrophages but not in the hepatocytes. High expression of pSTAT1, calculated as a fold change over pSTAT1 expression in healthy control, was prominent in the patient's total monocytes, myeloid cells CD11b+, dendritic cells (CD14-CD16- HLA-DR+) and neutrophils (CD66b+ CD16++) in response to IFNα, and IFNγ.

Conclusion: Compound heterozygosity for the I692del and V726A variants is associated with severe disease with clinical features atypical of classic FMF. These patients likely require an IL-1 inhibitor to normalize inflammatory biomarkers and should have close monitoring of inflammatory markers, SAA, renal function, and proteinuria to detect AA amyloidosis early. Episodes of cytokine storm should be treated aggressively. Functional studies in progress suggest a strong inflammatory signature in myeloid cells that necessitates further investigations.

Disclosure of Interest: None declared

Identifier: PT57

CLINICAL FEATURES OF PATIENTS WITH FAMILIAL MEDITERRANEAN FEVER OVER 50 YEARS OF AGE: A SINGLE-CENTER EXPERIENCE

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Introduction: Familial Mediterranean Fever (FMF) is the most common hereditary monogenic fever syndrome, and attack characteristics are affected by pathophysiological changes due to aging. The characteristics and frequency of attacks can change throughout the life of patients, in other words, the progression of disease is affected by pathophysiological changes with aging.
Objectives: It is still unclear whether the activity of FMF decreases with age, especially in patients over 50 years old due to limited data. The main objective of this cross-sectional study was to examine the effect of aging on the clinical features and course of FMF by analyzing the experience of a single tertiary center in older FMF patients.
Methods: Three hundred forty-three patients who were followed up with the diagnosis of FMF were included. The demographic characteristics of the patients, MEFV mutations, attack characteristics, and the treatments they received were analyzed retrospectively. Attack characteristics, frequency of attacks, and other characteristics of the patients were also analyzed and compared before treatment, after treatment, and the latest attacks.
Results: Among 343 patients, the median number of attacks per year before treatment was 12 (IQR:4-24). After treatment, it was 1 (IQR: 0-4), and during the last year, it was 0 (IQR: 0-3). A significant difference was found in the number of attacks before treatment, after treatment, and during the last year ($p<0.001$). The patients' VAS disease severity scores were evaluated before treatment, after treatment, and after the latest attacks. The mean VAS scores before and after treatment were 8.05 ± 1.78 and 2.91 ± 2.53, respectively ($p<0.001$). During the latest attacks, the mean VAS score of the patients significantly decreased to 1.75 ± 2.38 ($p<0.001$). In two groups based on the presence of an attack in the last year, the mean amount of current colchicine dose and the maximum dose of colchicine throughout treatment were greater in patients who had experienced an attack in the last year ($p=0.002$ and $p=0.02$, respectively). Patients who did not experience an attack in the last year were relatively older ($p=0.005$, Table 1).

Table 1: Characteristics of patients who did not experience any attack in the last year and patients who experienced at least one attack in the last year

	Patients who did not experience attacks (n=181)	Patients who experienced attacks (n=162)	p-value
Gender (Female), n (%)	102 (56)	122 (75)	**<0.001**
Age (years), mean ± SD	58.2 ± 6.43	56.9 ± 6.52	**0.005**

Colchicine dose during the latest follow-up (mg/day), mean ± SD	1.24 ± 1.0	1.35 ± 0.453	**0.002**
Maximum colchicine dose (mg/day), mean ± SD	1.53 ± 0.375	1.68 ± 0.485	**0.02**
Initial colchicine dose (mg/day), mean ± SD	1.38 ± 0.330	1.37 ± 0.429	0.801
Compliance with colchicine, n (%)	118 (65.2)	94 (58.0)	0.173
Response to colchicine, n (%)	173 (95.5)	152 (93.8)	0.467
Dose-skipping during colchicine treatment, n (%)	44 (24.3)	57 (35.2)	**0.028**
Resistance to colchicine, n (%)	17 (9.4)	28 (17.3)	**0.047**

Conclusion: Findings of our study suggest a potential association between aging and milder FMF symptomatology, indicating the possibility of reduced reliance on colchicine therapy in aging FMF patients. There was a notable decrease in attack frequencies and a discernible correlation between the reduction in patient complaints and the corresponding decrease in colchicine doses administered. The observed decline in symptom severity with age prompts further investigation into the underlying mechanisms and implications for FMF management.

Disclosure of Interest: None declared

Identifier: PT58

CANAKINUMAB TREATMENT IN PATIENTS WITH FAMILIAL MEDITERRANEAN FEVER: A TERTIARY CENTER EXPERIENCE

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Introduction: Canakinumab is an option of second-line agents in familial Mediterranean fever (FMF) after an insufficient colchicine treatment. The efficacy and safety of canakinumab in patients with FMF have been mainly proven by randomized controlled trials; however, real-life studies are needed to analyze the treatment retention and characterize the side effect profile as some patients might needed to be withdrawn from the canakinumab usage after suffering from new attacks.
Objectives: Here, we aimed to describe our examinations of the patients with FMF that were discontinued or were decided to be continued with canakinumab treatment.
Methods: In this study, we retrospectively reviewed the charts of the patients with FMF followed up at our tertiary autoinflammatory diseases clinic, diagnosed according to the Tel-Hashomer criteria, who had received at least three doses of canakinumab treatment. Pregnant patients were excluded from the analysis. The patients were analyzed for genetic mutations for FMF. Diagnostic delay, colchicine dose prior to canakinumab, CRP levels before canakinumab and the existence of the amyloidosis disease were recorded for the patients that were treated with canakinumab.
Results: A total of 110 FMF patients who had used canakinumab were identified. The patients were primarily female (%59,6), were aged 37.8 ± 12.2 and with the age of onset being 11.71 ± 9.997. Fifty-eight patients were homozygous for the M694V mutation (%56,86); twenty-three of the patients were among the failed discontinuation patients (%52,27), nineteen of them were the continued ones (%65,51) and sixteen of the patients were from the successful discontinuation patients (%55,17). %25,5 of the patients that were discontinued from the treatment were also diagnosed with amyloidosis (p:0,023). %93,3 of the continued patients were suffered from fever (p:0,048). Other parameters like inflammatory comorbidities, abdominal and chest pain, joint involvement (Table 1) were not detected significant with p score.

Table 1 Clinical Treatment Features

Parameter	**Failed Discontinuation**	**Continued**	**Successful Discontinuation**	**All Patients**
Diagnostic Delay	***5.00 ± 6.91***	***8.43 ± 12.03***	***8.37 ± 10.83***	***6.95 ± 9.8***
*Amyloidosis**	***%25.5 (12)***	***%10 (3)***	***%6.67 (2)***	***%15.9 (17)***
Colchicine Dose Prior to Canakinumab	***2.26 ± 0.68***	***2.30 ± 0.74***	***2.60 ± 1.14***	***2.4 ± 0.8***

CRP before Canakinumab	***58.17 ± 59.71***	***%80.7 (25)***	***1.30 ± 0.57***	***1.2 ± 0.4***
Inflammatory Comorbidities	***%40.4 (19)***	***%35.5 (11)***	***32.3 (10)***	***%36.7 (40)***
Abdominal Pain	***%80.9 (38)***	***%96.7 (29)***	***%83.3 (25)***	***%85.98 (92)***
Chest Pain	***%53.2 (25)***	***%50.0 (15)***	***%53.3 (16)***	***%52.3 (56)***
*Fever***	***%65.96 (31)***	***%93.3 (28)***	***%73.3 (22)***	***%75.7 (81)***
Joint Involvement	***%76.6 (36)***	***%83.3 (25)***	***%70.0 (21)***	***%76.6 (82)***

* Amyloidosis in patients with failed withdrawal (p: 0,023)
** Fever in patients with never withdrawn (p: 0,048)

Conclusion: As a result of our study, we reached a consensus that many patients who had fever as a complain were not qualifed for the discontinuation of canakinumab treatment. Moreover, patients with amyloidosis diagnose were not decided adequate for a fully discontinuation of canakinumab and were decided to be continued with the treatment. Noncompliance remains a major issue which necessitates the need for the measures to increase retention.
Disclosure of Interest: None declared

Identifier: PT59

CLINICAL PRACTISE STRATEGIES FOR THE DEFINITION OF COLCHICINE RESISTANCE IN FAMILIAL MEDITERRANEAN FEVER ACROSS THE COUNTRIES; A CLIPS NETWORK ANALYSIS

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Introduction: Although colchicine is the mainstay of the Familial Mediterranean Fever (FMF) treatment, about 5-10% of the patients are considered to be colchicine resistant. However, there is no globally agreed colchicine resistance definition and clear indications for use of biologic treatment options.

Objectives: We aimed to provide data reflecting the different colchicine resistance definitions and bDMARD indications that were stated by the physicians from different countries.

Methods: A survey on "Biologics in Monogenic Autoinflammatory Diseases", part of the "Clinical Implementation Strategies" (CLiPS) initiative, was conducted by the JIR cohort among physicians worldwide. Participants' answers to 25 questions on colchicine resistance were analyzed. The data were analyzed in two main parts "Colchicine resistance suspicion" and "Colchicine resistance decision" and a flow chart was created for these parts. Descriptive statistics were used. Responses that were deemed invalid or had a frequency below 5% were excluded from the flow chart.

Results: Responses from 223 physicians from 46 countries could be analyzed.Five potential criteria for defining colchicine resistance were evaluated. The most frequently endorsed criteria included attack severity (72% yes), complications (69% yes), and high activity scores (60% yes). In contrast, quality of life scales (70% no) and patient-reported outcomes (60% no) were less commonly supported.

The central question focused on attack frequency over the past 6 months and markers of subclinical inflammation. The most common response for attack frequency was 3–4 attacks (n=73, 46%). For subclinical inflammation, the most frequently reported markers were elevated C-reactive protein levels (n=157), erythrocyte sedimentation rate (n=79), serum amyloid A (n=79), and white blood cell count (n=60).

94 % of respondents increase colchicine to the maximum tolerated dose before diagnosing colchicine resistance. For ages <12 and 13-18 years, the common maximum dose was 1.6mg-2mg (45%, 44% respectively); for adults, it was 2.1mg-2.5mg (36%). The follow-up interval in the case of colchicine resistance suspicion was 3 months for more than half of the participants (51%). The most common reported follow-up duration before making a final decision was 3–4 months (47%). Colchicine resistance was confirmed if suspicion remained after this evaluation.

Conclusion: The study highlights various clinical approaches and decision-making processes for managing colchicine resistance in FMF by practitioners from around the world. The results provide a comprehensive framework for developing therapeutic strategies for FMF.

Acknowledgments: This article/publication is based upon work from COST Action CA21168 – Improving outcome of Juvenile Inflammatory Rheumatism via universally applicable clinical practice strategies (JIR-CliPS),supported by COST (European Cooperation in Science and Technology) - www.cost.eu

Disclosure of Interest: None declared

Identifier: PT60

EPIDEMIOLOGICAL AND ECONOMICAL FACTORS INFLUENCING THE COLCHICINE RESISTANCE DEFINITIONS FOR FAMILIAL MEDITERRANEAN FEVER ACROSS THE COUNTRIES; A CLIPS NETWORK ANALYSIS

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Introduction: Although colchicine remains the primary treatment modality of Familial Mediterranean Fever (FMF), approximately 5-10% of patients are considered colchicine-resistant. However, there is no universally accepted definition of colchicine resistance, nor are there clear indications for the utilization of biologic disease-modifying antirheumatic drugs (bDMARDs).

Objectives: We aimed to investigate whether clinical approaches to defining colchicine resistance in FMF differ based on physician experience, FMF prevalence, gross domestic product (GDP), drug availability, and reimbursement policies across countries.

Methods: A global survey entitled 'Biologics in Monogenic Autoinflammatory Diseases', conducted as part of the COST-funded Clinical Implementation Strategies (CLiPS) initiative and coordinated by the JIR cohort, analyzed physicians' responses to 25 questions related to colchicine resistance. Participants were categorized according to their level of experience: low (<5 years), medium (5-10 years) and high (>10 years). Responses were further categorized according to the prevalence of FMF in the respondent's country as low endemic, moderate endemic or high endemic. Countries were also grouped into low, medium and high GDP categories. Finally, responses were stratified into two groups based on the availability and reimbursement of biologicals: available and reimbursed (A/R) or not available and/or not reimbursed (not A/R). Comparisons were performed using the chi-square test or Fisher's exact test, where appropriate. Holm-Bonferroni correction was applied for tables larger than 2x2.

Results: In total, 223 responses from 46 distinct countries were included into the analysis. "Treatment or prevention of event-induced flares" was significantly more frequently stated as a bDMARD indication in high endemic countries compared to others (p=0.048). In the group with high experience, the following factors were more frequently considered in defining colchicine resistance than in the medium or low-experienced group: (i) ESR (p=0.049) and

Calprotectin (p=0.049), (ii) patient-reported outcomes (p=0.001), and (iii) missed school/work days (p=0.001). Furthermore, colchicine intolerance (p=0.048) was a significantly more prevalent indication for the use of biologic disease-modifying antirheumatic drugs (bDMARDs) compared to the other groups. In the high-GDP group, missing school/work days was significantly more frequently considered in the definition of colchicine resistance (p=0.04), while a *'1-month'* follow-up interval for suspected colchicine resistance was significantly less common (p=0.001) compared to other groups. In the *biologics A/R* group, elevated CRP (p=0.005) and SAA (p=0.008) during the attack-free period, as well as patient-reported outcomes (p=0.031), were significantly more utilized. Additionally, increasing colchicine dosage prior to defining resistance was more frequently employed in this group (p=0.004), whereas a *'1–2 month'* follow-up duration was significantly less common for confirming colchicine resistance (p=0.011).

Conclusion: The investigation elucidates the multifaceted clinical methodologies and decision-making processes for addressing colchicine resistance in FMF. Variations are significantly influenced by physician experience, FMF prevalence, gross domestic product (GDP), and the availability and reimbursement policies of biologic agents across different countries.

Disclosure of Interest: None declared

Identifier: PT61

TRISOMY 8 MOSAICISM WITH MULTIPLE AUTOINFLAMMATORY MANIFESTATIONS INCLUDING CHRONIC NON-BACTERIAL OSTEOMYELITIS

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Introduction: Trisomy 8 mosaicism is a rare genetic condition with heterogeneous phenotype. Features can include facial dysmorphism, tall stature, mild intellectual disability, camptodactyly, arthrogryposis, and vertebral, urinary and cardiac anomalies. Recurrent fevers, rash and a Bechet's-like syndrome have been described in constitutional trisomy 8 mosaicism, and in myelodysplastic syndromes with acquired trisomy 8 in bone marrow, thought due to NF-κB pathway activation[1-3]. To our knowledge this is the first report of chronic non-bacterial osteomyelitis (CNO) as part of the autoinflammatory phenotype in trisomy 8 mosaicism.
Objectives: To describe the autoinflammatory phenotype of this individual with trisomy 8 mosaicism, including CNO, and treatment strategies employed.
Methods: Case report
Results: The patient presented age 9 years with unilateral knee pain and fever. She was initially treated for distal femur osteomyelitis, but represented with multifocal pain and was diagnosed with CNO based on bone biopsy and multiple lesions on whole body MRI. Further history revealed recurrent fevers since early childhood, oral ulceration since age 6, intermittent pruritic photosensitive rash, livedo reticularis and night sweats. She had mild developmental delay. Height was on the 99.6th centile, with advanced bone age. Laboratory tests showed raised CRP (max 56mg/L), ESR (max 44mm/hr) and serum amyloid A (max 361mg/L). Immunology and infection screens were negative. Bone marrow aspirate revealed some leukocyte haemophagocytosis, though no hyperferritinaemia. Next generation sequencing of a panel of genes associated with autoinflammatory syndromes found no known pathogenic variants. Subsequently SNP microarray on DNA extracted from blood revealed a mosaic gain of chromosome 8, estimated to affect approximately 50% of cells. This was confirmed on karyotype, which showed trisomy of chromosome 8 in 7/10 cells examined, with no structural rearrangements.

In terms of management, NSAID (naproxen) was used first-line for CNO, with partial resolution of bony pains. She had an empirical trial of IL-1 blockade (anakinra 2mg/kg), but developed further oral ulceration and new genital ulceration, so this was stopped. She was trialled on colchicine but was unable to tolerate increased doses beyond 750micrograms/day. TNF-α blockade with weekly subcutaneous etanercept (800micrograms/kg weekly) temporarily resolved fevers, ulceration, CNO lesions, and normalised serum amyloid A. After 6 months, she had recurrence of symptoms, and MRI showed CNO lesions in new sites, including sacroiliac joints. Etanercept frequency was increased to every 4 days and colchicine was reintroduced at a low dose. She developed increasing deformities of fingers and wrists. MRI showed mild synovial enhancement with erosions of the carpal bones. Oral methotrexate was added. At this point the genetic diagnosis was discovered. Hand and wrist involvement was thought to represent progressive skeletal anomalies reported in affected individuals, therefore, methotrexate was stopped and colchicine dose gradually increased. There was further symptom improvement and serum amyloid A has remained undetectable for 2 years. She then developed convincing inflammatory arthritis of wrist and knee, so methotrexate was reintroduced. JAK inhibition may be a reasonable next step if the current combination is not adequate.

Conclusion: Trisomy 8 mosaicism is associated with autoinflammatory manifestations, with CNO being a newly described feature in this patient. The underlying molecular pathogenesis leading to these autoinflammatory features in Trisomy 8 mosaicism is yet to be fully elucidated.

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Disclosure of Interest: None declared

Identifier: PT62

IL1 BLOCKADE IN COLCHICINE RESISTANT FAMILIAL MEDITERRANEAN FEVER - REAL WORLD DATA

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Introduction: Canakinumab, an IL-1β inhibitor, has become a cornerstone in managing colchicine-resistant FMF, with emerging evidence suggesting that tapering its use may be feasible for patients achieving sustained remission.
Objectives: This study aims to describe the largest cohort of Familial Mediterranean Fever (FMF) patients to date, focusing on colchicine resistance and the use of anti-IL1 therapy, particularly canakinumab.
Methods: We used data from Clalit Health Services, the largest healthcare organization in Israel, to analyze all FMF patients. The cohort was examined for the use of IL-1 blockade therapy, with a specific focus on treatment patterns, including dose tapering and discontinuation.
Results: Among the cohort of 13,639 FMF patients, 535 (3.9%) were treated with canakinumab, and 178 (1.3%) received anakinra. The study population included 427 FMF patients treated with canakinumab, having at least 26 weeks of follow-up and dosing interval of at least every 8 weeks during the first year of treatment. Over a follow-up period of 123.9 weeks (2.4 years), the dosing interval for canakinumab was reduced, beginning at the mean of every 4.89 weeks during the first year of treatment and extending to the mean of every 5.34 weeks during the second year, and the mean of every 5.92 and 6.55 weeks during the third and fourth years accordingly. 175 (41.0%) patients discontinued canakinumab after a median of 65.1 weeks.127 (29.7%) patients discontinued colchicine therapy after the start of IL-1 blockade.
Conclusion: This study provides real-world evidence on the use of IL-1 blockers, specifically canakinumab, in managing colchicine-resistant FMF. The findings suggest that tapering and even discontinuation of IL-1 therapy is feasible in a subset of patients, offering a potential reduction in treatment burden while maintaining efficacy.
Disclosure of Interest: None declared

Identifier: PT63

CLINICAL CHARACTERISTICS AND TREATMENT STRATEGIES FOR A20 HAPLOINSUFFICIENCY IN JAPAN: A NATIONAL EPIDEMIOLOGICAL SURVEY

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Introduction: A20 haploinsufficiency (HA20) is a hereditary autoinflammatory disease caused by heterozygous loss-of-function variants in the *TNFAIP3* gene. Patients with HA20 present with autoinflammatory Behcet's disease (BD)-like symptoms and may also develop autoimmune diseases. The severity of HA20 varies, with no established clinical guidelines for treatment. For severe cases, administration of molecular target drugs (MTDs), such as anti-tumor necrosis factor (TNF)-α agents, anti-interleukin (IL)-1 agents, and Janus kinase (JAK) inhibitors, is reportedly effective. By contrast, MTDs were found to be ineffective or insufficiently effective in patients with intractable disease. Therefore, it is necessary to elucidate the clinical characteristics of, and suitable treatment methods for, HA20 patients. Herein, we conducted an epidemiological survey of the accumulated data and treatment strategies used in 72 patients with HA20 in Japan. Additionally, we focused on HA20 patients with intractable disease and analyzed their characteristics and treatments.
Objectives: This study aimed to elucidate the clinical characteristics of, and the efficacy of treatments attempted in, patients with HA20 in Japan.
Methods: Records of diagnosed or suspected cases of HA20 were extracted from the registry of the Primary Immunodeficiency Database in Japan (PIDJ), comprising patients who were treated at hospitals collaborating with the PIDJ project or were referred for consultation to the Japanese Society for Immunodeficiency and Autoinflammatory Disease. The diagnosis of HA20 was confirmed via functional analysis of the *TNFAIP3* variant. Questionnaires were sent to the attending physicians for each case, and the following clinical information was retrospectively obtained from medical records: demographics, clinical symptoms, laboratory data, initial diagnosis, treatment, and treatment effects. Treatment effects were evaluated by the attending physician as "effective" (defined as a condition in which symptoms improved to the extent that additional treatment was not required), "improvement", or "ineffective". In this study, "intractable patients" were defined as those who required a change of the initial MTD to alternative agents.
Results: Seventy-two HA20 patients were identified in Japan. And, 54 patients from 37 unrelated families were analyzed in detail. HA20 patients exhibited common features, including recurrent fever, gastrointestinal and musculoskeletal symptoms, and autoimmune disease; various organ disorders (e.g. neurological, liver, and pulmonary diseases) were less common complications. Molecular target drugs (MTDs) were administered in 44.4% of patients, among which anti-tumor necrosis factor (TNF)-α agents showed efficacy in 59.5% of patients. Eleven patients did not experience control of inflammation with initial MTDs, most commonly because of relapse due to secondary failure of MTDs. Anti-drug antibodies were related to the secondary failure of adalimumab in one patient and infusion reactions to infliximab in two patients. In such intractable cases, other treatments (e.g. switching the first MTD to an alternative agent or adding a Janus kinase inhibitor or immunomodulators, or allogeneic hematopoietic cell transplantation [HCT]) were attempted.
Conclusion: Our survey revealed that anti-TNF-α agents showed high efficacy. However, secondary failure of MTDs was a significant refractory-related factor in HA20 patients in Japan. Although anti-interferon therapies, thalidomide, and HCT might be potential treatment options, the results of this study suggest that further research is necessary to establish suitable treatments for HA20, especially for those with intractable disease.
Disclosure of Interest: None declared

Identifier: PT64

AA AMYLOIDOSIS COMPLICATING SYSTEMIC AUTOINFLAMMATORY DISEASES: DATA FROM THE UK NATIONAL AMYLOIDOSIS CENTRE

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Introduction: In systemic AA amyloidosis (AAA) the amyloid fibrils are derived from serum amyloid A protein (SAA), underlying causes include any condition that induces persistent systemic inflammation. AAA presents with proteinuria, progressive renal impairment & involvement of other organs.

Objectives: To describe AAA complicating systemic autoinflammatory diseases (SAIDS) in a cohort over 35 years
Methods: All new patients seen in a UK national referral centre with AAA were included. The medical records were reviewed until Dec 2024.
Results: Whole Cohort: 968 AAA patients were seen Jan 1990 - Dec 2024; 48% female, median age at diagnosis 55.8 (range 7.4-88) yrs.

SAID Diagnoses: 81 patients (8.4% of AAA) were clinically diagnosed with SAID, 41 (51%) FMF, 13 (16%) TRAPS, 11 (13.6%) CAPS, 6 (7.4%) MKD, 5 (6.2%) Stills Disease, 4 (4.9%) hidradenitis suppurative, 1(1.2%) Schnitzler's Syndrome. 46% female, median age at diagnosis with amyloid 45.5 (range 7.4-78.6) yrs.

Genetics: All of the CAPS & TRAPS had confirmatory genetics. 3 CAPS patients had late onset disease due to low level somatic mosaicism & 2 were siblings with R260W. TRAPS included 8 patients from 3 kindreds with C62Y, D71Del & T79M variants & 5 with no family history of amyloid. All TRAPS were European; CAPS although 70% European included South Asian & Black African ancestry. Of the clinically diagnosed with FMF, 30 have confirmatory genetics: 22 had 2 pathogenic variants in exon 10 (17 carried M694V, 7 homozygous; 3 M680I, 1 homozygous, 2 M694I & 7 V726A none homozygous) , 6 had dominant FMF (3 DelM694 & 2 P373L) & 2 V726A/F47L. 8 patients were heterozygous for a pathogenic exon 10 variant (6 M694V, 1 each of M694I & M680I) & 5 also carried E148Q VUS. One patient seen before genetic testing was available & 2 others had no supporting genetics. 7, including all 6 dominant FMF, were North European: 12 South European, 20 West Asian & 2 South Asian. Of the 6 labelled with MKD 4 were genetically confirmed, all were British (3 I268T/V377I (including 2 siblings), 1 L234P/V377I. 2 had non confirmatory genetics (V377I het & V377I/homozygous S52N VUS).

Variants in a second gene: 2 patients (MKD & FMF) carried a TNFRSFIA VUS, R121Q & P75L respectively. 1 TRAPS & 1 FMF carried NLRP3 VUS Q703K & 1 TRAPS case NLPR3 V200M. I each of TRAPS & CAPS were MEFV E148Q heterozygote. 2 patients labelled with Still's disease carried variants: MEFV F479/E167D & TNFAIP3 M788I

Treatment: 11/13 TRAPS were treated with long term IL-1 blockade to complete respons. 9/11 CAPS were treated with IL-1 blockade. 5 FMF patients received anti IL-1 therapies the others were managed with colchicine alone. Between MKD have been treated with anti TNF, anti IL-6 & anti IL-1 agents with varying responses. The Hidradenitis patients have responded poorly to treatment, all have been tried on at least one anti TNF agent.

Measures of systemic inflammation: Median (range) at presentation CRP 19 (1-219) mg/L, SAA 43.5 (1- 894) mg/L, wbc 8.7 (3.6 – 19.9) x 10^9/L, IgG 9.2 (1.1 – 26.8) g/L

Renal Function & other laboratory values: 16 patients (19.5%) were in ESRF at presentation, in the remainder: eGRF 62 (15->90) ml/min, serum Alb 36 (11-47) g/L, NT-pro BNP 390 (17- >70,000) pmol/L, Cholesterol 5 (2.7-7.1) mmol/L, Hb 115 (70-169) g/dL. A further 19 patients developed ESRF & 17 received transplants.

Survival: 26 patients died. Median survival by Kaplan Meier analysis 19.5 yrs, median age at death 74 yrs. Median time to progress to ESRF 15 yrs. Onset of renal failure had a significant ($p < 0.01$) impact on survival

Conclusion: AAA is a rare preventable complication of SAIDS, no cases have developed in patients managed by to the UK specialist treatment service. SAIDS account for 8.4% of AAA seen over the last 35 yrs & outcome is generally good with median renal survival of 15 yrs & patient survival of 19.5 yrs.

Disclosure of Interest: None declared

Identifier: PT65

UNRAVELING GENETIC COMPLEXITY: DIFFERENT DISEASES IN SIBLINGS WITH SHARED CLINICAL PRESENTATION

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Introduction: Adenosine deaminase 2 (DADA2) deficiency and laccase domain-containing 1 (LACC1) deficiency are both rare autosomal recessive diseases with overlapping clinical presentations, including fever, arthritis, rash, and elevated inflammatory markers. DADA2 is caused by loss-of-function mutations in the ADA2 gene, which encodes the adenosine deaminase 2 (ADA2) protein. The clinical spectrum of DADA2 is broad, including vasculitis and autoinflammatory manifestations. Homozygous loss-of-expression mutations in LACC1 are associated with early onset arthritis.
Objectives: We identify a novel homozygous mutation in the LACC1 gene as the genetic cause of a disease in a sibling of a DADA2 patient who had similar symptoms.
Methods: We conducted a chart review of clinical and laboratory data. We performed whole genome sequencing (WGS) on the patient and functional validation to confirm the pathogenicity of the identified variant
Results: We describe a 9-year-old girl who presented with persistent fever, arthritis, rash, and elevated inflammatory markers (Table 1). Her sister, 18 years old, has DADA2 deficiency due to a homozygous *ADA2* pathogenic mutation (c.754-2A>G). This was discovered when she was 13 years old, presenting with fever, arthritis, and rash, to which she responded well to anti-TNF therapy (Table 1). Surprisingly, targeted Sanger sequencing for our patient revealed a heterozygous ADA2 mutation, similar to her consanguineous parents. The fact that the patient didn't improve with anti-TNF therapy, which is usually effective for DADA2, further raised suspicion of an alternative diagnosis. *Consequently, we performed WGS for our patient and discovered a novel homozygous variant of uncertain significance in the LACC1 gene.* Functional studies performed on monocyte-derived macrophages from the patient confirmed the loss of LACC1 expression (Figure 1). Thus, the patient was treated with IL-6 blockade (tocilizumab), and achieved an excellent clinical response, resolving her fever, rash, and arthritis while also normalizing her inflammatory markers.
Conclusion: We identified a novel pathogenic variant in the *LACC1* gene in a patient whose symptoms overlapped with those of her sister, who has a mutation in the *ADA2* gene. This case highlights the important role of genetic and functional validation in providing an accurate diagnosis and guiding personalized treatment for rare autoinflammatory diseases with overlapping clinical presentations.
Acknowledgments: Patients and family
Disclosure of Interest: None declared

Identifier: PT66

NEUROLOGICAL MANIFESTATIONS IN CRYOPYRIN-ASSOCIATED PERIODIC SYNDROMES (CAPS): A RETROSPECTIVE MONOCENTRIC STUDY

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Introduction: Neurological manifestations can occur across the full spectrum of Cryopyrin-Associated Periodic Syndromes (CAPS), yet they remain underrecognized and poorly studied, particularly in adults.
Objectives: To describe the neurological manifestations of CAPS and identify factors associated with their occurrence.
Methods: In this monocentric retrospective study, we analyzed the characteristics of adult patients diagnosed with genetically (pathogenic or likely pathogenic *NLRP3* variant according to the Infevers database) confirmed CAPS who have attended at least once at Tenon Hospital, a French reference center for autoinflammatory diseases. Patients were first categorized based on the presence or absence of neurological symptoms. Next, those with neurological symptoms were divided into subgroups based on whether they presented with isolated headaches only or with a well-defined neurological syndrome. Neurological syndromes included meningitis, intracranial hypertension with hydrocephalus (IHH), central nervous system demyelinating disease (CNS DMD), and CNS angiitis. A patient could present with multiple syndromes. We then compared the characteristics of patients with neurological symptoms (excluding those with isolated headaches) to those without neurological symptoms.
Results: Overall, 67 patients with CAPS were included. Most were women (42/67) and Caucasian (48/63), with a median age of 44 years [IQR25–75: 32-59]. The median age at first CAPS manifestations was 3 years [IQR 0-7], while the median age at diagnosis was 38 years [IQR 22.5-53]. Pathogenic or likely pathogenic *NLRP3* variants included 14 de novo and 53 inherited variants across 14 different families. Fifty-seven patients were classified into three previously identified syndromes: Familial Cold Autoinflammatory Syndrome (FCAS, n=2), Muckle-Wells Syndrome (MWS, n=47), and Neonatal-Onset Multisystem Inflammatory Disease (NOMID/CINCA, n=8). Fourty-six (68.7%) patients reported neurological symptoms. Of these, 25 (54.3%) had isolated headaches without a clearly identifiable neurological syndrome, although none of these 25 patients had undergone a comprehensive neurological work-up, including brain MRI and CSF analysis. Eighteen (39.1%) patients presented with identified neurological syndromes: isolated meningitis (n=7), meningitis with IHH (n=4), meningitis and CNS DMD (n=3), isolated CNS DMD (n=2), meningitis with CNS DMD and IHH (n=1), and meningitis with IHH and CNS vasculitis (n=1). In addition, one patient exhibited bilateral optic atrophy, one had a behavioural disorder and seizures, and one experienced peri-orbital infiltration leading to optic neuropathy and oculomotor paralysis. Interestingly, patients with CNS DMD typically presented only with optic neuropathy or headaches and did not exhibit other focal neurological deficits, as is common in multiple sclerosis. Headache was the most frequent neurological symptom, even among patients with neurological syndromes. Patients with neurological symptoms, excluding isolated headaches, had significantly more *de novo* variants in *NLRP3* than those without (p=0.0063). Although sensorineural hearing loss occurrence was similar between the two groups, patients with neurological symptoms were more likely to use hearing aids, suggesting more severe auditory impairments (p=0.0278). The phenotypic distribution differed significantly, with more NOMID among patients with neurological symptoms (p=0.04502).
Conclusion: Neurological manifestations are common among adult patients with CAPS, yet underexplored. These findings highlight the need for comprehensive neurological assessments in patients presenting with headaches and emphasize the importance of further studies to determine whether these manifestations influence prognosis and warrant treatment intensification.

Disclosure of Interest: None declared

Identifier: PT67

TRANSLATIONAL AUTOINFLAMMATORY RESEARCH NETWORK (TARN): A GLOBAL NETWORK APPROACH TO ENHANCING CLINICAL TRIAL READINESS FOR RARE AUTOINFLAMMATORY DISEASES

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Introduction: Despite the identification of over 70 monogenic SAIDs, only five currently have FDA-approved therapies, highlighting the gap in clinical trial readiness in this field [1]. The Translational Autoinflammatory Research Network (TARN) was established to address this gap. Since its informal inception in 2016, TARN has grown into a robust multicenter network.

Objectives: The focus of this network is to

1. foster collaboration among researchers, clinicians, and patient advocates,
2. advance clinical trial readiness and
3. build a genomic database that will ultimately improve outcomes for patients suffering from SAIDs [2-5].

Methods: The core focus of the establishment process was to unite key stakeholders in the SAID research community, including clinical sites, patient advocacy groups (PAGs), and regulatory partners. A steering committee (SC) was established to manage TARN's activities. Regular SC meetings were held to ensure alignment on objectives, progress updates, and best practices. A governance structure for the network was discussed in the preliminary SC meetings to identify the organization and sub-committees. A mission statement was created and distributed to steering committee members for feedback. The network began the establishment phase by identifying and contacting potential investigators at major research institutions, clinical sites, PAGs and key opinion leaders involved in SAID research. We facilitated communication with clinicians, geneticists, and immunologists to bring together a multidisciplinary group of experts. We distributed the mission statement to potential stakeholders to gauge interest in the network. Formal partnerships were established through letters of intent (LOI) and Memorandums of Understanding (MOUs) with clinical sites and various international partners, including academic centers, and PAGs. These agreements formed the foundation for a coordinated network focused on advancing the field of SAIDs [6]. Projects were proposed and prioritized in the biweekly and SC meetings.

Results: The SC successfully created the mission statement, LOI and MOUs from over 60 clinical sites across the world, the countries of the clinical sites that signed included the USA, Canada, South Africa, India, Turkey, Saudi Arabia, Brazil, Chile, Germany, Mexico, Argentina, Australia, Spain. We also established partnership LOI's with over five PAGs, including the Autoinflammatory Alliance, the SJIA Foundation, the Canadian Autoinflammatory Network, the Aicardi-Goutieres Syndrome Advocacy Association, the CRMO Foundation and the Cure Blau Foundation that have all mutually agreed to partner with TARN [2]. TARN has also formed MOUs with societies and Liaisons and has notably signed an MOU with ISSAID. Through TARN's establishment, the SC was able to identify a priority projects for SAIDs that can be used in clinical trials. The SC also successfully submitted a large NIH grant application to further support the network. Furthermore, a website is currently being created for TARN (tarnnetworkdotcom).

Conclusion: TARN aims to revolutionize SAID management by enhancing clinical trial readiness, building a genomic database and fostering collaboration. TARN addresses the challenges of single-site trials in rare diseases by establishing a multi-site network. Prioritizing clinical trial development and adaptive trial structures, TARN unites researchers, clinicians, PAGs and societies to create an environment conducive to efficient therapy for SAIDs. Moving forward, TARN will optimize clinical trial infrastructure and advance projects to advance the field of SAIDs.

Acknowledgments: We would like to acknowledge the Autoinflammatory Alliance, the Childrens Health Foundation, and the Department of Pediatrics at Western University of Ontario for their support throughout the establishment phase of TARN
Disclosure of Interest: None declared

Identifier: PT68

THREE-YEAR FOLLOW-UP OF CANAKINUMAB DOSE EXTENSION IN CHILDREN WITH COLCHICINE-RESISTANT FMF: PERA-RG EXPERIENCE

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Introduction: Anti-interleukin-1 therapies have shown promising outcomes in familial Mediterranean fever (FMF) patients who are unresponsive to colchicine. However, there is a lack of conclusive data regarding the optimal duration and dosing regimens of these therapies in pediatric patients. A multicenter study conducted in Turkey reported favorable results with a standardized canakinumab dose extension protocol in FMF patients, albeit with a short follow-up period.

Objectives: This study aims to evaluate the long-term outcomes of the canakinumab dose extension protocol in colchicine-resistant FMF patients, specifically over a follow-up period of at least 3 years.

Methods: The dose extension protocol was developed through a consensus process in Turkey, utilizing a multicenter approach and the Delphi technique. According to the protocol, for patients who remain attack-free during the first six months of canakinumab treatment, the dosing interval can be doubled. If patients continue to remain attack-free for one year following this adjustment, the dosing interval can then be tripled. This retrospective study involved FMF patients diagnosed and managed at seven centers in Turkey. All included patients had initiated canakinumab treatment due to inadequate response to colchicine, with their treatment regimens aligned with the consensus protocol. Data for the study were collected from patients' medical records.

Results: The study included 45 patients who initially began canakinumab treatment with monthly dosing. After six months of treatment, the dosing interval was extended to every two months. The median follow-up period after starting canakinumab was 48 months (IQR: 11.5 months). FMF attacks occurred in 7 patients (15.56%) during the bimonthly dosing phase, prompting a return to monthly dosing without further attempts to extend the interval. Among the remaining 38 patients (84.44%), the dosing interval was further extended to every three months after one year of bimonthly treatment. However, 11 of these patients required a return to bimonthly dosing due to attacks during the three-month interval. Of the 10 patients who achieved long-term remission with the three-month dosing interval, canakinumab treatment was discontinued. Following discontinuation, 5 patients remained attack-free, while the other 5 experienced attacks, necessitating the resumption of therapy. Seventeen patients were receiving canakinumab every three months. One patient was lost to follow-up, leaving 16 patients (35.56%) who currently continue this regimen. The median follow-up duration after the second dose extension for this group is 32 months (IQR: 6.5 months).

Conclusion: The protocol mentioned for the dose extension of canakinumab treatment appears promising. Further extensive studies with larger cohorts and prospective randomized controlled trials are needed to explore anti-interleukin-1 treatment dosage regimens more comprehensively

Disclosure of Interest: None declared

Identifier: PT69

BEYOND MEFV: HOW ADDITIONAL AID-ASSOCIATED MUTATIONS SHAPE FAMILIAL MEDITERRANEAN FEVER IN CHILDREN

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Introduction: The clinical presentation and severity of FMF can vary widely, and some patients exhibit atypical features suggestive of additional genetic influences depending on the impact of mutation on protein function. The presence of monogenic, digenic, or oligogenic inheritance of gene variants of autoinflammatory diseases (AID) in patients presents a challenge to the clear interpretation of their clinical significance.

Objectives: This study aimed to explore the impact of concomitant mutations in AID associated genes alongside *MEFV* mutations on the clinical phenotype of children with FMF.

Methods: Medical records of 3150 children with definitive FMF diagnosis according to the Tel Hashomer/Eurofever/PRINTO autoinflammatory recurrent fever criteria from three referral pediatric rheumatology centers were retrospectively reviewed. A total of 72 patients who underwent genetic panel screening for genes associated with AID syndromes (*NLRP3, NLRP12, MVK, TNFRSF1A, TNFRSF11A, NLRP7, NOD2, IL10-RB, CARD14, LPIN2, ADA2, PSMB8,* and *PSTPIP1*) were included in the study. The cohort was divided into two groups: Group 1 with only MEFV mutations and Group 2 with MEFV and additional AID mutations. Demographic data, genetic profile, clinical features, laboratory findings, disease activity and severity scores (AIDAI, ISSF, PRAS), and treatments were recorded and compared between the two groups.

Results: Group 1, consisting of 41 patients (56.9%) carried monoallelic or biallelic variants of *MEFV* gene and Group 2, consisting of 31 patients (43.1%) carried combination of monoallelic or biallelic variants of *MEFV* and at least one AID-associated gene variants.

Group 1 included patients displaying heterozygous mutations on *MEFV* gene in 33 (80.5%) subjects, compound heterozygous mutations in six (14.6%) patients, and homozygous mutations in two (4.9%) patients. In Group 2, 24 patients (77.4%) exhibited heterozygous *MEFV* mutations, five patients (16.1%) carried compound heterozygous mutations, and two patients (6.5%) carried homozygous *MEFV* mutations. The most prevalent variant of *MEFV* gene in both groups was the heterozygous mutation on exon 10 (52.5% vs. 58.1% for Group 1 vs. Group 2). Variants associated with AID belong to those genes: NOD2 (n=10), MVK (n=9), NLRP3 (n=7), NLRP12 (n=4), ADA2 (n=1), TNFRSF1A (n=2), IL10RB (n=2), PSMB8 (n=2), CARD14 (n=1), LPIN2 (n=1), PSTPIP1 (n=1), TNFRSF11A (n=1), NLRP7 (n=1).

Nineteen (46.34%) patients in Group 1 and 11 (35.48%) patients in Group 2 were female ($p = 0.355$). The median age at symptom onset was significantly younger in Group 2 ($p = 0.032$). Similarly, the median age at diagnosis was significantly younger in Group 2 (42 months, range 3–177) compared to Group 1 (63 months, range 16–190; $p = 0.031$).

Oral aphthae, lymphadenopathy, and early-onset disease were significantly more common in Group 2 compared to Group 1 ($p = 0.002$, $p = 0.005$, $p = 0.032$, respectively). Notably, laboratory analyses revealed higher levels of white blood cells, C-reactive protein, and serum amyloid A in Group 2 ($p = 0.041$, $p = 0.011$, $p = 0.048$, respectively). Additionally, Group 2 exhibited significantly higher initial AIDAI scores and a greater number of attacks annually ($p < 0.001$ and $p = 0.011$, respectively) (Table1).

Conclusion: In conclusion, the coexistence of *MEFV* mutations with additional AID-associated gene variants is associated with an earlier onset of symptoms and younger age at diagnosis. The presence of features, such as oral aphthae and lymphadenopathy, may serve as indicators of these additional genetic variants. Patients with combined mutations exhibited higher disease activity scores and a greater frequency of attacks at diagnosis compared to those with only *MEFV* mutations. These findings highlight the potential role of concomitant mutations in influencing the clinical phenotype and severity of FMF.

Acknowledgments: None

Disclosure of Interest: None declared

Identifier: PT70

GERANYGERANIOL SUPPLEMENTATION LEADS TO AN IMPROVEMENT IN INFLAMMATORY PARAMETERS AND REVERSAL OF THE DISEASE SPECIFIC PROTEIN AND METABOLIC SIGNATURE IN PATIENTS WITH HYPERIGD SYNDROME

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Introduction: Mevalonate kinase deficiency (MKD), also known as hyper-IgD syndrome, is a metabolic disorder characterized by a disruption in the mevalonate pathway. This disruption leads to a deficiency of downstream metabolites, including geranylgeranyl pyrophosphate (GGPP). The precise mechanisms by which the lack of isoprenoids, such as GGPP, contributes to the characteristic inflammatory manifestations of MKD remain to be fully elucidated.

Objectives: This pilot study aimed to evaluate the safety and efficacy of geranylgeraniol (GG) supplementation in six patients with MKD (four females and two males, aged 12 to 51 years, all compound heterozygotes for mutations in the *MVK* gene) included over the last 2 years. Four patients were treated with anakinra on-demand during attacks, while one 51-year-old woman received regular anakinra therapy (every 1-2 days) and maintenance corticosteroid treatment. Twelve years old girl was using only antiinflammatory treatment with NSAID and corticosteroids in attacks.
Methods: Standard laboratory tests assessed basic immunology and metabolic profiles. Proteomic analysis was conducted using the SomaLogic SomaScan 7K assay. Metabolomic analysis was performed using gas chromatography-time-of-flight mass spectrometry.
Results: All patients tolerated the GG supplement (GG Gold®30 Annatto Extract 500mg, 30% Geranylgeraniol, 150mg) well, with no significant side effects. Elevated inflammatory markers decreased in some patients, while they remained unchanged in others if originally low. GG supplementation did not significantly alter lipid profiles, IgD levels, or basal B-cell profiles.

Proteomic analysis revealed substantial changes in protein expression profiles following GG treatment compared to baseline. Notably, GG significantly upregulated proteins involved in cytoskeletal regulation and cell motility, such as Rho GTPases and receptor tyrosine kinases. Conversely, pathways associated with innate immunity, neutrophil degranulation and cytokine signaling were significantly downregulated.

Metabolomic analysis demonstrated similar findings, with a reversal of the metabolomic signature observed in MKD patients after 3 months of GG supplementation. Specifically, levels of fumarate and 2-aminobutyric acid, metabolites involved in metabolic processes intersecting with the mevalonate pathway, decreased. Some metabolites characteristic of MKD that decreased after GG supplementation remain unidentified, warranting further investigation.

Conclusion: This pilot study demonstrates that GG supplementation in MKD patients alters both proteomic and metabolomic profiles, mirroring previously reported findings. While the clinical effect in adult patients was relatively mild, a more pronounced response was observed in the 12-year-old child not receiving IL-1 blockade therapy. Further studies are necessary to comprehensively evaluate the long-term effects and clinical benefits of GG supplementation in MKD patients.
Disclosure of Interest: None declared

Identifier: PT71

PUTTING THE PREDICT-CRFMF SCORE TO THE TEST: PROSPECTIVE PERFORMANCE EVALUATION

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Introduction: Managing familial Mediterranean fever (FMF) and addressing the disease burden caused by persistent inflammation can be challenging. Recognizing the benefits of predictive models in achieving early disease control in colcihine resistance (cr-FMF) patients, our group developed the P*REDICT-crFMF score: a novel model for predicting colchicine resistance in children with FMF.* This score was externally validated on a large independent cohort, demonstrating high sensitivity (82%) and specificity (79%) in identifying the risk of colchicine resistance.

Objectives: In this study, we aimed to validate and present prospective data of this new scoring system developed to predict colchicine resistance in FMF based on the baseline characteristics of the patients.

Methods: Data from patients presenting for the first time after the introduction of the PREDICT-FMF scoring system were analyzed. Preliminary findings from two tertiary pediatric rheumatology centers were reviewed. Inclusion criteria included patients diagnosed with FMF after 2022, under 18 years of age at diagnosis, and followed for at least 6 months. The parameters determined to predict resistant FMF in the logistic regression model were evaluated based on a cut-off value of 9.

Results: Between January 2023 and December 2024, 83 patients were admitted to the paediatric rheumatology outpatient clinic with the diagnosis of FMF. Among these 83 cases, 10 (12%) patients were resistant to colchicine, and 73 (88%) patients responded to colchicine. Approximately half (43.4%) of the entire cohort and 60% of the cr-FMF patients were female.The cr-FMF group and the responsive group were similar in terms of age at diagnosis (p = 0.75). The follow-up period was significantly longer in the resistant FMF group (p = 0.03).

At least one pathogenic exon 10 mutation was found in 90.4% (n=74) of the patients. All patients with colchicine resistance had exon 10 homozygous or compound heterozygous mutations on exon10. In colchicine-responsive patients, 50.7% had exon 10 homozygous or compound heterozygous mutations on exon 10 and 49.3% had other exon mutations on MEFV gene. In this cohort, the sensitivity and specificity of the PREDICT-FMF score for the cut- off value of 9 were 80% and 91%, respectively. (Table 1)

Table 1. Sensitivity and specifity of the PREDICT cr-FMF score

	Colchicine-resistant, n	**Colchicine-responsive, n**	
Predictivite score≥9	8	6	PPV: 57%
Predictivite score<9	2	67	NPV: 97%
	Sensitivity: 80%	Specifity: 91%	

PPV; positive predictive value, NPV; negative predictive value

Conclusion: This practical scoring system demonstrated high sensitivity and specificity, offering a valuable tool for identifying FMF patients at higher risk of colchicine resistance and enabling personalized disease management at diagnosis. We conclude that this scoring system is worthy of prospective application in larger case series.

Disclosure of Interest: None declared

Identifier: PT73

DISEASE PRESENTATION, RESPONSE TO TREATMENT AND OUTCOME OF PEDIATRIC AND ADULT PATIENTS WITH DADA2 (DEFICIENCY OF ADENOSINE DEAMINASE 2): RESULTS FROM THE EUROFEVER REGISTRY

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Introduction: DADA2 is a monogenic autoinflammatory condition characterised by a broad spectrum of clinical manifestation, ranging from cutaneous to severe systemic vasculitis with multiorgan involvement, immunodeficiency and
bone marrow failure. Few data are nowadays available about the clinical characteristic, the response to treatment and the outcome of this disease.
Objectives: To analyse the data of the DADA2 patients enrolled in the Eurofever registry.
Methods: The data analysed were extracted from the Eurofever registry, which is hosted in the PRINTO website. The patients were included in the study in the presence of clinical manifestations consistent with DADA2, a confirmatory genotype or a pathologic ADA2 enzymatic activity. Demographic data, clinical manifestations, treatment, safety and outcome were analysed.
Results: In May 2024 baseline and clinical information were available of 92 DADA2 patients (43M:49F), from 23 centers, in the Eurofever registry; of these, follow-up data were available for 63 patients (mean follow-up duration 2.8 years). 71 patients (77%) had a confirmatory genotype, while 21 a non-confirmatory genotype. 17 patients had a positive family history (12 couples of siblings were included in the registry). The mean age at enrolment was 12.5 years (74 paediatric and 18 adult patients), at disease onset 7,4 years (SD 8,6) and at diagnosis 15.2 years (SD 12), with a mean delay of 8 years.

The disease course was continuous in 46% of patients, recurrent in 27%, continuous with recrudescence in 27%. 81% of patients presented skin involvement during their disease course, 58% neurological, 53% musculoskeletal, 41% gastrointestinal, 38% of lymphoid organs, 24% haematological, 17% cardiovascular, 14% ocular and 5% genitourinary. In 4 patients a neoplasm occurred.
Synthetic DMARDS were used in 34 patients. Azathioprine and cyclophosphamide, used in 10 and 3 patients respectively, were withdrawn for inefficacy; thalidomide, used in 3 patients, was withdrawn for side effects. Mofetil mycophenolate was used in 6 patients, still ongoing at last follow-up in 2, while methotrexate in 14 patients, still ongoing at last follow-up in 8, of those 5 associated to anti-TNF.
76 patients (82%) received treatment with anti-TNF: 66 patients were treated with etanercept (in 63 treatment was ongoing al last follow-up), 17 patients with adalimumab (in 10 treatment was ongoing at last follow-up). IL-1 and 6 inhibitors were used in 7 and 1 patients respectively, withdrawn for inefficacy.

24 adverse events were reported, while on treatment; of these, 11 were serious: 2 were disease-related, 3 resolved with surgery, 4 were infections and one (hepatic nodular hyperplasia) required drug-change. One patient attempted suicide while on biological treatment.
79% of patients achieved a complete control of the disease during follow-up.. 2 patients died: one for sepsis at the age of 52, one for lung cancer at the age of 28.

Conclusion: The study analyses a large series of DADA2 patients with prolonged follow-up, confirming the clinical heterogeneity of this condition and the difficulty in the molecular diagnosis. Anti-TNF drugs confirms their efficacy and good safety profile in this condition.

Disclosure of Interest: None declared

Identifier: PT74

CLINICAL OUTCOMES OF BARICITINIB TREATMENT IN AICARDI-GOUTIÈRES SYNDROME: A RETROSPECTIVE COHORT STUDY AT GREAT ORMOND STREET HOSPITAL

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Introduction: Aicardi-Goutières Syndrome(AGS) is a severe genetic disorder that significantly diminishes quality of life due to its impact on the brain,immune system and skin.Currently,there is no cure,and treatments are primarily supportive,aiming to manage symptoms and improve patient comfort. Baricitinib,a Janus kinase(JAK) inhibitor,has been investigated as a potential treatment for AGS.By inhibiting JAK1 and JAK2,baricitinib may reduce the excessive interferon signaling characteristic of AGS,potentially alleviating some of the inflammatory symptoms associated with the disorder.
Objectives: In this real-world approach study,we report our experience of the use of baricitinib in patients with AGS seen in a large tertiary referral centre.
Methods: This was retrospective case series conducted at Great Ormond Street Hospital.The study population included 16 children(median age: 83 months,6 (37.5%) female) with molecularly confirmed AGS who were offered baricitinib treatment.Clinical,demographic,laboratory,treatment,and imaging data were collected at three time points:baseline(prior to treatment initiation) and two follow-up assessments after treatment initiation.The primary clinical outcomes included neurological function,changes in inflammatory markers and radiological findings(MRI).
Results: 75%(12/16) patients presented between 4 weeks to 2 years old,18%(3/16) presented in the neonatal period and 6 %(1/16) presented older than 2 years old.Developmental delay was the most common presenting symptom,observed in 81%(13/16) of patients.Seizures were reported in 43%(7/16),and chilblains were present in 25%(4/16).Baricitinib treatment was initiated in 50%(8/16) of patients,at median 2 years post initially diagnosis.The reasons for families/patients declining therapy were mainly the risk of infectious complications and need for regular blood test monitoring. The response to baricitinib varied among patients.Some exhibited improvements in symptoms such as irritability, seizures, and chilblainswhile others showed limited or no improvement in neurodevelopmental status or irritability. Of note dystonia was present in 87%(14/16) of patients at baseline,with improvement noted with 12% of patients treated during follow-up.Baseline CSF neurotransmitter analysis revealed abnormalities in 75%(6/8) of patients,including elevated pterins,tetrahydrobiopterin, dihydrobiopterin,and total neopterin.Post-baricitinib testing in one patient continued to show elevated pterins.MRI findings at baseline showed white matter signal changes and reduced white matter volume in 56%(9/16) of patients.From the 8 patients that received baricitinib,the interim imaging findings showed stable similar changes in 25%(2/8) patients where interim imaging was done.Latest follow-up imaging for patients who received baricitinib showed stable similar findings in 50%(4/8) patients. In 12.5%(1/8) there was progressive white matter changes,in another 12.5%(1/8) there was progressive volume loss and atrophy and in another 12.5%(1/8) there was progressive calcification.

Intercurrent infections occurred in 37%(3/8) of treated patients.Two of these patients stopped treatment due to these infectious complications. Interferon gene expression was assessed prospectively in 25%(4/16) of patients:IF127, IFI144L and IFIT1 gene expression remained elevated most patients while SIGLEC1 gene expression normalized in all.

Conclusion: Overall, our report indicates a benefit of baricitinib treatment on certain systemic features of AGS,but a minimal measurable effect on the associated neurological phenotype.In developing future treatment strategies for AGS it is essential to prioritise early diagnosis and intervention along with ensuring that therapeutic agents effectively penetrate the central nervous system.These factors are crucial for preventing irreversible brain damage in AGS patients.
Disclosure of Interest: None declared

Identifier: PT75

PAEDIATRIC AUTOIMMUNE AND AUTOINFLAMMATORY DISEASE-RELATED CATATONIA IS ASSOCIATED WITH ELEVATED CSF INTERFERON-A TITRES AND EFFICIENTLY TREATED WITH IMMUNOADSORPTION IN SEVERE CASES

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Introduction: Paediatric catatonia is an underdiagnosed neuropsychiatric syndrome, especially when related to inflammatory brain disorders. Its pathophysiology and optimal treatment still need to be determined.
Objectives: To describe catatonia related to autoimmune and autoinflammatory disease and its association to interferon alpha (IFN-α).
Methods: We conducted a retrospective monocentric study between January 2017 and October 2024 in a French tertiary referral centre. A multidisciplinary team clinically evaluated all patients. Blood/cerebrospinal fluid (CSF) assessments were also performed, with specific evaluation of type I interferon (IFN I) pathway signalling (IFN activity and Simoa digital ELISA), as well as radiological investigations.
Results: We included seven paediatric patients demonstrating catatonia respectively related to juvenile systemic lupus erythematosus (n=4), Aicardi-Goutières syndrome (n=1) and juvenile dermatomyositis (n=2). Catatonic patients presented high levels of blood and CSF circulating IFN-α protein, which were higher in the CSF than in the blood of treatment naïve patients (n=4). Four out of seven patients were resistant to both steroid and cyclophosphamide pulses and benefited from immunoadsorption (IA). The median number of IA sessions was 22 (20-25) over 5-8 weeks, associated with a dramatic improvement of catatonia with decreased blood and CSF IFN-α.
Conclusion: Our data support an IFN-α-driven hypothesis of catatonia. In cases of severe and refractory catatonia associated with IFN I-related disease, IA may represent a promising and effective treatment option. The implication of IFN-α in non-immune mediated catatonia should be prospectively explored.
Disclosure of Interest: None declared

Identifier: PT76

LOSS OF PSMD7 CAUSES DYSREGULATED PROTEIN DEGRADATION, ENHANCED INFLAMMASOME ACTIVATION, AND INTERFERON RESPONSES

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Introduction: Mutations in genes encoding the proteasome subunits have been associated with autoinflammatory syndromes. Necrotizing fasciitis (NF) is a life-threatening soft tissue inflammation. It is typically caused by bacterial infection, but recent studies have shown that certain germline mutations can drive an excessive NLRP3 inflammasome response and tissue damage, causing an autoinflammatory form of NF. In this form, the bacterial load is either absent or disproportionately low relative to the severity of inflammation. A patient presenting with severe NF was found to carry heterozygous variants predicted to be deleterious in three genes (*PSMA5*, *TRIM23*, and *PSMD7*). Among these *PSMD7* variant was truncating and led to reduced protein expression. *PSMD7* encodes a 26S proteasome subunit essential for ubiquitinated protein degradation. Dysregulated protein degradation has been associated with enhanced inflammasome activation. Notably, the patient showed a good response to IL-1β antagonist therapy, and the imminent amputation of the limb was avoided.

Objectives: To study the role of the gene variants in innate immune signaling, NLRP3 inflammasome activation, and proteasome function.
Methods: Patient's PBMC-derived macrophages were stimulated with lipopolysaccharide (LPS) and NLRP3 inflammasome activators, thereafter expression and activation of NLRP3 inflammasome proteins, and interferon-stimulated genes (ISG) were studied. The mechanisms were studied using CRISPR Cas9-edited THP-1 monocytes bearing heterozygous *PSMD7 and TRIM23* knockouts (KOs).
Results: In response to LPS, patient's cells exhibited elevated IL-1β levels, indicating excessive NLRP3 inflammasome activation and an enhanced interferon response. To explore the mechanism, intracellular signaling was studied in *TRIM23* and *PSMD7* KO monocytic cell lines. *TRIM23* KO did not enhance IL-1β secretion. However, similar to patient macrophages, following LPS stimulation, *PSMD7* KO cells showed significantly increased IL-1β secretion and elevated expression of *IFNB1* and ISGs, compared to mock-transfected cells. While proteasome chymotrypsin-like activity remained unaffected in *PSMD7* KO cells, untreated cells accumulated higher levels of total and K48-ubiquitinated proteins. Proteasomal dysfunction was linked to increased NLRP3 inflammasome activation, as shown by the massive secretion of IL-1β in the presence of proteasome inhibitors bortezomib and ONX-0914 in both *PSMD7* KO and mock cells.
Conclusion: Ubiquitination is a key post-translational modification, which regulates inflammatory responses by controlling signaling, protein transport, and degradation. Ubiquitination also controls the activation of NLRP3 inflammasome and the degradation of its components, NLRP3, ASC, and IL-1β. Mutations in proteasome lid proteins that restrict the access of polyubiquitinated proteins to the proteasome can cause their accumulation. This may sensitize immune cells to excessive inflammasome activation, eliciting the secretion of the strong proinflammatory cytokine IL-1β, which recruits lymphocytes and induces fever, potentially predisposing to hyperinflammation and NF.
Acknowledgments: This study was supported by Jane and Aatos Erkko Foundation (6347-6aed0)
Disclosure of Interest: None declared

Identifier: PT77

NEONATAL-ONSET VASCULITIS DRIVEN BY PATHOGENIC VARIANTS IN THE SRC FAMILY KINASE HAEMATOPOIETIC CELL KINASE (HCK): A REPORT OF TWO FAMILIES AND A NOVEL MUTATION

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Introduction: Haematopoietic cell kinase (HCK) is a member of the SRC family of tyrosine kinases and is expressed in cells of lymphoid and myeloid lineage. In 2021, a single case report of a mutation in *HCK* leading to pulmonary and cutaneous vasculitis was published (1). We now report on three further cases including a family with a novel mutation and cutaneous-limited phenotype.

Objectives: To determine the cause of severe neonatal-onset vasculitis in three cases from two unrelated kindreds and to highlight the importance of re-analysis of genetic sequencing in unsolved cases.

Methods: Retrospective case-note review, whole exome sequencing (WES), Sanger sequencing and gene expression using quantitative reverse transcription PCR (RT-qPCR). Functional work on patient cells including: protein expression analysis using Western blot; and assessment of surface integrin and intracellular phosphorylated-STAT signalling activation using flow cytometric analysis.

Results: Proband A (Family A) was born to unrelated healthy parents and presented with rash at four hours of life. Biopsy showed leukocytoclastic vasculitis, the rash persisted, and by two years of age she developed worsening pulmonary haemorrhage and splenomegaly. Inflammatory markers were normal and there was no response to anti-inflammatory treatments including prednisolone and trials of: ciclosporin; tacrolimus; colchicine; hydroxychloroquine; mycophenolate mofetil; anakinra; adalimumab; and baricitinib. Initial targeted gene panel and later WES revealed no genetic cause. However, reanalysis using an updated bioinformatics pipeline incorporating the use of Exomiser and referencing the new case report identified a de novo heterozygous *HCK* mutation (c.C1545A; p.Y515X), prompting allogeneic haematopoietic stem cell transplantation.

Proband B and his father (Family B) also presented with rash on the first day of life with normal inflammatory markers. Biopsy showed leukocytoclastic vasculitis and the rash recurred through infancy, triggered by vaccination or illness, but self-resolving. Neither proband nor father developed lung disease or required immunosuppression. WES of Proband B initially revealed no genetic cause. However, reanalysis revealed that he and his father also carried a novel rare heterozygous *HCK* mutation (c.A1565T; p.Y522F).

Functional analysis revealed reduced HCK protein expression consistent with increased degradation of the mutant protein, and increased surface integrin expression and enhanced STAT signalling activation in patient cells.

Conclusion: The leukocyte signalling molecule HCK relies on an inhibitory tyrosine (Y522) in the c-terminal tail to prevent inappropriate pro-inflammatory signalling. The nonsense mutation in Proband A causes loss of this tyrosine, while Family B have a missense mutation in which the inhibitory tyrosine is replaced with phenylalanine, leading to constitutive activation. Since Family B do not have lung involvement and the rash in the father resolved in childhood, we hypothesise that missense mutations in HCK are less deleterious.

In conclusion, we report the second case of the newly-described HCK-vasculitis, and report a further family with a novel missense mutation driving a self-resolving cutaneous vasculitis. We also highlight the importance of re-analysing genetic sequencing data in unsolved cases. This is especially pertinent in the field of autoinflammation where new disease-gene discoveries continue to be made on an annual basis.

Reference: 1) Kanderova V, et al. Early-onset pulmonary and cutaneous vasculitis driven by constitutively active SRC-family kinase HCK. J Allergy Clin Immunol. 2022; 149(4), 1464-1472

Acknowledgments: NIHR-GOSH Biomedical Research Centre and GOSH Children's Charity
Disclosure of Interest: None declared

Identifier: PT78

PRE-CLINICAL CHARACTERIZATION AND CLINICAL EVALUATION OF MAS825, AN ANTI-IL-1 BETA / ANTI-IL-18 BISPECIFIC ANTIBODY FOR THE TREATMENT OF INFLAMMASOMOPATHIES

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Introduction: Inflammasomes are multimeric protein complexes that are sensing "danger signals" to activate protective immune mechanisms. However, the over-activation of the inflammasomes is associated with the onset and progression of several autoinflammatory and autoimmune diseases, including cryopyrin-associated periodic fever syndromes, familial mediterranean fever and/or other arthropathies. Inflammasome pathway activation is marked by increased production of the two effector cytokines IL-1β & IL-18 as well as pyroptosis, which are further fueling cascades of response pathways in innate and adaptive immunity (eg. IL-6, IFNs) leading to organ specific as well as systemic inflammation.

IL-1 inhibitors (eg, canakinumab, anakinra) and IL-6 inhibitors (eg, tocilizumab, tocilizumab-aazg) are biologics approved in some regions to treat inflammasomopathies. However, an unmet medical need exists in patients which have inadequate responses to IL-1/IL-6 inhibitors and develop severe disease courses with glucocorticoid-dependency and life-threatening complications such as macrophage activation syndrome (MAS) and/or lung disease (LD) or in regions where no drugs are approved. In some monogenic inflammasomopathies, highly increased serum IL-18 levels are measured which are not fully downregulated by IL-1/IL-6 pathway inhibition. Furthermore, IL-18 neutralization seems to provide some clinical benefit in patients with NLRC4-gain of function (GoF) mutations and XIAP deficiency. Therefore, we hypothesize that IL-18 together with IL-1β has a pathogenic role in monogenic inflammasomopathies. In pre-clinical models, simultaneous IL-1β & IL-18 inhibition (as compared to single IL-1β or IL-18 inhibition) provides a survival advantage.

Objectives: Therefore, we generated bispecific antibodies to simultaneously neutralize IL-1β & IL-18 with the aim to provide superior efficacy compared to IL-1/IL-6 inhibitors. We achieved simultaneous IL-1β & IL-18 neutralization in one molecule with the generation of the first-in-class IL-1β/IL-18 bispecific antibody MAS825.
Methods: In vitro investigations revealed a high binding affinity to both soluble IL-1β & IL-18 and we measured a high potency of MAS825 in different cellular bioassays. The biochemical and biophysical properties of MAS825 were found to be suitable for further development. No safety signals were monitored in pre-clinical toxicological studies and when MAS825 was administered in healthy volunteers, safety and tolerability was demonstrated after single doses of MAS825. Serum analysis demonstrated that IL-1β & IL-18 pathway markers (IL-6 & IFN-γ, respectively) were reduced after MAS825 administration.
Results: In the MAS-COVID trial (SARS-Cov-2 infected patients with pneumonia and impaired respiratory function), a single dose of MAS825 reduced serum levels of pro-inflammatory cytokines (IL-6, IFN-γ) and MAS825 treated patients had a more rapid clearance of the virus which was associated with a lesser duration of oxygen support, lower ICU admissions, and shorter stay in ICU as compared with those in the control arm. In a hidradenitis suppurativa Ph2 platform study, MAS825 treatment with a total of 5 doses lead to a higher percentage of HiSCR 50 responders at week 16 as compared to the pooled placebo arm. The two Ph2 studies confirmed the safety and tolerability of MAS825 and currently, the long-term treatment with MAS825 is investigated in the MASter-1 study that compromises monogenic, potentially IL-1β & IL-18-driven inflammasomopathies, such as NLRC4-GoF, XIAP deficiencies and CDC42 mutations.
Conclusion: MAS825 could be a treatment option in autoinflammatory diseases where both IL-1β & IL-18 are implicated in the pathophysiology
Disclosure of Interest: J. Kovarik Employee of: Novartis, M. Kiffe Employee of: Novartis, M. Rowlands Employee of: Novartis, R. Siegel Employee of: Novartis, G. Junge Employee of: Novartis, M. Badman Employee of: Novartis

Identifier: PT79

PRECLINICAL EVALUATION OF LENTIVIRAL GENE THERAPY FOR THE TREATMENT OF DADA2: ENGRAFTMENT AND BIODISTRIBUTION STUDIES IN HUMANISED NBSGW MICE

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Introduction: Deficiency of adenosine deaminase type 2 deficiency (DADA2) is caused by bi-allelic loss-of-function mutations in *ADA2*. While anti-TNF therapy is effective for the autoinflammatory and vasculitic components of the disease it does not correct marrow failure or immunodeficiency. Allogeneic stem cell transplantation (HSCT) offers a potential cure is limited by challenges such as graft versus host disease and donor availability. Our previous preclinical studies demonstrated that lentiviral-mediated ADA2 gene therapy, could restore ADA2 enzyme activity in patient-derived cells, correct macrophage inflammatory activation and reduce endothelial activation *ex vivo.*
Objectives: The objective of this study was to evaluate the biodistribution and engraftment potential of lentiviral-mediated ADA2 gene therapy in healthy donor- and DADA2 patient-derived hematopoietic stem cells (HSC) *in vivo*.
Methods: A humanized NBSGW mouse model (NOD, B2mnull, SCID, IL2Rγnull) was used to evaluate the engraftment potential and biodistribution of lentivirally transduced HSC. Healthy donor-derived and DADA2 patient-derived hematopoietic stem cells (HSC) were transduced with a lentiviral vector containing the ADA2 gene. Transduction efficiency and engraftment were evaluated by PCR analysis to detect viral integration, along with histological assessments of non-hematopoietic organs to identify potential adverse tissue changes. The multilineage differentiation and engraftment capacity of the transduced HSC were monitored in vivo, and functional assessment of ADA2 enzyme activity was conducted to confirm therapeutic restoration in the patient-derived HSC.
Results: Lentiviral transduction of healthy donor HSC successfully preserved their multilineage differentiation and engraftment capacity in the NBSGW mice, with no adverse effects on HSC functionality post-transplantation. PCR analysis confirmed the absence of viral integration in non-hematopoietic organs, ensuring the precision and safety of the approach. Histological evaluations showed no abnormal tissue changes in any of the organs. In DADA2 patient-derived HSC, ADA2 transduction resulted in restored enzyme expression, suggesting an improvement in cellular function. Additionally, transduced patient-derived HSC showed enhanced engraftment potential, further supporting the therapeutic promise of this approach for DADA2.
Conclusion: These findings lay a strong foundation for further clinical development of ADA2 gene therapy as a potential curative treatment for DADA2, advancing toward clinical application.
Acknowledgments: Action Medical Research, Lifearc grant, Rosetrees Trust and GOSH Children's Charity.
Disclosure of Interest: None declared

Identifier: PT80

REPORT OF ELEVEN PATIENTS WITH INHERITED ARPC1B DEFICIENCY: FOUNDER GENE EFFECT FROM NEPAL

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Introduction: Inherited ARPC1B deficiency (A1BD) is a rare autosomal recessive syndromic combined immunodeficiency that usually manifests in infancy with a myriad of infective, allergic, and autoimmune/inflammatory features. Only about 34 patients with $A_{1B}D$ have been reported in the literature thus far.

Objectives: To describe clinical and genotypic features of 11 patients with A1BD with unique features from Nepal.

Methods: Data on clinical-epidemiological features, immuno-hematological parameters, treatment, and outcome were explored from the medical records. Homozygosity mapping and haplotype analysis were also performed.

Results: Similar to previous reports, we noted infective and autoimmune/allergic manifestations in all of our patients. Unique features noted in our study include rheumatoid factor (RF) positive chronic arthritis (mimicking RF+ juvenile idiopathic arthritis), significantly elevated anti-tissue transglutaminase antibody titers, generalized skin hyperpigmentation, distal phalangeal enlargement, frontal bone hypertrophy, hypertrophic skin scars, and hyperkeratosis. Nine cases harbored the founder splice-site variant c.64+2T>A in the ARPC1B gene. Two cases have unique compound heterozygous mutations. Long-term outcomes in our patients were significantly worse than reported previously. Comparative phenotypic analysis showed significantly greater proportions of otitis, gastroenteritis, lymphadenopathy, arthritis, inflammatory bowel disease-like manifestations, and elevated IgA. Genetic analysis indicates the founder gene effect of the detected variant in Nepal.

Conclusion: This is the first and largest cohort of A1BD ever reported from a single center. c.64+2T>A is a founder variant in Nepalese patients with A1BD.

Disclosure of Interest: None declared

Identifier: PO001

A NOVEL IKBKB VARIANT INCREASES PROTEIN STABILITY AND DRIVES PERSISTENT AUTOINFLAMMATION

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Introduction: NF-κB signaling is essential for immune and inflammatory responses, regulating cell activation, proliferation, and survival. Genetic defects in the IKK/NF-κB pathway, particularly involving IKKβ, have been associated with immunodeficiencies and autoinflammatory diseases.

Objectives: This study investigates the clinical, genetic, and functional impact of a novel *IKBKB* variant in a patient with recurrent fever and systemic inflammation.

Methods: Whole exome sequencing identified a novel *IKBKB* variant. The structural impact was predicted using *in silico* analysis. RNA sequencing explored potential pathways, with real-time PCR and Western blotting evaluating NF-κB signaling. Proinflammatory cytokines were quantified using ELISA. Luciferase reporter analysis, co-immunoprecipitation, and cycloheximide chase assays were performed in HEK293T cells to assess NF-κB activity, protein interactions, and protein stability.

Results: A 41-year-old man with a 10-year history of recurrent fever, systemic inflammation, and immune abnormalities was found to carry a rare heterozygous missense variant, c.1106A>G (p.Q369R), in *IKBKB* (NM_001556.2), encoding IKKβ. *In-silico* analysis predicted the variant to be damaging, which may affect the ubiquitin-like domain of IKKβ. In patient-derived PBMCs, RNA sequencing revealed the NF-κB and TNF pathways enrichment. The mRNA levels of *IKKβ*, *IκBα*, and *MCP-1* showed an upward trend without stimulation compared to healthy controls. Functional studies showed sustained IκBα phosphorylation after 30 minutes of TNF-α/LPS stimulation, and increased basal levels of IKKβ and IκBα in patient-derived PBMCs. Plasma cytokine levels were significantly elevated, including IL-6, IL-1β, and TNF-α. Overexpression of *IKBKB* variant Q369R in HEK293T cells showed enhanced NF-κB activity, increased phosphorylation of IKKβ, IκBα, and p65 before and after TNF stimulation, and slower degradation of IKKβ and phosphorylation of IKKβ compared to the wild-type. However, interactions with p65 remained unaffected.

Conclusion: The *IKBKB* variant Q369R enhances the protein stability and prolongs NF-κB activation. These findings elucidate a mechanism contributing to autoinflammation and potential therapeutic targets for managing autoinflammatory diseases.

Acknowledgments: We would like to acknowledge the patient for his consent to participate in the study.

Disclosure of Interest: None declared

Identifier: PO002

PATHOPHYSIOLOGICAL MECHANISMS REGULATING THE PENETRANCE OF MEFV GENE VARIANTS

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Introduction: Familial Mediterranean fever (FMF) is a hereditary auto-inflammatory disease caused by mutations in the MEFV gene. This gene codes for pyrin, a protein that plays a key role in regulating inflammation. Pathogenic mutations in MEFV cause pyrin dephosphorylation, activating the pyroptosome responsible for inflammatory symptoms. FMF manifests as recurrent episodes of fever, abdominal, chest and joint pain, and can lead to serious complications such as amyloidosis. Although FMF is predominantly an autosomal recessive disease, around 30% of clinically symptomatic patients have only one pathogenic variant, suggesting the existence of a second modifying factor or allelic exclusion. Apoptosis-associated speck-like protein (ASC) is a critical component of most inflammasomes, which are the main actors of the inflammatory responses. Upon activation of inflammasomes, ASC forms large protein aggregates called "specks". This filamentous structure creates multiple caspase-1 activation sites and serves as a signal amplification mechanism for inflammasome-mediated cytokine production. ASC-Speck formation can be used as a readout to identify cells undergoing inflammasome activation in response to various stimuli triggering inflammasome pathway to assess the pathogenicity of a given MEFV variant.

Objectives: By combining clinical data from a cohort of patients investigated for FMF at CHUSJ Sainte-Justine, functional test results, genetic analyses of the MEFV gene and Nanopore transcriptomic data, we intend to unveil the mechanisms responsible for the penetrance of this disease.

Methods: We used a flow cytometry-based assay to assess ASC speck formation following inflammasome agonist stimulation in peripheral circulating monocytes of 38 patients harboring genetic variations in the *MEFV* gene. We performed a transcriptomic study through long-read Nanopore sequencing and long-range MEFV-specific q-PCR on cDNA from PBMCs of patients carrying the M684V variant in MEFV: one homozygous symptomatic patient, two heterozygous patients (one symptomatic, the other asymptomatic), and one healthy control.

Results: Through the analysis of the 38 patients with *MEFV* genetic variation, we demonstrated that our ASC-Speck Flow Assay correctly identified FMF patients with genetic variant affecting the compared to healthy controls and patients with other autoinflammatory disorders. Interestingly, the flow cytometric assay helped discriminate patients with monoallelic variants who exhibit abnormal pyroptosome activation from patients with monoallelic variants and normal pyroptosome activation, suggesting it could be a diagnostic tool for guiding appropriate management of patients. We are currently analyzing the results of Nanopore sequencing using unsupervised pathway analyses and studying the specific allelic expression of the MEFV gene in selected cases to determine whether allelic exclusion could explain the difference in symptoms between patients with monoallelic variants.

Conclusion: This study will allow us to better inform preventive and therapeutic strategies for patients presenting with recurrent fever and genetic variation in the *MEFV* gene and address certain knowledge gaps related to the genetic and molecular mechanisms of the disease.

Disclosure of Interest: None declared

Identifier: PO003

UNRAVELING THE CELLULAR MECHANISMS UNDERLYING INFLAMMASOPATHIES USING GENETIC MOUSE MODELS

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Introduction: Inflammasomes are innate immunity signaling hubs that are activated when a sensor protein recognizes cellular stress, after which the activated protease caspase-1 cleaves its substrate Gasdermin D (GSDMD). The N-terminal GSDMD fragment subsequently triggers a lytic form of cell death termed pyroptosis, which is accompanied by the release of the IL-1β and IL-18 pro-inflammatory cytokines that contribute to mounting an inflammatory response.

Inflammasopathies are a group of auto-inflammatory diseases (AIDs) caused by gain-of-function (GOF) mutations in genes encoding inflammasome sensor proteins. For instance, GOF mutation in the genes encoding Pyrin or NLRP3 underly the development of Familial Mediterranean Fever (FMF) or cryopyrin-associated periodic syndromes (CAPS), respectively. Both of these inflammasopathies are characterized by increased IL-1β production, leading to the successful use of IL-1-antagonizing therapeutics in these disease.

Objectives: We aim to identify the key cellular sources for IL-1β in FMF and CAPS, as well as the cell death mechanisms that drive the secretion of IL-1β from these autoinflammation-provoking cell types.
Methods: We are using genetic mouse models of FMF and CAPS combined with cell type-specific or full body deletion of inflammasome signaling proteins. Immunophenotyping of these complex genetic models aims to elucidate the cellular and molecular mechanisms of IL-1β production and ensuing autoinflammation in these mouse models.
Results: To mimic FMF we use mice expressing a hybrid murine-human Pyrin protein containing the human FMF-associated Pyrin^{V726A} mutation. We crossed these mice with mice harboring conditional caspase-1 alleles, allowing to abolish caspase-1 expression in these Pyrin^{V726A} expressing mice specifically in particular immune cell types. We evaluated autoinflammation severity in the resulting mice in order to pinpoint the cells in which Pyrin^{V726A} inflammasome activity drives autoinflammation.

Conversely, for identifying the cell types driving CAPS we are using a mouse model allowing cell-type specific expression of a murine Nlrp3^{A350V} GOF protein. Specifically expressing this CAPS-associated Nlrp3^{A350V} mutant in either macrophages or neutrophils (Nlrp3$^{Mac\text{-}A350V}$ and Nlrp3$^{Neu\text{-}A350V}$) was sufficient to cause severe systemic inflammation. We are currently investigating the role of GSDMD in the development of the pathology in these mouse models to compare the role for GSDMD-mediated cell death in driving CAPS pathogenesis originating either from macrophages (pyroptosis) or from neutrophils (NETosis).

Conclusion: Our ongoing research helps understanding the cellular level of how inflammasomes and GSDMD-mediated cell death modes cooperate to propel auto-inflammation in various driver cell types in FMF and in CAPS. Detailed results of this ongoing unpublished work will be presented on the ISSAID meeting.
Disclosure of Interest: None declared

Identifier: PO005

ELEVATED SERUM GASDERMIN D LEVELS IN PATIENTS WITH FAMILIAL MEDITERRANEAN FEVER

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Introduction: Familial mediterranean fever (FMF) is an autoinflammatory disorder arising from the pathogenic variations in the *MEFV* gene. These variations lead to overactivation of pyrin inflammasome resulting in GSDMD cleavage and GSDMD mediated inflammatory cytokine release.
Objectives: In this study, we aimed to explore serum levels of GSDMD among FMF patients and compare them with healthy and diseased controls.
Methods: In total 76 blood samples were collected from attack-free FMF patients (n=14), FMF patients with attack (n=18), patients with acute appendicitis (n=24), and healthy volunteers (n=17). Serum levels of GSDMD were determined via enzyme-linked immunosorbent assay (ELISA).

	FMF (during attack) *(Median + IQR) (n=18)*	FMF (attack-free) *(Median + IQR) (n=14)*	Appendicitis *(Median + IQR) (n=24*	Healthy control *(Median + IQR) (n=17)*
Age (years, mean ± SD)	34.5 ± 12.6	37.18 ± 13.57	41.8 ± 23.05	35.71 ± 7.8
Gender (females, %, n)	38.9 (7)	**50 (6)**	41.7 (10)	64.7 (11)
GSDMD (ng/mL)	3.1 (2.37-4.52) [a]	**2.85 (2.52-3.0)** [b]	3.0 (2.4-6.5) [c]	1.9 (1.6-2.6) [a, b, c]
CRP (mg/L)	45.07 (13.18-66.24) [a, d]	2.71 (1.66-3.81) [b, d, e]	22 (6.5-89)[c, e]	0.95 (0.55-1.00) [a, b, c]
WBC	8.8 (7.2-11.1) [a]	7.0 (6.5-9.05) [e]	11.88 (7.59-14.42) [c, e]	**6.9 (5.6-8.4)** [a, c]
NEUT	**6.2 (5.1-9.2)** [a, d]	4.1 (3.5-4.7) [d, e]	**9.14 (5.38-11.55)** [c, e]	5.6 (3.9-6.2)[a, c]

[a] Statistically significant difference (p-value< 0.05) between FMF patients with attack and healthy volunteers. [b] Statistically significant difference between attack-free FMF patients and healthy volunteers. [c] Statistically significant difference between patients with appendicitis and healthy volunteers. [d] Statistically significant difference between FMF patients with and without attack. [e] Statistically significant difference between attack-free FMF patients and patients with appendicitis.

Results: FMF patients exhibited increased serum GSDMD levels during attack and attack-free periods compared to healthy controls (p-values: 0.001, 0.002). Patients with appendicitis had significantly elevated GSDMD levels than healthy volunteers (p-value: 0.000). FMF patients with attack and patients with appendicitis had higher GSDMD levels,

but this difference did not reach statistical significance. FMF patients with attack and patients with appendicitis were found to have comparable GSDMD levels.

Serum GSDMD levels and clinical features of patients are summarized in the table

ROC curves indicated good discriminatory power for GSDMD in differentiating FMF patients with attack, FMF patients without attack, and patients with appendicitis from healthy individuals (AUC values: of 0.830, 0.828, and 0.837, respectively).

Conclusion: This study demonstrated that increased serum GSDMD is not exclusive to FMF and has limited diagnostic value, only differentiating disease and health states, despite its importance in pathogenesis. Nonetheless, these outcomes illustrate enhanced priming for pyroptosis in FMF patients even during remission. Targeting pyroptosis represents a novel therapeutic landscape.

Disclosure of Interest: None declared

Identifier: PO006

CELL MIGRATION DEFECT IN HYPERIMMUNOGLOBULIN D SYNDROME PATIENT CELLS

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Introduction: Hyperimmunoglobulin D Syndrome (HIDS) is a rare autoinflammatory disease caused by mutations in MVK gene, which encodes the mevalonate kinase enzyme., responsible for catalyzing the phosphorylation of mevalonic acid. The mutations in MVK gene cause Mevalonate Kinase Deficiency (MKD), comprising phenotypic manifestations ranging from HIDS to mevalonic aciduria (MVA). Currently the proposed mechanism for the pathogenesis of this disease includes defective prenylation of RhoA, inhibiting proper RhoA placement in the cell membrane and its activation. RhoA inhibition leads to the disinhibition of the pyrin inflammasome, causing the autoinflammatory features of the disease. RhoA is an important player in the regulation of cellular migration, an important step of the inflammatory process.
Objectives: This study seeks to investigate how cell migration is affected in the inflammatory process in HIDS patients.
Methods: Primary cells (PBMCs or fibroblasts) of 4 pediatric HIDS patients (G18R/V377I, G140R/Q290R, V377I/V377I, V377I/V377I) along with healthy controls and FMF patients, were derived from either blood samples or skin punch biopsy samples. PBMCs were isolated using Lymphosep, then cultured in Opti-MEM with LPS. Negative control comprised unstimulated cells, while LPS stimulation along with arachidonic acid inhibition was used to inhibit the pyrin inflammasome. Cell migration assay was performed by seeding monocytes in Thincert membranes, then visualizing live cells in the lower compartment after 2 hours. Skin samples were explanted to form fibroblast cultures, which were cultured in DMEM with %10 FBS. Fibroblast cells migration was assessed using the wound healing assay. Briefly, cells were seeded and cultured until confluency, when a “wound” was created using a pipette tip to scratch the cell monolayer. Microscopic images were taken at time points 0, 6, 9 and 12 hours to measure wound width.
Results: HIDS PBMCs showed defective cell migration in stimulated and unstimulated conditions, compared to healthy control cells; whereas FMF patients’ PBMCs showed increased cell migration in both stimulated and unstimulated conditions. Accordingly, HIDS fibroblasts showed slowed wound healing compared to healthy control fibroblasts ($p = 0.0014^{**}$ at 6 hours).
Conclusion: Our results suggest that HIDS-causing *MVK* mutations interfere with the process of cell migration. These findings are surprising considering inflammation is a key characteristic of the disease, where cell migration plays an important role. Furthermore the significant defect in cell migration is observed not only in immune system related cells but also in fibroblasts of HIDS patients. Further research into the mechanisms behind this finding may allow for better understanding and treatment options for HIDS.
Acknowledgments: This project was supported by the Scientific and Technological Research Council of Türkiye (Grant number: 122S379) and Hacettepe University Scientific Research Projects Coordination Unit (Grant number: TYL-2018-17354, THD-2024-21311).
Disclosure of Interest: None declared

Identifier: PO007

HUMAN PRIMARY MONOCYTES CELL DEATH AND IL-1B PRODUCTION IS DIFFERENTLY REGULATED IN FMF PATIENTS COMPARED TO HEALTHY CONTROLS

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Introduction: Increasing evidence implicates cell death pathways linked to IL-1β are more complex (1, 2). These cell death regulatory mechanisms have not yet been systematically explored in Familial Mediterranean Fever (FMF) (3).
Objectives: This study investigated how cell death is regulated in human primary monocytes from healthy donors and FMF patients.
Methods: Monocytes were isolated from PBMC's with MACS using negative selection from 10 healthy donors and 11 FMF patients. Monocytes were incubated at 37^{o}C, 5% CO_2 with 1 hour of medium, RIPK1 inhibitor (Nec-1) (20 uM), caspase-1/4 inhibitor VX-765 (20 uM), or RIPK3 inhibitor GSK782 (25 uM), followed by 16 hours with caspase-8 inhibitor Z-IETD-FMK (10 uM), LPS (& nigericin) (5 ng/mL; 6.7 uM), TNFα & IFNγ (50 ng/mL; 50 ng/mL), or staurosporine (10 uM). Cell death was visualized with Incucyte S3 using Incucyte® Cytotox Green Dye and analyzed using Incucyte software. Supernatants were collected and ELISA for IL-1β, IL-6 and TNFα was performed.
Results: In human primary monocytes, staurosporine, and the combination of LPS/nigericin induced cell death, while LPS alone and the combination of TNFα/IFNγ did not. Z-IETD-FMK alone induced cell death, that could be inhibited by nec-1. In contrast, nec-1 increased cell death induced by LPS & nigericin and staurosporine. VX-765 did not have any effect on cell death. GSK872 did not affect staurosporine-induced cell death, but slightly induced cell death by LPS/nigericin. Similar to nec-1, GSK872 showed to inhibit lytic cell death induced by Z-IETD-FMK.

We observed an increase in IL-1β production when monocytes were stimulated with LPS, LPS/nigericin, and Z-IETD-FMK. In contrast to having no effect on cell death induced by LPS/nigericin, VX-765 significantly inhibited IL-1β production, and showed a trend toward inhibition of Z-IETD-FMK-induced IL-1β. Nec-1 and GSK872, however, inhibited IL-1β production by Z-IETD-FMK, as well as LPS/nigericin. While IL-6 followed the same trend as IL-1β, TNFα production was only induced by LPS and the combination LPS/nigericin. TNFα production was not dependent on Nec-1, but showed a reduction in the presence of VX-765 and GSK872 in monocytes from healthy donors.

When compared to monocytes from healthy donors, monocytes from FMF patients showed overall less cell death sensitivity. Nec-1 and GSK872 affected cell death in FMF monocytes in the same way as in healthy monocytes. However, VX-765 increased cell death induced by Z-IETD-FMK in FMF monocytes, contrary to healthy monocytes. Whereas VX-765 showed a trend towards a decrease in Z-IETD-FMK-induced IL-1β by healthy monocytes, we observed a trend towards increased IL-1β production in FMF monocytes. Another notable difference was that GSK872 enhanced IL-6 production in FMF monocytes stimulated with LPS/nigericin, whereas this had no effect on healthy monocytes. In FMF monocytes we observed that the TNF production induced by LPS/nigericin was dependent on caspase-1/4 inhibitor VX-765.

Conclusion: We were able to show that the classically known cell death pathways pyroptosis, apoptosis and necroptosis affect each other in human primary monocytes, thereby showing that cell death in human monocytes is a more complex network than previously described. Strikingly, caspase-8 inhibition alone in the absence of any other stimulus induced cell death and production of IL-1β in human primary monocytes, which was at least dependent on RIPK1 and RIPK3. Cell death induced by caspase-8 was even further increased in the presence of caspase-1/-4 inhibition, which in parallel showed a trend towards increased IL-1β production. In FMF patients, we found dysregulated cell death regulatory mechanisms and IL-1β production, which suggest novel autoinflammatory mechanisms that could help explain pathology in in FMF.
Disclosure of Interest: None declared

Identifier: PO008

COMPREHENSIVE ANALYSIS OF IMMUNE DYSREGULATION INDUCED BY A NOVEL GAIN-OF-FUNCTION UNC93B1 HOMOZYGOUS MUTATION IN LUPUS

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Introduction: UNC93B1 is a key regulator in TLR signaling. Investigation of its pathogenesis in systemic lupus erythematosus (SLE) will help to construct deeper insights into SLE development.

Objectives: This study investigates the details of immune dysregulation in lupus induced by novel *UNC93B1* mutation with a SLE patient and mouse models.

Methods: The patient's mutations were identified by whole exome sequencing (WES). Bulk and single-cell transcriptional analysis of the patient's peripheral blood mononuclear cells (PBMCs) and splenocytes from *Unc93b1* transgenic mice were used to investigate inflammatory responses. Quantitative PCR, flow cytometry, luciferase assay, immunoblotting, immunoprecipitation, immunohistochemistry, immunofluorescence, and cytokine detection were used to define the immunological and molecular signatures in HEK293T, RAW264.7 cell line and samples from *Unc93b1* transgenic mice.

Results: We carried out comprehensive analysis of immune dysregulation caused by a novel homozygous gain-of-function *UNC93B1* p.R95L mutation in an early-onset SLE patient and R95L knock-in mouse models. The patient's PBMCs revealed significantly elevated inflammation in T cells and myeloid cells. Mechanistic studies show that the UNC93B1 R95L mutation weakens the interaction between UNC93B1 and TLR7 and selectively hyperactivates TLR7/8, but not TLR3/9, through enhanced ssRNA binding affinity without affecting TLR7/8 translocation. *In vitro* assays and R95L knock-in mouse models further demonstrate that this mutation induces multi-organ inflammation, mediated by type I IFN and NF-κB pathways. Mouse models also manifest cell-type-specific inflammatory signatures, notably in dendritic and B cells.

Conclusion: Our results highlight UNC93B1's unique role in immune regulation through TLR signaling and SLE development and offer insights into the potential for targeting TLR7/8 in SLE therapy.

Acknowledgments: We thank the patient and the unaffected controls for their support during this research study.

Disclosure of Interest: None declared

Identifier: PO009

CYP3A4 REGULATION BY MIR-505-5P: A NOVEL INSIGHT INTO COLCHICINE RESISTANCE IN FMF PATIENTS

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Introduction: Familial Mediterranean Fever (FMF) is the most common autosomal recessive autoinflammatory disease. Daily colchicine therapy is the standard treatment, but approximately 5-10% of patients exhibit colchicine resistance despite receiving the maximum tolerable dose. These patients often require biological treatments such as anakinra or canakinumab to control inflammation.

Objectives: This study investigates the potential role of microRNAs (miRNAs) in colchicine resistance in FMF patients and their possible effect on regulation of drug metabolism genes.

Methods: Microarray analyses were performed on colchicine-resistant and colchicine-responsive FMF patients to identify differentially expressed miRNAs. Bioinformatic tools were used to predict miRNAs involved in drug metabolism. Validation of miRNA expression and target gene interactions was conducted using qRT-PCR. The interaction between miR-505-5p and CYP3A4 was confirmed by using 3'UTR luciferase assays. A colchicine-resistant HEPG2 cell line was generated to perform functional analyses related to miRNA and target gene expression.

Results: Microarray analysis revealed a decrease in miR-186-3p, miR-548a-3p, and miR-7-5p levels, while miR-505-5p and miR-4482-3p were upregulated in colchicine-resistant FMF patients. Bioinformatic analysis identified miR-505-5p as a regulator of drug metabolism and drug resistance-related genes. qRT-PCR validated the increased expression of miR-505-5p in colchicine-resistant FMF patients. Target gene studies in HEPG2 cells demonstrated that miR-505-5p directly regulates CYP3A4 expression, confirmed by 3'UTR luciferase assays. Colchicine-resistant HEPG2 cells showed similar miRNA and CYP3A4 expression patterns as observed in colchicine-resistant FMF patients.

Conclusion: This study highlights the role of miR-505-5p in regulating CYP3A4, contributing to colchicine resistance in FMF patients. These findings may provide new insights into the mechanisms underlying drug resistance and open avenues for developing targeted miRNA based therapies in autoinflammatory diseases.

Acknowledgments: This project has been funded by The Technical and Scientific Research Council of Turkey, 218S522 and Hacettepe University Scientific Research Projects Coordination Unit (TSA-2025-21789)

Disclosure of Interest: None declared

Identifier: PO010

DISTINCT SERUM IMMUNOREACTIVITY PATTERNS IN MULTIPLE SCLEROSIS AND BEHÇET'S DISEASE: A COMPARATIVE ANALYSIS

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Introduction: Behçet's disease (BD) and multiple sclerosis (MS) are distinct immune-mediated disorders that share overlapping neurological manifestations, complicating diagnosis. Serum immunoreactivity to medium (NF-M) and light (NF-L) isoforms of neurofilament is observed in BD and MS, respectively. This overlap may pose challenges for tissue- or serum-based immunoassays used in the diagnostic process.

Objectives: This study aimed to compare tissue neurofilament immunoreactivity patterns between MS and BD patients and to evaluate their diagnostic specificity.

Methods: Mouse brain tissue sections were immunolabeled with sera from 49 individuals diagnosed with BD or MS, and examined using confocal microscopy to identify distinct staining patterns associated with each disease. Additionally, spectral confocal reflectance (SCoRe) microscopy was utilized to confirm myelin structures immunolabeled with MS sera.

Results: Immunoreactivity consistent with fine filamentous NF-M labeling in axons was observed in great majority of BD patient sera. In contrast, MS patient sera exhibited a thick filamentous staining pattern associated with oligodendrocytes and their myelin-forming processes, as confirmed by SCoRe microscopy analysis. Unlike BD, no fine filamentous immunolabeling of axons was observed in MS samples.

Conclusion: This study highlights distinct neurofilament immunoreactivity patterns in BD and MS patient sera, underscoring their potential use in differential diagnosis. The fine filamentous axonal staining characteristic of BD contrasts with the oligodendrocyte-associated thick filamentous staining seen in MS, providing a novel serological tool for distinguishing between these two conditions.

Acknowledgments: This study funded by Hacettepe University Scientific Research Projects Coordination Unit (TSA-2019-17549)

Disclosure of Interest: None declared

Identifier: PO011

INVESTIGATION OF THE MECHANISMS UNDERLYING THE ALTERED EXPRESSION OF MIR-197-3P IN PATIENTS WITH FAMILIAL MEDITERRANEAN FEVER

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Introduction: Familial Mediterranean Fever (FMF) is the most common autoinflammatory disorder caused by mutations in the *MEFV* gene, which encodes the pyrin protein. In our previous studies, the reduced expression of miR-197-3p has been reported in FMF patients, indicating that its downregulation may play a role in the heightened inflammatory state characteristic of this condition. The underlying reasons for this reduction have not been previously investigated.
Objectives: This study aims to investigate the molecular mechanisms responsible for the decreased expression of miR-197-3p in FMF, focusing on potential transcriptional regulatory mechanisms. The primary objective is to assess the gene expression levels of pri-miR-197-3p (primary miRNA) and pre-miR-197-3p (precursor miRNA) and to evaluate the role of DNA methylation in the proximal promoter regions of *MIR197* and its host gene, *GNAI3*, as a potential factor contributing to the reduced expression of mature miR-197-3p.
Methods: The expression levels of pri-miR-197-3p and pre-miR-197-3p were analyzed in lipopolysaccharide (LPS)-treated, TNF-α-treated, IL-1β-treated, and untreated peripheral blood mononuclear cells (PBMCs) from FMF patients and control groups using quantitative real-time PCR (RT-qPCR). Ethics committee approval for the study was obtained from the Hacettepe University Non-Interventional Clinical Research Ethics Committee with the approval number GO 22/866. To assess DNA methylation status, bisulfite sequencing was performed on the proximal promoter regions of the *MIR197* gene and the promoter of its host gene, *GNAI3*, in PBMCs from patient and control samples.
Results: Gene expression analysis revealed a significant downregulation of pri-miR-197-3p and pre-miR-197-3p in untreated FMF patients compared to healthy controls. These findings suggest that transcriptional regulatory mechanisms may be involved in the reduced expression of pre-miR-197-3p. Bisulfite sequencing analysis of the *MIR197* promoter showed no significant differences in methylation between FMF patients and controls. However, hypermethylation was observed at CpG sites in region 2 of the *GNAI3* promoter in FMF patients. Although it did not reach statistical significance, this result implies that miR-197-3p may be regulated by the *GNAI3* promoter rather than its own promoter
Conclusion: The results demonstrate that the downregulation of miR-197-3p in FMF patients is not associated with changes in DNA methylation of the *MIR197* and *GNAI3* promoter but may be linked to transcriptional regulatory mechanisms. The findings highlight the need for further exploration of alternative regulatory mechanisms, such as histone modifications, transcription factor accessibility, RNA-binding proteins, and competing endogenous RNAs (ceRNAs) interactions. Identifying these mechanisms could reveal potential targets for therapeutic intervention in FMF and other autoinflammatory diseases.
Acknowledgments: This study was supported by the Scientific Research Projects Coordination Unit (BAP) of Hacettepe University under the Grant Number TKB-2023-20399. The authors thank to BAP for their supports.
Disclosure of Interest: None declared

Identifier: PO012

ASSESSMENT OF C26:0 LYSOPHOSPHATIDYLCHOLINE AND CHITOTRIOSIDASE LEVELS IN PATIENTS WITH DEFICIENCY OF ADENOSINE DEAMINASE 2

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Introduction: Deficiency of adenosine deaminase 2 (DADA2) is a monogenic autoinflammatory disease caused by biallelic genetic variants associated with loss of function in the ADA2 gene. One of the recently proposed hypotheses for the role of ADA2 protein suggests that it is a lysosomal enzyme, with DNAse activity (1). In Aicardi-Goutières Syndrome (AGS), a prototype inborn error of the nucleic acid metabolism, an increase in the levels of C26:0 lysophosphatidylcholine (C26:0 LPC) has been reported (2). Furthermore, in several lysosomal diseases, the levels of chitotriosidase (ChT), an enzyme produced by activated macrophages, are significantly increased (3). Data on the expression of C26:0 LPC and chitotriosidase in DADA2 are still lacking.
Objectives: To evaluate the levels of C26:0 LPC and chitotriosidase in individuals with DADA2.
Methods: We collected dried blood spot (DBS) samples from patients with DADA2. C26:0-LPC, levels were determined in the DBS samples by high-performance liquid chromatography coupled to tandem mass spectrometry, along with the levels of adenosine (Ado) and deoxyadenosine (dAdo). ChT levels were determined in the DBS using a using fluorescent substrate, as previously described (4). All analyses were performed in duplicate. The Ethics Committee of the Hospital de Clinicas de Porto Alegre approved the project (#DIPE 2024-0101).
Results: Three patients with DADA2 were included in this study, all with an inflammatory and vasculitic phenotype (all females, with ages of 34, 25, and 23 years). All subjects were on anti TNF treatment (etanercept), although with incomplete symptomatic resolution. The levels of all evaluated biomarkers were in the normal range (table 1).

Table 1 – Levels of DBS biomarkers in three patients with DADA2

	Subject 1	Subject 2	Subject 3	Reference range
Ado	0.24	0.28	0.21	<3.42 µmol/L
dAdo	0.01	0.01	0.01	<0.03 µmol/L
C26:0 LPC	0.22	0.25	0.32	<0.78 µmol/L
ChT	21.1	24.4	20.1	7.0-89.9 nmol/h/mL

Conclusion: The normal ranges of Ado and dAdo in this sample are in accordance with previous reports and are compatible with a biological role for ADA2 not directly related to its deaminase activity. The results of this study also

suggest that C26:0-LPC and ChT are not highly sensitive biomarkers for vasculitic DADA2. As a next step, we intend to evaluate other biomarkers related to the presumed lysosomal DNAse activity of ADA2.

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Disclosure of Interest: None declared

Identifier: PO015

PSTPIP1 P.E250K VARIANT ATTENUATES PROTEIN EXPRESSION AND PODOSOME FORMATION IN PATIENT-DERIVED MACROPHAGES

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Introduction: PSTPIP1 (Proline-Serine-Threonine Phosphatase Interacting Protein 1) defects are implicated in a group of autoinflammatory diseases collectively known as PAID. PSTPIP1 is an F-BAR domain-containing protein involved in the regulation of actin cytoskeleton polymerization. Previous studies have shown that several PSTPIP1 variants can disrupt podosome formation in macrophages. Here, we investigated the functional impact of the p.E250K variant of PSTPIP1 in patient-derived macrophages.

Objectives: To analyze PSTPIP1 protein levels and characterize the kinetics of podosome formation in primary macrophages derived from five patients harboring the PSTPIP1^{E250K} variant.

Methods: PSTPIP1 protein levels were measured using Western blot. Confocal microscopy was employed to assess podosome characteristics in fixed cells. LifeAct-mStayGold mRNA-transfected macrophages were imaged to visualize podosome dynamics in living cells.

Results: Macrophages from patients with the p.E250K variant exhibited significantly reduced PSTPIP1 protein levels compared to controls. A marked decrease in the mean podosome count per cell was observed in patients relative to control group. Moreover, the proportion of cells lacking podosome structures was significantly higher in p.E250K macrophages. However, live cell imaging revealed that, despite the reduction of mean podosome count, p.E250K variant significantly enhanced podosome stability.

Conclusion: Our study provides the first evidence that the PSTPIP1 F-BAR domain mutation p.E250K may exert dual effects on primary macrophages. While the mutation reduces the number of podosome-forming cells, it simultaneously increases podosome stability. In addition, the p.E250K variant negatively impacts PSTPIP1 protein levels in macrophages. These findings reveal a previously unrecognized role of PSPTIP1 in podosome dynamics regulation and offer new insights into the molecular mechanisms underlying the pathophysiology of PAID.

Disclosure of Interest: None declared

Identifier: PO016

THE ROLE OF FATTY ACIDS IN FAMILIAL MEDITERRANEAN FEVER

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Introduction: Inflammasome activation is a tightly regulated multi-step process with multiple checks and balances to control inflammation. While critical for immune defense, its dysregulation can lead to autoinflammatory conditions. However, the mechanisms governing the activation and shutdown of inflammasomes remain incompletely understood. In *Familial Mediterranean Fever* (FMF), gain-of-function mutations in the MEFV gene affect the C-terminal B30.2 domain of the Pyrin protein, though how these mutations influence Pyrin inflammasome activation remains elusive. Emerging evidence highlights the significant role of lipid metabolism in inflammatory processes, contributing both to inflammation and its resolution.

Objectives: This study investigates the interplay between fatty acid metabolism and immune cell function in FMF and related autoinflammatory diseases, with a focus on the role of polyunsaturated fatty acids such as arachidonic acid (ARA).

Methods: We analyzed human serum samples from healthy controls and FMF patients using advanced lipidomics to identify alterations in lipid metabolism. Pathway analysis was performed to pinpoint key enzymes and pathways driving these metabolic changes. Additionally, in vitro experiments were conducted to assess the effects of ARA on Pyrin inflammasome activation.

Results: Llipidomic analysis revealed significant alterations in lipid metabolism in FMF patients compared to healthy controls. Pathway analysis identified phospholipase A2 as a pivotal driver of these metabolic changes. Notably, we observed that ARA, a polyunsaturated fatty acid, inhibited Pyrin inflammasome activation in vitro.

Conclusion: Our findings suggest that, in addition to its well-known proinflammatory properties, ARA may also possess anti-inflammatory effects by inhibiting Pyrin inflammasome activation. This novel perspective enhances our understanding of FMF pathogenesis and highlights lipid metabolism as a potential target for innovative therapeutic strategies in FMF and other autoinflammatory disorders.

Disclosure of Interest: None declared

Identifier: PO017

INVESTIGATION OF INNATE LYMPHOID CELLS IN CHILD PATIENTS DIAGNOSED WITH FAMILIAL MEDITERRANEAN FEVER WITH SPONDYLARTHRITIS

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Introduction: Familial Mediterranean fever(FMF) is the most common monogenic autoinflammatory disease. FMF can be associated with many diseases such as Spondyloarthropathy(SpA). The attention of association between FMF and SpA in paediatric patients has increased in the last decade. The importance of Th17 differentiation in the pathogenesis of SpA and the immunological mechanisms are well known. However, from the perspective of FMF, the pathogenesis of the associated adaptive immunity-related diseases are not known.
Objectives: In this study, we aimed to evaluate the ILC cells(ILCs), which are the mirror image of T cells that can regulate the adaptive immune system, and their associated cytokines.
Methods: Fifteen FMF, 11 SpA and 13 FMF/SpA patients and 14 healthy control groups who were followed up in Erciyes University Paediatric Rheumatology department were investigated.The numbers and frequencies of ILCs in peripheral blood were analysed in healthy controls, FMF, SpA and FMF/SpA groups. The numbers and frequencies of ILCs in synovial fluid(SF) were analysed in SpA and FMF/SpA groups. Proinflammatory cytokines were analysed by ELISA in the blood plasma of all groups and in the synovial fluid of the SpA and FMF/SpA groups. Gene expressions of pro-inflammatory cytokines in PBMCs and total ILCs signature cytokines derived from PBMCs were analysed by real-time qPCR.
Results: Total and subgroup ILC cells in blood samples and SF were not different in all groups. Total ILC and subtypes in PBMC and SFMC were compared with each other. Total ILC and subtypes in both compartments were not statistically different. In the healthy control group, compared to the FMF and FMF/SpA, IL-2 levels were significantly higher. IL-6 level was significantly higher in the FMF/SpA compared to the control and FMF groups. IL-8 level was significantly higher in FMF/SpA compared to all other groups. IL-22 level was significantly higher in FMF compared to control and SpA groups. IP-10 level was significantly higher in FMF/SpA compared to all other groups. Synovial fluid was collected from SpA and FMF/SpA patients before the injection of the intra-articular steroids, and the production of pro-inflammatory cytokines were assessed. The results showed that the levels of IP-10 and IL-17 produced by the SpA patients increased compared to the FMF/SpA patient group($p \leq 0.05$). Gene expressions of pro-inflammatory cytokines in total PBMCs from FMF, SpA and FMF/SpA patients and healthy controls were compared. The results showed that TSLP was expressed at increased levels in the SpA patient compared to healthy controls and FMF patients($p \leq 0.05$) Total ILCs were sorted by flow cytometry from PBMCs of FMF, SpA and FMF/SpA patients and healthy controls. Gene expressions of cytokines produced in total ILCs were analysed. The results showed that an increased in gene expression of IL-4 in the FMF/SpA group compared to the FMF group ($p \leq 0.05$). A statistically significant increase in gene expression of IL-5 was observed in the FMF/SpA group compared to the control and FMF groups ($p \leq 0.05$). When the FMF/SpA patient group was compared with the other groups in terms of GM-CSF gene expression, it was observed that increased levels of this cytokine were produced in the FMF and SpA patient groups and healthy controls ($p \leq 0.05$)
Conclusion: The lack of difference between the groups in ILC cells may be due to the difficulties associated with the detection of ILC cells. Increased IP-10 levels in synovial fluid may provide a new perspective on the pathogenesis. Although there was no difference in ILC levels, increased type 2 gene expression may indicate the importance of type 2 immunity in the pathogenesis.
Disclosure of Interest: None declared

Identifier: PO019

ASEPTIC ABSCESS SYNDROME: LINKS TO MONOGENIC AUTOINFLAMMATORY DISEASES

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Introduction: Aseptic abscess syndrome (AAS) is an inflammatory disease first described in 1995. It involves sterile collections of neutrophils in deep organs, mainly intra-abdominal, particularly in the spleen, leading to clinical symptoms such as fever and abdominal pain. Extra-abdominal involvement, including skin manifestations, is also possible. Microbiological tests are negative, and antibiotics are ineffective, but the abscesses respond well to corticosteroids. Relapses are common, often requiring immunosuppressants or biologics.

AAS is rare, with the largest series comprising 71 patients in France. It is associated with conditions like neutrophilic dermatoses (e.g., pyoderma gangrenosum, Sweet syndrome), inflammatory bowel diseases, and relapsing polychondritis. AAS shares traits with autoinflammatory diseases, involving innate immunity cells. Variants in the *PSTPIP1* gene have been reported in diseases linked to AAS, such as hidradenitis suppurativa. Studies have explored a potential link between the *PSTPIP1* gene and AAS, but no definitive conclusions have been reached regarding *PSTPIP1* as a monogenic cause of AAS. The rarity of the condition, the lack of multiplex families, and the phenotypic variability of AAS have likely made it difficult to identify the underlying gene(s).

Objectives: The aim of our study was to explore the possibility of a monogenic etiology for the development of aseptic abscesses.
Methods: We included French patients with AAS based on criteria defined by André et al. Exome sequencing was performed. Rare variants of interest in genes associated with immunity were analyzed.
Results: We included 10 patients with a mean age of 28.5 ± 10 years, half of whom were women. All had splenic abscesses, with additional abscesses in the liver (n=2) and skin (n=3). Three patients had associated diseases: Crohn's disease (n=1) and ankylosing spondylitis (n=2). Treatments included corticosteroids (n=9) and immunosuppressants (n=8). Relapses occurred in 8 patients.

No point mutations were identified in the 10 patients in the *PSTPIP1* gene. One patient had a pathogenic genotype consistent with mevalonate kinase deficiency. Another patient had a likely hypomorphic variant in the *PLCG2* gene. This variant was previously associated with an APLAID phenotype in an patient with sterile liver abscesses and necrotizing liver granuloma. Another patient with typical AAS had a variant in the *NLRC4* gene.

Conclusion: Our preliminary findings suggest that AAS could be associated with monogenic autoinflammatory diseases like MKD or APLAID. It remains to be determined whether these associations are causative or contributory to the AAS phenotype.
Acknowledgments: Members of French Study Group on Aseptic Abscesses : Romain ALTWEGG, Alexandra AUDEMARD-VERGER, Fairouzé BANI SADR, Fabrice BONNET, Guillaume CADIOT, Jerome CONNAULT, Nathalie COSTEDOAT-CHALUMEAU, Amandine DERNONCOURT, Hélène DESMURS CLAVEL, Stanislas FAGUER, Jean-Marc GALEMPOIX, Sophie GEORGIN-LAVIALLE, Patrick JEGO, Wendy JOURDE, Jean-Emmanuel KAHN, François LIFERMANN, Alexandre Thibault

Jacques MARIA, Maria NACHURY, Jerome RAZATOMAERY, Clea ROUILLON, Laurent SAILLER, Benoit TRAVERT, Jean-François VIALLARD
Disclosure of Interest: None declared

Identifier: PO020

THE IMPACT OF NEXT GENERATION SEQUENCING: TEN YEARS' EXPERIENCE OF THE GREAT ORMOND STREET HOSPITAL AUTOINFLAMMATION CENTRE OF EXCELLENCE (GOSH-ACE)

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Introduction: The introduction of targeted gene panel sequencing has revolutionised the approach to genetic testing in paediatric rheumatology, particularly for autoinflammatory diseases (AID). There has been progression from gene panels to genome-wide "agnostic" sequencing to keep pace with new disease-gene discovery, phenotypic variability, and an ever-increasing number of disease phenocopies. Thus, in 2022, we moved from targeted gene panel sequencing to whole exome sequencing (WES) as our primary mode of genetic testing in our highly specialised GOSH Autoinflammation Centre of Excellence (GOSH-ACE).
Objectives: To summarise our approach to genetic diagnosis and discovery in AID, and to describe the clinical impact of next-generation sequencing (NGS) over ten years.
Methods: Targeted-enrichment gene panel or WES were performed in-house or by Informed Genomics Limited. Variants were annotated with ANNOVAR and filtered with an R pipeline incorporating standard population-frequency/predicted pathogenicity approaches and novel bioinformatic tools including Exomiser and ExomeDepth. Clinical data were provided by the referring clinician and encoded using Human Phenotype Ontology (https://hpo.jax.org/).
Results: Prior to 2022, 476 patients underwent testing using either a neuroinflammation or broader inflammation and vasculitis panel; a further 177 patients have since undergone WES. Median age at time of testing was 10.6 years (range=0-68) and 48.7% were female. All patients had an inflammatory phenotype, including but not limited to recurrent fever; vasculitis/vasculopathy; neuroinflammation; Behçet's disease; systemic lupus erythematosus (SLE); systemic sclerosis; systemic-onset juvenile idiopathic arthritis; or juvenile dermatomyositis.

Targeted panel testing provided a diagnostic genotype in 25.8% (n=123/476); while 23.2% (n=41/177) of cases who underwent WES had a diagnostic genotype. Despite these similar diagnostic yields, WES was considered overall superior to panel testing as it enabled regular updating of the virtual panel analysis pipeline; and real-time reanalysis of "unsolved" cases following a change in clinical phenotype or a novel disease-gene association discovery.

New genotype-phenotype associations discovered using WES include: *WDR1* (periodic fevers, immunodeficiency and thrombocytopenia, PFIT); *PRKCD* (monogenic juvenile-onset SLE); *TRAP1 (*severe systemic autoinflammation with multifocal osteomyelitis); *MEFV* S208 (autoinflammation with vasculitis and eosinophilia); *DNASE2* (autoinflammation with pancytopenia and intestinal inflammation); *CBL* (cerebral arteriopathy); *LYN* (cutaneous small-vessel vasculitis and liver fibrosis); and *IRAK4* (neuroinflammation, autoinflammation, splenomegaly and anaemia, NASA).

WES led to a clinically actionable incidental genotype finding in 28 cases (15.8%), including cancer and cardiomyopathy predisposition syndromes.

Conclusion: The diagnostic yield of contributory genotypes is surprisingly similar for gene panel testing and WES. However, WES offers the advantage of more robust in silico reanalysis over time for unsolved cases, incorporation of novel bioinformatics tools, and additional diagnostic yield by detection of clinically important incidental genotypes. Regarding this latter point, careful and explicit patient consent regarding return of incidental findings is imperative when using WES in routine practice.

It is inevitable that whole genome sequencing (WGS) will replace WES in the future. However, the routine use of WGS is currently limited by our lack of understanding of non-coding regions of the genome, the higher cost of sequencing, and

data storage requirements. Therefore, for the time-being, WES remains our first-line approach to genetic testing for patients with inflammatory phenotypes.

Acknowledgments: NIHR GOSH Biomedical Research Centre, Rosetrees Trust and GOSH Children's Charity.
Disclosure of Interest: None declared

Identifier: PO021

TWO NOVEL GAIN-OF-FUNCTION VARIANTS IN ELF4 IN PATIENTS WITH SYSTEMIC UNDEFINED AUTOINFLAMMATORY DISEASE

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Introduction: Deficiency in X-linked *ELF4* (DEX) has been recently identified as a novel autoinflammatory disease, characterized by variable inflammatory symptoms, including oral mucosal ulceration and skin inflammation. *ELF4* is a member of the E-twenty-six domain (ETS) gene family of transcription factors, which regulates genes involved in different cellular pathways. Most of the reported disease-causing mutations are located in the DNA-binding domain within the central part of the protein. Phenotypic differences between patients carrying loss-of-function mutations and those with missense mutations suggest that the type of variant affects the DNA-binding ability of ELF4. Little is known about the functional impact of variants located in the C-terminal region of *ELF4*.

Objectives: To describe two novel *ELF4* variants located in the C-terminal region of the encoded protein and to characterize the clinical features of patients (pt) carrying these variants.

Methods: A customized "Clinical Exome" panel for both patients and respective parents was sequenced on Illumina NovaSeq6000® platform. *In silico* analysis was performed on the basis of the patient's clinical phenotype. The variants were evaluated and categorized in accordance with the ACMG recommendations.

Results: We identify 2 patients followed at Rheumatology Division of Bambino Gesù Children's Hospital carrying a variant in *ELF4*. Patient 1 (Pt1) is a 17 years old boy who presented since the age of 18 months with monthly episodes of fever characterized by latero-cervical lymphadenopathy, oral aphtosis pharyngitis and marked increase of acute phase reactants, normal in well-being. Because of the clinical features and the complete response to single dose of glucocorticoids, a clinical diagnosis of PFAFA was made leading to tonsillectomy without benefit. Colchicine therapy was started with complete clinical response. Patient 2 (Pt2) is a 5 years old boy who presented since the age of 5 months with recurrent episodes of fever characterized by, latero-cervical lymphadenopathy, irregular oral aphtosis, pharyngitis and urticarial rash responsive to single dose of glucocorticoids. The patient was clinically diagnosed as PFAPA. Genetic testing for autoinflammatory disease was performed given the early age of onset and the persistence of episodes overtime. Genetic tests identified two novel hemizygous missense variants in *ELF4* gene (NM_001421.4), c.1835T>C (p.Val612Ala) in Pt1 and c.1817C>A (p.Thr606Asn) in Pt2. Both variants were inherited from the heterozygous mothers (both presented with recurrent episodes of fever during childhood), are not reported in the gnomAD database for general population frequency, neither are described in the literature. The c.1835T>C variant resides in an evolutionarily conserved region and encodes the aminoacid change p.Val612Ala with a CADD score of 25.60, while the c.1817C>A encodes the aminoacid change p.Thr606Asn with a CADD score of 22.60, despite being located in a less conserved region.

Conclusion: We report two novel mutations in close proximity within the C-terminal region of ELF4 in two male patients with an atypical PFAPA-like phenotype (no response to tonsillectomy and persistence of episodes). Functional studies are currently underway to confirm the impact of these variants on protein function. If validated, these results could expand the known mutational and phenotypic spectrum of ELF4-associated autoinflammatory conditions.

Disclosure of Interest: None declared

Identifier: PO022

A RARE AUTOINFLAMMATORY SYNDROME ASSOCIATED WITH A C2ORF69 FRAMESHIFT MUTATION: A CASE REPORT

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Introduction: C2orf69 mutation is a rare genetic condition associated with autoinflammation and progressive neurological disorders.
Objectives: This case report discusses the clinical features and course of a patient with a frameshift mutation.
Methods: Case report
Results: A female patient presented at 46 days old with septic arthritis in the right hip. Two months later, arthritis was observed in the left elbow. Due to recurrent septic and aseptic arthritis episodes, the patient was referred to our clinic at 4 months of age. Physical examination revealed dysmorphic facial features, neuromotor developmental delay, microcephaly, and growth retardation in terms of both height and weight (below -2 SDS). The patient also exhibited recurrent fever episodes and elevated acute-phase reactants. Family history revealed first-degree cousin marriage.

Magnetic resonance imaging (MRI) showed significant atrophic widening of bilateral frontotemporal cortical hemispheric sulci in the FLAIR sequence. Clinical exome sequencing did not identify any significant findings, and the patient was initially followed up with a diagnosis of "undifferentiated autoinflammatory syndrome." Anti-IL-1 therapy was initiated. At 9 months, the patient developed multiple seizure episodes, which were controlled with a combination of antiepileptic medications.

Whole-exome sequencing (WES) revealed a **C2orf69 NM_153689.5:c.298del (p.Gln100Serfs*18)** frameshift mutation. This mutation results in an early stop codon, leading to a loss of protein function. The genetic analyses of the parents are still pending, and the family has been referred for genetic counseling. The patient is currently 27 months old and is being followed up under Anti-IL-1 therapy.

Conclusion: This case highlights the association between C2orf69 frameshift mutation and autoinflammatory syndrome with progressive neurological disorders. The role of C2orf69 in mitochondrial function and glycogen metabolism suggests that these mutations may lead to a wide clinical spectrum. Recognizing this rare mutation is critical for early diagnosis, appropriate treatment, and genetic counseling. Further genetic and clinical studies are essential to better understand the pathogenesis of this syndrome.
Acknowledgments: none
Disclosure of Interest: None declared

Identifier: PO023

A NOVEL STAT4 VARIANT AS THE POTENTIAL CAUSE OF A LONG-LASTING CASE OF DISABLING PANSCLEROTIC MORPHEA

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Introduction: Disabling pansclerotic morphea (DPM) is a rare inflammatory condition characterized by progressive fibrosis at multiple tissues, representing the most severe form among the scleroderma spectrum. Recent investigations have identified rare *gain-of-funtion STAT4* variants as the cause of the disease in different DPM pedigrees.
Objectives: Identification of the underlying genetic defect in a patient with long-lasting DPM and characterization of the variant's pathogenicity.
Methods: Patients' data were collected from medical charts. Genetic studies were performed in the proband and her healthy first-degree relatives by using both Sanger and next-generation sequencing (NGS). Different experimental work is in progress to characterize the pathogenicity of the detected variant.
Results: We identified a 28 years-old woman born from a non-consanguineous couple, with no familial history of autoinflammatory disease or primary immunodeficiency. At the age of 3 years, she started to suffer from fever, hepatosplenomegaly, lymphadenopathies and rapidly progressive skin lesions, establishing a first diagnosis of generalized morphea at the age of four. The course of the skin involvement was chronic, with progressive sclerosis of large corporal areas, appearance of hyper- and hypopigmented areas, multiple scars and ulcers that often became over-infected. As consequence of progressive fibrosis, different musculoskeletal manifestations were detected including muscle atrophy, progressive joint ankylosis, and in flexo deformities. Furthermore, since the age of 6-7 years, different respiratory manifestations were detected including dyspnea and progressive respiratory insufficiency. During the course of the disease, several treatments were administered, with frequent partial or negative responses with the exceptions of glucocorticoids and tocilizumab.

On the basis of previous published evidence, we hypothesized that rare variants in *STAT4* might be the cause of the patient's disease. *STAT4* was first analyzed in the patient using Sanger sequencing, which detected the previously unreported c.1807C>T heterozygous transition in exon 20. This nucleotide exchange is predicted to lead to the p.His603Tyr substitution, which is absent in all available databases (gnomAD, Kaviar, INFEVERS, Franklin, ClinVar). Interestingly, the p.His603 amino acid residue is highly conserved across species and is located in the SH2 domain of the protein, the same domain where all previously reported DPM-associated *STAT4* variants concentrate. The frequency of the novel *STAT4* variant in patient's peripheral blood was 46.2%, which is concordant for the frequency of germline variants. Finally, genetic analyses in healthy relatives (parents and brother) yielded negative results, supporting for its *de novo* nature in the proband.

Conclusion: We describe a novel case of DPM as a consequence of a novel and *de novo STAT4* variant, expanding thus the genetic diversity of this rare inflammatory condition. Additional experiments are currently in progress to characterize the molecular mechanisms of the disease consequence of this novel variant.
Acknowledgments: PID2021-125106OB-C31 grant from the Spanish Ministry of Science and Innovation co-funded by Agencia Estatal de Investigación / European Regional Development Fund.
Disclosure of Interest: None declared

Identifier: PO024

A NOVEL NONSENSE MUTATION IN LPIN2 ASSOCIATED WITH MAJEED SYNDROME: CASE REPORT AND INSIGHTS INTO GENE EXPRESSION

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Introduction: Majeed syndrome (MIM# 609628) is a rare autosomal recessive autoinflammatory disorder caused by biallelic variants in *LPIN2 gene,* characterized by chronic recurrent multifocal osteomyelitis (CRMO), congenital dyserythropoietic anemia (CDA), and, less commonly, neutrophilic dermatosis. To date, 20 unique mutations have been reported in 35 individuals with molecularly confirmed Majeed syndrome.

Objectives: To report a new case of Majeed syndrome caused by a novel homozygous nonsense variant that creates a stop codon in exon number 4 in LPIN2 gene.

Methods: Whole-exome sequencing (WES) was performed in the index case, followed by Sanger sequencing of *LPIN2* gene in the parents. Additionally, RT-qPCR analysis was conducted to assess LIPIN2 mRNA expression in peripheral blood mononuclear cells (PBMCs) from the affected patient, her mother, and healthy control.

Results: We report a 14-month-old Arabic girl, born to consanguineous parents, with a history of prolonged fever, chronic arthritis, and severe anemia. The patient was referred as a case of refractory systemic Juvenile Idiopathic Arthritis (sJIA). Bone marrow aspiration demonstrated significant dyserythropoiesis with no evidence of malignancy. WES was performed and identified a novel *LPIN2* homozygous variant c.469C>A p.(Arg157*), which creates a stop codon in exon number 4. Sanger sequencing confirmed that both parents were heterozygous carriers of the variant. Furthermore, RT-qPCR analysis of LIPIN2 mRNA expression in PBMCs demonstrated a significant reduction in relative *LIPIN2* gene expression in the patient carrying the homozygous variant (c.469C>T) compared to both his mother and the control samples. Subsequently, the patient was started on Canakinumab, an interleukin-1β blocker, and showed significant clinical and biochemical responses.

Conclusion: Patients with Majeed syndrome may present with features resembling sJIA, including chronic arthritis and fever, without necessarily exhibiting neutrophilic dermatitis. Our findings expand the spectrum of pathogenic variants associated with Majeed syndrome and demonstrate the impact of this novel variant on gene expression

Disclosure of Interest: None declared

Identifier: PO025

WHOLE EXOME SEQUENCING IN PAEDIATRIC-ONSET COGAN'S SYNDROME

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Introduction: Cogan's syndrome is a rare variable vessel vasculitis, describing sensorineural hearing loss (SNHL), inflammatory ocular disease (typical Cogan's, interstitial keratitis; atypical Cogan's, uveitis) and vestibular dysfunction.
Objectives: We hypothesised that within a cohort of paediatric-onset Cogan's syndrome (typical or atypical), there would be a subgroup with monogenic disease, either autoinflammatory and/or associated with SNHL.
Methods: Whole exome sequencing (WES) was performed by Informed Genomics Ltd and analysed using an in-house R pipeline incorporating the use of virtual gene panels for inflammation and SNHL; copy number variant analysis (ExomeDepth); a phenotype-driven prioritisation tool (Exomiser); and HLA-typing (HLA-HD). Clinical information was encoded using Human Phenotype Ontology terms (https://hpo.jax.org) and variants were assessed by a multi-disciplinary team according to ACMG guidelines.
Results: 10 individuals with Cogan's syndrome were enrolled. 5/10 (50%) were females, median age of onset 12.8 years (range 5.8,15.7). 10 (100%) had auditory involvement, 9 (90%) ocular, 9 (90%) vestibular dysfunction, 7 (70%) neurological involvement, 4 (40%) renal, 1 (10%) large vessel vasculitis and 8 (80%) systemic involvement, including fever, weight loss and fatigue. A conservative estimate of the proportion of monogenic contribution based on Class 4 or Class 5 variants was 30% (n=3); although suspected monogenic contribution to the phenotype was overall identified in 50% (n=5; Table). A novel *de novo* heterozygous variant in *NLRP3* was identified in a patient whose phenotype closely matches those reported recently with an atypical form of autosomal dominant Cryopyrin-associated periodic syndrome (CAPS). One patient had a *de novo* Class 3 heterozygous variant in *ALPK1*, associated with ROSAH, a recently described autoinflammatory condition associated with uveitis; 2 patients had variants in genes associated with non-inflammatory causes of hearing loss; and 1 patient had genetic confirmation of sickle cell anaemia, commonly associated with hearing loss, and sometimes with uveitis. No HLA association was identified.

Case (n=10)	Gene	Variant DNA change; Amino acid change (zygosity)	Associated disease (Inheritance)	ACMG Class	Clinical Interpretation
1	No genotype to explain phenotype				
2	*NLRP3*	c.C2744G; p.T915R (het)	CAPS (AD)	4	Novel variant
3	*ALPK1*	c.A2204C; p.H735P (het)	ROSAH syndrome (AD)	3	Novel variant
4	*ADGRV1*	c.G1849A; p.V617M (het)	Usher syndrome (AR)	3	An individual with compound heterozygous variants (c.G1849A & c.A6994T) reported in Usher syndrome

		c.G3289A; p.G1097S (het) c.A6994T; p.I2332F (het)			type 2C. Unable to ascertain from our workflow if variants are in *cis* or *trans*; parental studies underway
5-7	No genotype to explain phenotype				
8	*MYO7A*	c.1617dupC; p.K542Qfs*5 (het)	AD deafness, Usher syndrome (AR)	5	Case report of this variant in heterozygous state as the cause of a hearing loss syndrome and 2 reports of this variant, in heterozygous state, along with an additional *MYO5A* variant in the context of Usher syndrome
9	No genotype to explain phenotype				
10	*HBB*	c.A20T; p.E7V (hom)	Sickle cell anaemia (AR)	5	Confirms diagnosis of sickle cell anaemia

Conclusion: In this cohort of paediatric-onset Cogan's syndrome, up to 50% had either monogenic diseases associated with autoinflammation, or genetic factors contributing to the phenotype, with implications for treatment, prognosis and the wider family. We thus advocate for genetic testing in individuals labelled with Cogan's syndrome, especially paediatric-onset, and interrogation of the genome for alternative diagnoses. We suggest that paediatric-onset Cogan's syndrome represents a blended phenotype of monogenic disease, including autoinflammatory, as well as some with an autoimmune aetiology.

Acknowledgments: NIHR GOSH Biomedical Research Centre

Disclosure of Interest: None declared

Identifier: PO026

LATE ONSET OF AN AUTOINFLAMMATORY DISEASE: IDENTIFICATION AND FUNCTIONAL CHARACTERIZATION OF A MOSAIC VARIATION OF NLRC4

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Introduction: Autoinflammatory diseases (AIDs) typically begin in childhood with spontaneously resolving febrile episodes, accompanied by inflammation of the skin, serous membranes, and synovial tissues. *NLRC4* encodes an essential component of the NLRC4 inflammasome, which is a multiprotein complex involved in activating inflammatory pathways. NLRC4 has been implicated in very rare and severe forms of AIDs, mostly occurring in children, often characterized by enterocolitis and potentially aggravating into macrophage activation syndrome (MAS). So far, only 3 mosaic variations have been reported in adult patients.

Objectives: The objective of this study was to identify the molecular basis of an AID that began in adulthood with severe inflammatory episodes characterized by high fever associated with joint and abdominal pain without MAS.

Methods: The patient's leukocyte genomic DNA was analyzed using deep sequencing (1100 X) of a panel of AID genes. Functional evaluation of the identified variation in *NLRC4* was conducted after the expression of the corresponding recombinant protein in HEK293T cell line expressing different protein partners (ASC and Caspase1) enabling the detection of specks, a hallmark of NLRC4 inflammasome activation, and transfected with a reporter gene of the NF-κB pathway.

Results: The patient, a 28-year-old man, had unlabeled psychosis since the age of 19. From the age of 21, severe inflammatory episodes were reported with no established link between his psychiatric illness and the occurence of inflammatory episodes. Sequencing revealed the presence of a mosaic variation in *NLRC4*, c.398C>T p.(Thr133Ile), with the mutant allele present at a ratio of 5%. Study of the NF-κB pathway showed a significant increase in NF-κB activity in cells expressing the mutated protein as compared to those expressing the wild-type protein. Moreover, a significant increase of the formation of specks in cells expressing the mutant NLRC4 was observed in comparison to those expressing the wild-type protein.

Conclusion: This study identified a novel mosaic variation in *NLRC4* which manifests in adulthood without MAS. Functional studies demonstrated the gain-of-function pathogenic effect of the identified variation on inflammation.

Acknowledgments: We thank the patient for his participation in the study.

Disclosure of Interest: None declared

Identifier: PO027

EVALUATING GENETIC VARIANTS AND THEIR CLINICAL CORRELATIONS IN UNDIFFERENTIATED SYSTEMIC AUTOINFLAMMATORY DISEASES (USAIDS)

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Introduction: Undifferentiated systemic autoinflammatory diseases (USAIDs) pose significant challenges in both diagnosis and treatment. Some pathogenic (P)/ likely pathogenic (LP) variants, variants of uncertain significance (VUS), or polymorphisms may be associated with certain clinical features.
Objectives: This study aimed to assess the association between genetic variants identified in patients classified with USAID and their clinical manifestations.
Methods: The genetic results of 55 USAID patients were reviewed. Patients who met the criteria for defined autoinflammatory diseases according to the Eurofever/PRINTO autoinflammatory disease classification criteria were excluded from the analysis. At the time of diagnosis, 55 patients had undergone genetic testing: 25 through clinical exome sequencing (CES) and 30 through whole exome sequencing (WES). The resulting genomic variants were classified according to the guidelines of ACMG/AMP. The association between participants' age at diagnosis, family history, clinical features, and genetic variants was evaluated. The median levels of C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and serum amyloid A were calculated using four control measurements taken during the interattack periods over the course of a year.
Results: This study included 55 adult Turkish patients (aged 18-68 years), 37 women (67.3%) and 18 men (32.7%), who were followed up in the Rheumatology department. The mean age of the study population was 40±14.3 years at the time of enrollment. The majority of the study population had systemic inflammation even in asymptomatic periods (76.4%, n=42), and the median level of CRP was 5.2 mg/L (IQR: 4), ESR was 21 (IQR: 9) and amyloid A 12.1 (IQR: 7.5) mg/L at interattack period.. The most frequent symptoms were abdominal pain, fever and arthritis which were evident in 40, 25 and 22 percent of patients respectively. The mean number of attacks was 4.4 per year . Most patients responded to colchicine(n=21, 40.4%), IL-1 inhibitors(anakinra/canakimumab, n=7, 13.5%) and corticosteroids (n=3, 5.8%).

Patients underwent genetic testing. In the genetic analysis, 49 variants were identified in the immune pathways (mean 0.9-range 0-3 per person). Nineteen variants were classified as P/LP (19/49) and 30 as VUS (30/49). When these variants were evaluated by zygosity and clinical findings, it was determined that 17 patients (30.9%) with 10 P/LP and 7 VUS variants identified to be associated with a monogenic disease. The most altered genes were *MEFV* in 6 (10.9%) patients, primary immunodeficiency diseases (PID), and primary immunodysregulatory diseases (PIRD) genes (*CORO1A, CEBPE, DPP9, LRBA, STXBP3, CRACR2A, PLCG2 and NFKB1, JAK1*) in 8 (14.5%) patients. Three patients with hearing loss had clinically relevant variants in *CDH23, PTPRQ, GJB2* genes as a blended phenotype. In addition, 7 patients with heterozygous LP/P variant (in the gene with recessive disease mode) and 11 patients with heterozygous VUS (in the gene with dominant disease mode) were identified and genotype-phenotype correlation of these variants was interpreted

Conclusion: USAID is a diagnosis of exclusion. Identifying pathogenic and VUS variants and evaluating their association with clinical findings is crucial. A positive family history and early onset support the diagnosis of autoinflammatory diseases. Immune dysregulation may also be observed in patients followed up with a diagnosis of autoinflammatory disease. In some patients, abnormalities in multiple pathways may contribute to clinical symptoms. It is essential to adopt a broad perspective during the evaluation process.
Disclosure of Interest: None declared

Identifier: PO028

CLINICAL UTILITY OF EXOME SEQUENCING IN ADULTS WITH AUTOINFLAMMATORY DISORDERS: A PROSPECTIVE STUDY ON 138 PATIENTS

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Introduction: Autoinflammatory disorders (AIDs) are rare immune disorders, some of which are genetic in origin, characterized by aseptic inflammation involving various organs in the absence of autoimmunity evidence. To date, genetic diagnosis of AIDs is essentially based on Next Generation Sequencing (NGS) panels of a limited number of selected genes, with Sanger sequencing now only used for a minority of AIDs presenting with highly specific clinical features (*e.g*. familial Mediterranean fever, VEXAS syndrome). NGS panels have a diagnostic yield of approximately 10%.
Objectives: Our aim was to assess the relevance of Whole Exome Sequencing (WES) in routine clinical practice in AIDs, which to date has been little evaluated in this indication especially among adults.
Methods: A WES strategy was applied over a 30-month period for the genetic diagnosis of adult patients referred to our national reference center for AIDs. A genetic origin was considered possible in cases of 1) onset in childhood, 2) intra-familial transmission of the disease, 3) association with non-immune anomalies such as dysmorphia, 4) clinical features suggestive of genetic AID, 5) unclassified AID or 6) AID previously classified but with an atypical clinical course and/or response to treatments.
Results: A hundred and thirty-eight patients were studied by WES, 29 (21%) of whom had previously had an NGS AIDs panel considered inconclusive. The median age at onset of symptoms was 14 years (IQR 5; 24). Similar cases in 1st and 2nd degree relatives were noted in 46 (33%) of them and 7 (5%) were from a consanguineous union. The WES provided a molecular diagnosis in 19 patients (14%): 18 of them had never been previously explored using a NGS panel (16.5% of 109) and 1 had a previous inconclusive panel (3% of 29). A total of 10 patients were diagnosed with diseases explored by most of large AIDs dedicated NGS panels that could therefore have been detected using this approach: CAPS *(n=4),* PRAAS *(n=2, PSMG2* and *PSMB9*), TRAPS *(n=1), RIPK1* AD GOF (n=1)*,* PAAS (n=1)*, TNFRSF13B* related CVID (n=1). A further 9 patients were diagnosed with diseases that would have been missed by AID NGS panels including 1 case of *PPM1D* clonal hematopoiesis associated with autoinflammation and 8 cases of nonimmune diseases. These included hereditary angioedema related to AD *F12* (n=1), Turner syndrome (n=1), Rett syndrome (n=1), Noonan syndrome (n=1), congenital hemolysis related to *SPTA1* (n=1), X-linked ichthyosis (n=1), 2q37 micro-deletion (n=1) and neurodevelopmental disorder related to an AD *PURA* variant (n=1). Of note, 8 patients (6%) were identified as carrying variants of interest requiring further evaluation - currently in process. These included patients who had never had any large NGS panel (n=6/109, 6%) and others with an inconclusive panel (n=2/29, 7%).
Conclusion: In an expert center for AIDs, WES as a first-line genetic exploration for adults with AIDs allowed a diagnosis in 16.5% of cases, a diagnostic rate that appears to outperform AID dedicated NGS panels. This improved diagnostic yield seems to be mostly explained by the detection of genetic diseases of non-immune mechanisms with complex clinical presentations mimicking autoinflammation.

Abbreviations: CAPS: cryopyrin associated periodic syndrome, PRAAS: proteasome associated autoinflammatory syndrome, TRAPS: TNF receptor associated periodic syndrome, PAAD: pyrin associated autoinflammatory syndrome, AD: autosomic dominant, GOF: gain of function

Disclosure of Interest: None declared

Identifier: PO029

MEFV MUTATIONAL SPECTRUM AND CLINICAL MANIFESTATIONS IN GEORGIAN FMF PATIENTS

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Introduction: Familial Mediterranean fever (FMF) is a hereditary autoinflammatory disorder caused by mutations in the *Mediterranean fever* (*MEFV*) gene. Despite a known high *MEFV* carrier rate of 15% and its neighbourhood to endemic countries Armenia and Turkey, the overall situation concerning FMF in Georgia is still largely inextricable.

Objectives: This ongoing study aims at investigating *MEFV* mutations and clinical manifestations among FMF patients in the transcaucasian Republic of Georgia.

Methods: Over 300 Georgian subjects with FMF symptoms or/and family history have so far been recruited. Genotyping for twelve *MEFV* mutations plus three *SAA1* isoforms is performed using FMF-SAA1 StripAssay (ViennaLab Diagnostics). To date, full medical records and genotypes are available for 136 patients matching Tel-Hashomer criteria.

Results: Of the 136 clinically diagnosed FMF patients, 71 (52.21%) were female and 65 (47.79%) were male, with a mean age of 28.66 ± 16.63 years. We distinguished 16 different genotypes, M694V/M694V and M694V/WT being the most common homozygous and heterozygous ones, respectively. M694V (66.44%), V726A (11.64%) and E148Q (8.90%) were the most frequent *MEFV* mutations. None of the tested *MEFV* variants was found in 43 (31.62%) of FMF patients. *SAA1* 1.1, 1.3 and 1.5 was present in 47.79%, 1.84% and 50.37% of alleles, respectively. Reported clinical manifestations included periodic attacks of fever (87.50%), abdominal pain (84.56%), arthralgia (71.32%), chest pain (45.59%), myalgia (44.12%) and skin rash (21.32%). A family history of FMF was reported by 50 (36.76%) subjects. Currently only 46 (33.82%) FMF patients receive colchicine therapy. Among the most striking observations was an extensive delay between the reported FMF onset (median: 9.00 years of age) and confirmed diagnosis (median: 25.50 years of age).

Conclusion: The *MEFV* mutational spectrum in Georgia is heterogenous, with similarities to neighbouring Armenia and Turkey. Awareness, as well as accessible diagnostic and therapeutic options for FMF, seem still insufficient and widely unavailable.

Disclosure of Interest: None declared

Identifier: PO031

HARDY-WEINBERG DISEQUILIBRIUM OF MEFV DISEASE ASSOCIATED GENOTYPES IN A LARGE ISRAELI COHORT OF INDIVIDUALS TESTED FOR PRENATAL CARRIER STATE OF GENETIC DISEASES

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Introduction: The distribution of FMF genotypes in a large, stable population with random mating is expected to obey the Hardy Weinberg (HW) equation.

Objectives: To test if disease associated FMF genotypes maintain the HW equilibrium in a large database of subjects seeking prenatal carrier screening for family planning.

Methods: We analyzed data from a large cohort of 12902 subjects who performed genetic screening for 450 recessive diseases. The screening included 21 MEFV variants, including 4 relatively common variants (p.M694V, p.V726A, p.E148Q and p.A744S) which we previously showed to be disease-associated. The combined allelic frequency of these 4 variants was defined as p, while all other alleles were defined as q. The expected number homozygotes and compound heterozygotes formed from the combination of these 4 variants (homozygotes and compound heterozygotes) was compared to the observed, according to the HW equation: $p^2+ 2pq +q^2=1$. The difference between the observed and expected subject numbers was analyzed for statistical significance using the chi-square test.

Results: We found 138 subjects homozygous or compound heterozygous for the combination of these 4 variants, as compared to 106.6 expected (1.3 fold increase in the observed over the expected : 95% CI 1.003-1.67, p=0.044). In contrast, such an increase was not detected for all other MEVF variants included in this panel.

Table 1: HW disequilibrium of combined MEFV genotypes in a carrier screening database.

FMF associated variants	Count	p	q
	2438	0.091	0.9089

Genotypes	p^2	2pq	q^2	OR	95%CI	p value (p2)
obserevd, n	138	2070	10694	1.3	1.003-1.6	0.04
expected, n	106.6	2132.7	10666.2			

Conclusion: We observed an increase in MEFV disease associated genotypes in this large population cohort. This reason for this increase is not entirely clear to us, however it may reflect increased awareness among FMF patients for the prevention of genetic diseases. Our results may also suggest that in the era of large-scale family planning, the HW equilibrium of genotypes distribution might no longer be taken for granted.

Disclosure of Interest: None declared

Identifier: PO033

DEFINITION OF DISEASE PHENOTYPES IN PEDIATRIC SAPHO SYNDROME: A NATIONAL MULTICENTRIC STUDY

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Introduction: Pediatric SAPHO(pSAPHO)is a rare autoinflammatory disease characterized by chronic non-bacterial osteitis (CNO) and different dermatologic manifestations (Palmo-plantar pustulosis (PPP), psoriasis vulgaris (PV), acne, hidradenitis suppurativa (HS),pyoderma gangrenosum(PG)).Two different phenotypes of pSAPHO upon skin manifestations have been desscribed in a ssmall cohort of patients: i) acne-HS group (males, pubertal onset with refractory skin manifestations), ii) PPP-PV group (females, prepubertal onset with osteoarticular manifestations).
Objectives: to confirm the presence of different pSAPHO phenotypes according to skin manifestations in an italian multicenter cohort, *vs* CNO patients without skin disease
Methods: pSAPHO retrospectively enrolled from 15 Italian Centers in the Eurofever Registry. Patients divided into an acne-HS and a PPP-PV group and compared to a CNO group without skin manifestations.Comparison of frequencies between groups was performed by the means of the Chi-square test or by the Fischer's Exact test
Results: 54 pSAPHO with skin manifestations(35 acne-HS and 19 PPP-PV) were enrolled and compared to 167 CNO.In the Acne-HS-PG group 82.9% were males,with disease onset in pubertal age (median 13.3 years) characterised by skin manifestations with the appearance of osteoarticular symptoms in the following year.In the PPP-PV group 84.2% were females,with disease onset with osteoarticular manifestations in prepubertal years (median 10.2 years) followed by skin manifestations in the following year. In CNO there were no gender differences,median age at disease onset 9.5 years.A significant difference was found between the 3 groups in terms of sex ($p< 0.0001$) and age at onset ($p<0.0001$).All patients showed long bones involvement,while an axial pattern (sterno-clavicular-spine-sacroiliacs) was more frequent in acne-HS and PPP-PV when compared to CNO ($p<0.001$). In CNO,NSAIDs (84%,$p<0.001$), methotrexate(20%), salazopyrin(SSZ 30%) and bisphosphonates (BP,50%) were generally efficacious, and 36% required a biologic therapy. In PPP-PV, MTX (20%), SSZ (30%) and BP (50%) were initially used, but in 60% biologic therapy was needed to control the bone disease, while skin manifestations responded well to topical treatments or DMARDS. In acne-HS steroids were more frequently used (54.3%,$p<0.001$) and biological therapy was needed in 80% ($p<0.001$) in order to control the refractory skin disease and sysstemic inflammation (combination Adalimumab/MTX more efficacious).
Conclusion: The data confirm in a large multi-center national study, the presence of 2 phenotypes of pSAPHO based on skin manifestations with different sex, age at onset, bone involveement and response to therapiess. These phenotypes need a different therapeutic approach according to skin manifestations, and highlight the need of a new disease classification
Disclosure of Interest: None declared

Identifier: PO034

MACROPHAGIC ACTIVATION SYNDROME IN STILL'S DISEASE: A MULTICENTER OBSERVATIONAL COHORT STUDY

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Introduction: Macrophage activation syndrome (MAS) is a severe and rare, potentially life-threatening complication, affecting about 10-20% of patients with Still's disease. It is characterized by hyperinflammatory state with fever, cytopenia, hyperferritinaemia, hypofibrinogenemia, hypertriglyceridemia and liver dysfunction. Patients with macrophage activation syndrome in pediatrics represent a poorly studied population. New treatments are being increasingly used in the management of these patients, yet the efficacy and long-term outcomes of these therapies remain poorly known.

Objectives: Among this study, our objectives are to describe the clinical characteristics, the treatment strategies used and the outcome of patients with Still's disease who presented a MAS.

Methods: Multicenter, observational, retrospective patient cohort study through the Juvenile Inflammatory Rheumatism (JIR) cohort, using routine care collected data (2014-2024).

Results: In this cohort, in Switzerland, there were 46 patients with Still's disease, of whom 28% (n= 13) presented at least one episode of MAS. The mean age of patients presenting a MAS was 9,3 years old (SD 4,6). The male to female sex ratio was 0,3/1. 62 % (n= 8/13) of the patients presented MAS at the time of diagnosis of Still's disease. 46 % (n= 6/13) of the patients presented only one episode of MAS, and the others from 2 to 4 recurrences.

When presenting a MAS, the most frequent symptoms were arthritis, fever and skin lesions. The mean ferritin value during episodes of MAS was 12'100 ug/L. Added to high doses of corticosteroids, anakinra (IL1-Ra) was used in 62 % (n = 13/21) episodes of MAS, and ciclosporine in 38% of cases (n=8/21). Other treatments used were Tocilizumab (IL-6Ra) and immunoglobulins (IVIG).

8 patients treated with anakinra as long term therapy presented recurrence of MAS. In this cohort, 4 patients received finally a treatment of MAS825 (anti-IL-1β/IL-18), new experimental treatment. Since introduction of MAS825, they presented no recurrence of MAS.

Conclusion: In this cohort there was a high proportion of patients with Still's disease who presented MAS. The majority presented more than one episode. Most of the cases were treated with anakinra or ciclosporine, added to high doses of corticosteroids. Including larger international cohort with more patients' data from the whole JIR cohort network is expected. This would enable to better characterize the phenotype of patients with Still's disease presenting MAS and their outcome.

Disclosure of Interest: None declared

Identifier: PO035

USE AND SAFETY OF DIFFERENT BISPHOSPHONATES IN CHRONIC RECURRENT MULTIFOCAL OSTEOMYELITIS AND A COMPARISON OF THE SIDE EFFECT PROFILE BETWEEN CHRONIC RECURRENT MULTIFOCAL OSTEOMYELITIS AND OTHER UNDERLYING DIAGNOSES

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Introduction: Bisphosphonates were first used successfully in children with osteogenesis imperfecta, later expanding to secondary osteoporosis and inflammatory bone diseases where side effects and acute phase responses may be variable.
Objectives: We aimed to examine the side effects of pamidronate and zoledronate in patients with chronic recurrent multifocal osteomyelitis (pwCRMO) and compare the side effects of zoledronate between pwCRMO and patients with different underlying diagnoses.
Methods: pwCRMO diagnosed at GOSH between April 2019-December 2024 were included. In pwCRMO, pamidronate was used between 2019-August 2023, and zoledronate was used from August 2023-December 2024. Patients with different diagnoses who received zoledronate over a 10-month period were included. Parents of pwCRMO were interviewed via telephone regarding the side effect profile. All medical reports, including pre- and post-infusion electrolytes, vitamin D, CRP, bone and renal profile were reviewed from electronical patient files.
Results: Thirty-five pwCRMO and 25 patients with other diagnoses treated with bisphosphonates were included. Among pwCRMO, 15 were treated with zoledronate and 20 with pamidronate, whereas all non-CRMO patients received zoledronate.

In pwCRMO, significant reductions in calcium and phosphorus were observed after both pamidronate and zoledronate (for all $p<0.05$). CRP increased significantly only in pamidronate group ($p=0.02$), whereas zoledronate resulted in a significant increase in alkaline phosphatase ($p=0.01$). There were no significant differences in the side effect profile of pamidronate and zoledronate in pwCRMO. The most reported adverse events were flu-like symptoms (pamidronate: 65%; zoledronate: 66.7%) and fever (pamidronate: 50%; zoledronate: 63.6%).

When comparing pwCRMO treated with zoledronate and other patients, calcium levels decreased significantly in both groups ($p<0.01$). However, phosphorus levels decreased significantly only in the CRMO group ($p<0.001$). Regarding side effects, fever was significantly more frequent in pwCRMO ($p=0.008$), and hypophosphatemia was higher in this group (60% vs. 5%, $p=0.002$). Flu-like illness was similar in both groups.

Conclusion: Zoledronate and pamidronate have been used in CRMO treatment with similar side effect profiles. Checking renal functions, bone profile and vitamin D levels before infusion and prescribing calcium supplementation post-infusion is important to prevent side effects. Fever and flu-like symptoms were observed in over half of bisphosphonate-naïve pwCRMO, hence regular paracetamol use for 24-48 hours after the first infusion might help alleviate side effects.
Disclosure of Interest: None declared

Identifier: PO036

ARE BLOOD MONOCYTES USEFUL IN DIFFERENTIATING PFAPA FROM FMF? INSIGHTS INTO THEIR LIMITS AND COMPLEMENTARY MARKERS

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Introduction: PFAPA (Periodic Fever, Aphthous Stomatitis, Pharyngitis, and Adenitis) is the most common auto-inflammatory disease (AID) in France. Diagnosing PFAPA can be challenging due to overlapping clinical features with other AIDs, such as Familial Mediterranean Fever (FMF). Monocytes have been reported to increase in some autoimmune diseases, infection, inflammation and allergy. Our aim was to compare blood monocyte levels during attacks in PFAPA and FMF

Objectives: Our aim was to compare blood monocyte levels during attacks in PFAPA and FMF

Methods: We conducted a single-centre retrospective study of PFAPA and FMF patients (homozygous or heterozygous) followed at a tertiary university hospital and included in the BAMARA rare disease database. Demographic characteristics and white blood cell count during attacks were collected. Comparisons between the PFAPA and FMF groups were made using the Mann-Whitney U test ($p < 0.05$ considered significant). ROC curve analysis and Youden index were used to determine optimal thresholds for monocytes and PLR (Platelet-to-Lymphocyte Ratio).

Results: Data from 73 PFAPA and 82 FMF patients were analyzed. During attacks, monocyte levels were significantly higher in PFAPA patients than in FMF patients (respectively, median 1450/mm³ [range: 430–2546] vs median 750/mm³ [range: 180–1776]) ($p < 0.0001$). A monocyte threshold of 954.5/mm³ was identified as clinically relevant to differentiate PFAPA from FMF, but it showed modest discriminatory power (AUC = 0.34).

PLR was higher in PFAPA patients than in FMF patients, with a median PLR of 5.8 versus 3.5 ($p<0.001$). ROC curve analysis showed that PLR had better discriminative power, with an AUC of 0.72 and an optimal threshold of 4.5.

Conclusion: Both monocyte levels and PLR were elevated in PFAPA compared with FMF. Monocyte counts alone have limited diagnostic utility. Its clinical importance lies in its ability to complement clinical judgement, particularly when PFAPA and FMF overlap. It could be replaced by PLR, which has better discriminatory power (AUC = 0.72) and may serve as a useful biomarker for differentiating PFAPA from FMF during attacks. Further studies are needed to validate its clinical utility.

Disclosure of Interest: None declared

Identifier: PO037

WORLDWIDE EVALUATION OF CLINICAL PRACTICE STRATEGIES (CLIPS) FOR LUNG INVOLVEMENT IN STILL'S DISEASE WITHIN THE JIR-CLIPS NETWORK: A COST ACTION

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Introduction: Recent literature has documented that some pediatric patients with Still's Disease may develop severe lung disease (LD).

Objectives: To explore clinical strategies for managing lung involvement in Still's Disease and compare findings with expert recommendations.

Methods: We conducted a global survey of physicians on LD management in Still's Disease, funded by a COST (European Cooperation for Science and Technology) action CA21168. Questionnaires were distributed since September 2022 through the JIR cohort network and national societies. Findings were compared to EULAR/PreS recommendations.

Results: Three hundred and seventy-two physicians answered the survey. Ten percent of participants (n=39/372) reported having treated at least one patient with lung disease. Most of these participants were pediatricians (n=32).

The use of CT scans was widespread among pediatricians, with 78% reporting consistent use and 21% occasional use aligning with recommendations. Echocardiography was quite frequently performed (always by 78% and sometimes by 21%) and is mentioned in the guidelines as helpful in evaluating pulmonary hypertension.

Bronchoalveolar lavage appears to be frequently used (always by 21%, sometimes by 52%, never by 21%) while lung biopsies were never used by 31% of participants and only sometimes by 69%. Although this technique is recommended in the guidelines, its inconsistent use raises concerns. Non-invasive approaches, such as medical history (e.g., early-onset disease, recurrent macrophage activation syndrome, or drug reactions), clinical signs (e.g., clubbing, rash), radiological findings, and biomarkers, may serve as alternatives without resorting to invasive procedures. We hypothesize that lung biopsies are reserved for complex cases in clinical practice.

Regarding biomarkers, ten participants (30%) reported using IL-18 as part of the follow-up process in Still's Disease-LD. IL-18 is useful for both diagnosis and follow-up but its underuse suggests that education and broader access may be necessary to optimize its integration into routine care. Surprisingly, the IFN signature is widely used by respondents (77% using it systematically or occasionally), although it is not specifically cited in current recommendations. This might be due to the potential use of JAK inhibitors in treatment.

HLA testing was performed by most of the participants (always or sometimes = 69%) and could influence the therapeutic approach or follow-up if HLADRB1*15 allele is detected (58%). Current recommendations suggest further research into the utility of HLA markers across the broader population of patients with Still's disease as its value in clinical practice remains debated among experts.

As recommended, most pediatricians (87%) chose not to discontinue IL-1 or IL-6 inhibitors if LD developed, switching biologics when needed. Add-on therapies are also encouraged in the latest guidelines. Our data suggests that T cell-targeted immunosuppressants could be a viable option, with a preference for JAK inhibitors (selected by 26 participants) followed by cyclosporine (n=10) and mycophenolate mofetil (n= 9). Steroids remained part of the management strategy for lung disease (n=8).

Conclusion: The recently released EULAR/PReS recommendations offer a valuable framework for improving LD diagnosis and management in Still's Disease. However, gaps persist between these guidelines and real-world practice, particularly in early screening and biomarker use. This is especially critical as patients with Still's Disease are treated globally, including in emerging and developed countries. Bridging these gaps will require raising clinician awareness and improving access to diagnostic tools and therapies to validate the recommendations across diverse healthcare settings.
Disclosure of Interest: None declared

Identifier: PO038

SYNDROME OF UNDIFFERENTIATED RECURRENT FEVER (SURF): CLINICAL AND GENETIC INSIGHTS FROM A MONOCENTRIC HOMOGENEOUS COHORT OF 101 PATIENTS

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Introduction: The Syndrome of Undifferentiated Recurrent Fever (SURF) is a recently identified autoinflammatory condition. Patients with SURF experience recurrent fevers often accompanied by arthralgia and abdominal pain, resembling Familial Mediterranean Fever (FMF) but without mutations in the MEFV gene. Like FMF and in contrast to PFAPA, SURF patients respond well to colchicine. Our recent study demonstrated that in vitro analysis of pyrin inflammasome activation differentiates SURF from FMF and PFAPA, providing further evidence that SURF represents a distinct, yet still poorly characterized, patient group.

Objectives: To provide an updated and comprehensive clinical (observational and longitudinal) and genetic characterization of a homogeneous cohort of 101 patients with SURF, managed at a tertiary referral center for systemic autoinflammatory diseases.

Methods: Patients with pediatric-onset SURF followed at the Giannina Gaslini Institute in Genoa, Italy, were enrolled in the *Eurofever Registry* upon providing informed consent. We longitudinally analyzed the clinical records of the 101 SURF patients, who were genetically negative for at least the MEFV gene and did not meet the classification criteria for PFAPA. Descriptive statistics were conducted for the entire cohort. Treatment responses to colchicine and IL-1 blockers were categorized as complete, partial, or resistant. The Kruskal-Wallis test was used for continuous variables, while Fisher's exact test was applied to compare categorical variables across treatment response groups. Univariable and multivariable Cox regression models were employed to identify clinical factors associated with response to colchicine therapy. In 61 of the 101 patients, deep genetic analysis was performed using whole genome sequencing and an extended gene panel encompassing 189 autoinflammatory disease-related genes.

Results: In the described cohort, which was predominantly of Caucasian origin (98.8%), only 18.8% of patients reported a family history of recurrent fever. The median age of onset was 2.6 years (IQR 1.00–5.00), while the median age at diagnosis was 6.51 years (IQR 4.45–10.49), reflecting a substantial diagnostic delay of 2.6 years (IQR 1.46–4.99). The median duration of febrile episodes was 4 days (IQR 3–5), with a median of 12 episodes per year (IQR 12–20). The most prevalent symptoms in the cohort were fever (100%), arthralgia (72.3%), abdominal pain (65.3%), and myalgia (55.5%). PFAPA-like symptoms were less frequent in this cohort, both in their overall occurrence and episodic frequency patterns. Specifically, exudative tonsillitis, oral aphthosis, and lateral cervical lymphadenopathy were reported as occurring "often" or "sometimes" rather than "always." Cox regression analysis identified longer febrile episode duration, lateral cervical lymphadenopathy, and oral aphthosis as univariate factors associated with colchicine resistance. Multivariate analysis confirmed oral aphthosis as an independent predictor of colchicine resistance in this cohort. Nine patients received IL-1 blocking therapy (anakinra and/or canakinumab) as a second-line treatment, which demonstrated overall efficacy. Deep genetic panel testing conducted on 61 patients identified a novel heterozygous variant in the SYK gene in one patient presenting with synovitis.

Conclusion: Our study presents the largest homogeneous, single-center and longitudinal cohort of SURF patients described to date. The clinical features, particularly the low frequency of PFAPA-like symptoms and the good response to colchicine - negatively influenced by the presence of PFAPA-like symptoms - strengthen the evidence that SURF may represent a distinct group, likely driven by polygenic inheritance.

Acknowledgments: Not applicable.

Disclosure of Interest: S. Palmeri: None declared, M. Ponzano: None declared, G. Recchi: None declared, C. Conti: None declared, M. Bustaffa: None declared, D. Sutera: None declared, C. Matucci-Cerinic: None declared, R. Bertelli: None

declared, F. Penco: None declared, I. Prigione: None declared, R. Papa Conflict with: Speaking from SOBI. , I. Ceccherini: None declared, S. Volpi Conflict with: SV received speaker's fee from SOBI and consultancies Boehringer. , R. Caorsi Consultant for: from SOBI, Conflict with: Speaking fee from SOBI, M. Gattorno Conflict with: MG received consultancy and speaker fee from Novartis, Sobi, Fresenius Kabi, Kiniksa

Identifier: PO039

DECODING THE SYNDROME OF UNDIFFERENTIATED RECURRENT FEVER: CLINICAL INSIGHTS, BIOMARKERS, AND TREATMENT OUTCOMES FROM A NATIONAL UK AUTOINFLAMMATORY CENTRE

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Introduction: The Syndrome of Undifferentiated Recurrent Fever (SURF) is a condition characterized by repeated episodes of fever without a clearly identifiable cause, often accompanied by symptoms such as fatigue, joint pain, rash, or lymphadenopathy. These episodes may occur spontaneously or be triggered by minor infections or stress.
Objectives: to analyze clinical, demographic, and laboratory characteristics of patients with undifferentiated recurrent fever and identify phenotypes and biomarkers associated with the condition
to assess treatment outcomes and their relationship with key clinical and laboratory parameters, including inflammatory markers like CRP and SAA.
Methods: Data were obtained through a retrospective review of the database encompassing all patients referred for evaluation of suspected autoinflammatory syndrome to the national autoinflammatory centre in London, UK. Inclusion criteria required patients to lack a definitive molecular diagnosis following next-generation sequencing (NGS) and to have attended at least two follow-up appointments in the autoinflammatory clinic.
Results: Clinical, demographic, and laboratory data were collected from patients referred to the national autoinflammatory centre London, UK for evaluation of undifferentiated recurrent fever. The cohort included 177 females and 163 males, 222 (75%) Caucasians, with a median age of symptom onset of 25 years and a median age at diagnosis of 27 years. Common clinical features included rash (65%), arthralgia (52.4%), arthritis (55.8%), fatigue (48%), myalgia (38.2%) and headaches (37%), while lymphadenopathy was observed in 47 % of patients. Laboratory findings revealed mean CRP and SAA levels of 15.65 mg/L (SD 21.03) and 72.57 mg/L (SD 121.15). Other key laboratory markers, including creatinine (median 70.5 µmol/L), albumin (median 46 g/L), and neutrophils (median 4.2×10^9/L), were within expected ranges but demonstrated variability among patients. Treatment outcomes were highly diverse with the most commonly used being colchicine, glucocorticoids, and NSAIDS, reflecting the heterogeneity of the patient population.
Conclusion: This analysis underscores the complexity of managing undifferentiated recurrent fever and highlights the need for further investigation into its clinical and molecular underpinnings.
Disclosure of Interest: None declared

Identifier: PO040

THE ASSESSMENT OF IL-15 IN PATIENTS WITH STILL'S DISEASE, IN VITRO AND EX-VIVO FINDINGS

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Introduction: Still's disease is a systemic inflammatory disorder of unknown aetiology affecting both children and adults. Both innate and adaptative arms of the immune system are involved in the pathogenic mechanisms underlying this disease [1]. To date, little is known about the potential pathogenic role of interleukin (IL)-15 in the context of Still's disease.
Objectives: In this study, we evaluated sera levels of IL-15 in patients with Still's disease. We also assessed the IL-15 pathway in peripheral blood mononuclear cells (PBMCs) as well as of synovial tissues in patients with Still's disease.
Methods: We assessed sera from patients with Still's disease followed at the Rheumatology Division of L'Aquila (IT), and at the Immunology and Clinical Medicine Unit of Campus Biomedico of Rome (IT). We evaluated sera levels of IL-15 in patients with active disease (n=40), inactive disease (n=16), and healthy controls (HCs) (n=24) by ELISA. In addition, by a bulky RNA sequencing, key molecules of the IL-15 pathway (IL-15, IL-15RA, IL-2RB, JAK1, JAK3, STAT3, STAT5A, mTOR, PI3K, AKT1, KRAS, RAF, MAPK1, mTORC1, BCL-2, IFN-γ, TNF, c-myc, c-fos, NF-kB e IFN-γ) were assessed in PBMCs of patients with Still's disease (n=4) and matched HCs (n=3). Finally, a bulky RNA sequencing was performed in synovial tissues from patients with Still's disease (n=2) and matched HCs (n=2).
Results: Eighty serum samples from Still's disease were analyzed. Sera levels of IL-15 were significantly higher in patients with active Still's disease [median 9.35 pg/ml (4.32-19.76)] when compared with patients with inactive disease [4.23 pg/ml (2.27-12.34)] and HCs [7.194 pg/ml (4.21-10.11)] ($p<0.005$). In addition, the values of IL-15 correlated with the presence of macrophage activation syndrome (MAS) ($r=0.347$, $p=0.001$). Assessing mRNA relative expression in PBMCs, STAT5A, PI3K, RAS, RAF, NF-kB, appeared to be down-regulated in Still's disease than HCs. By RNA-sequencing analysis in synovial tissues, we observed that IL-15, IL15RA, IL2RB, STAT5A, STAT3, TNF, IFN-γ, PI3K, RAS, RAF, and JAK3 were up-regulated in patients with Still's disease than HCs.
Conclusion: Our results suggest that IL-15 could play a key role in the pathogenesis of Still's disease, especially in active disease with MAS. The assessment of synovial tissues provided new insights into the possible role of IL-15 pathway as additional mechanistic disease step in these patients.

[1] Ruscitti P, et al. Nat Rev Rheumatol. 2024; 20(2):116-132.

Disclosure of Interest: None declared

Identifier: PO041

PREDICTIVE FACTORS FOR RELAPSE IN ADULT-ONSET STILL'S DISEASE: A RETROSPECTIVE COHORT STUDY

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Introduction: Adult-onset Still's disease (AOSD) is a rare systemic autoinflammatory disorder affecting young adults, characterized by fevers, a salmon-colored rash, arthritis, and systemic manifestations. Its symptoms overlap with other conditions, complicating diagnosis. Relapses in AOSD marked by systemic or joint symptom recurrence, significantly impair quality of life and may cause long-term damage and morbidity. Understanding predictors of relapse is crucial for optimizing management and reducing morbidity.
Objectives: This study aimed to identify clinical and laboratory parameters at diagnosis that predict relapse risk in AOSD patients.
Methods: A retrospective cohort of 87 AOSD patients diagnosed between January 2012 and August 2024 at two tertiary rheumatology centers was analyzed. Diagnosis was based on Yamaguchi and Fautrel criteria. Relapse was defined as systemic or articular symptom recurrence with elevated inflammatory markers after remission.

Clinical, demographic, and laboratory data were collected, including biochemical (CRP, ferritin, albumin), hematological (neutrophil counts, platelets), and mixed ratios (CRP/Albumin, Neutrophil/Albumin). Phenotypes were categorized as systemic-dominant or joint-dominant.

Treatment data, including first-line csDMARD and steroid use, were evaluated for relapse associations. Statistical analyses included Mann-Whitney U tests, chi-square tests, and logistic regression, with results presented as odds ratios (ORs) and 95% confidence intervals (CIs).

Results: Patients were divided into Relapse (n=31) and Non-Relapse (n=56) groups. Median follow-up duration was significantly longer in the Relapse group compared to the Non-Relapse group (94.7 vs. 52.9 months; p=0.02). Time to first relapse in the Relapse group (median 34.6 months) was similar with follow-up duration in the Non-Relapse group.

Splenomegaly was less frequent in the Relapse group (13.8% vs. 38.2%; p=0.01). Joint-dominant phenotypes were more prevalent in the Relapse group (41.9% vs. 19.6%; p=0.04) and were significantly associated with relapse risk (OR: 9.53; CI: 2.21–41.06).

Laboratory findings revealed higher CRP levels (median 165 vs. 101.5 mg/L; p<0.01), with CRP >100 mg/L strongly associated with relapse risk (OR: 15.57; CI: 2.97–81.64). Ferritin >5000 ng/mL (OR: 3.63; CI: 1.28–10.30), elevated neutrophil counts (17.6 vs. 10.2 × 10^9/L; p=0.01), hypoalbuminemia (<3 g/dL), and derived ratios, including CRP/Albumin (58.4 vs. 29.6; p<0.001) and Neutrophil/Albumin (5.6 vs. 3.4; p=0.006), were significantly higher in the Relapse group.

First-line csDMARD use was more frequent in the Relapse group compared to the Non-Relapse group (77.4% vs. 44.6%; p=0.003), whereas solo steroid use was significantly higher in the Non-Relapse group (37.5% vs. 16.1%; p=0.03).

Conclusion: Elevated CRP (>100 mg/L), ferritin (>5000 ng/mL), and hypoalbuminemia (<3 g/dL) at diagnosis, along with joint-dominant phenotype, are strong predictors of relapse in AOSD. Splenomegaly, more common in the Non-Relapse group, may reflect a systemic phenotype less prone to recurrence.

The higher frequency of first-line csDMARD use in the Relapse group (77.4% vs. 44.6%) likely reflects national treatment policies requiring csDMARD initiation in most patients. However, in joint-dominant phenotypes and those with elevated

inflammatory markers, this phase may be insufficient for disease control. Rapid escalation to biologic therapies, such as IL-1 or IL-6 inhibitors, could help achieve better outcomes by minimizing relapse risk and long-term joint damage.

Early recognition of high-risk patients based on clinical and laboratory predictors is essential to optimize therapeutic strategies, reduce relapse frequency, and improve disease management in AOSD.

Disclosure of Interest: None declared

Identifier: PO042

EVALUATION OF THE PATIENTS WITH CHRONIC NON-BACTERIAL OSTEOMYELITIS BASED ON MAGNETIC RESONANCE IMAGING

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Introduction: Chronic non-bacterial osteomyelitis (CNO) is an autoinflammatory disease characterised by non-infectious inflammation of bone. Clinical symptoms are important in the diagnosis of CNO, but magnetic resonance imaging (MRI) is considered the gold standard imaging modality for diagnosis and follow-up.

Objectives: The aim of our study was to evaluate the clinical features and the evolution of radiological findings during the disease course of CNO patients.

Methods: Forty-five CNO patients were included in the study. Demographic, clinical and laboratory characteristics were evaluated retrospectively. Whole-body MRI scans were performed annually. MRI findings were evaluated during the course of the disease and the evolution of bone lesions was assessed.

Results: Twenty-five (55.5%) of the patients were boys and the mean age of the patients was 13.6 (±3.8) years. The mean age at diagnosis of CNO was 11.0 (±3.8) years. The median (min-max) time from symptom onset to diagnosis was 7 (0.5-42.0) months. The most common symptom at diagnosis was localised pain (86%). Other symptoms and findings included generalised pain (30.2%), fever (20.9%), rash (16.3%), weight loss (9.3%), enthesitis (23.3%), arthritis (20.9%), sacroiliac tenderness (39.5%) and sacroiliitis (25.6%). 32.6% of patients had co-morbidities, the most common being familial Mediterranean fever, followed by spondyloarthritis, uveitis, psoriatic arthritis, inflammatory bowel disease and Takayasu's arteritis. The median erythrocyte sedimentation rate was 28 (2-93) mm/h,C-reactive protein was 9.6 (0.35-313.0) mg/L. The median CHAQ score at diagnosis was 2.2 (0-10.4). The most common treatment used in patients was non-steroidal anti-inflammatory drugs (90.7%), followed by methotrexate (60.5%), steroid (30.2%), etanercept (16.3%), adalimumab (11.6%), sulfasalazine (7%) and infliximab (2.3%). The median number of sensitive bone sites was 1 (0-5), while the median number of affected bone lesions on MRI was 4 (1-11) at diagnosis. After a median of 32 (1-141) months of treatment, the median number of sensitive bone sites was 0 (0-2) and the median number of affected bone lesions on MRI was 2 (1-6) at last follow-up.

Involved bone	At diagnosis	At last control
Femur, n (%)	32 (71.1)	5 (11.1)
Pelvis, n (%)	25 (55.6)	6 (13.3)
Tibia, n (%)	27 (40.0)	5 (11.1)
Foot, n (%)	20 (55.6)	5 (11.1)
Sacroiliac, n (%)	13 (28.9)	6 (13.3)
Fibula, n (%)	13 (28.9)	1 (2.2)
Humerus, n (%)	11 (24.4)	3 (6.6)

Radius, n (%)	7 (15.6)	
Ulna, n (%)	6 (13.3)	1 (2.2)
Hand, n (%)	7 (15.6)	1 (2.2)
Scapula, n (%)	10 (22.2)	1 (2.2)
Vertebrae, n (%)	7 (15.6)	
Clavicle, n (%)	6 (13.3)	1 (2.2)
Sternum, n (%)	4 (8.9)	
Mandible, n (%)	1 (2.2)	1 (2.2)

Conclusion: We found that the number of clinically active lesions in CNO differed from the number of active lesions detected by MRI. Lesions detected by MRI should also be included in the assessment of disease activation in CNO patients.

Disclosure of Interest: None declared

Identifier: PO043

STILL'S DISEASE OVER 2 DECADES: LEARNING FROM THE PAST

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Introduction: Systemic juvenile idiopathic arthritis (sJIA, Still's disease) remains a therapeutically challenging entity despite dramatic improvement of disease outcomes with the introduction of biologic disease-modifying therapies. Timely change of established practices in accordance with new discoveries is a hallmark of high-quality clinical care.
Objectives: Review of the unit clinical practice in sJIA management and its evolution over the last two decades.
Methods: Retrospective electronic record review (2005-2020) and prospective (2021-2024) data collection on patients with sJIA followed at our unit from disease onset or its relapse.
Results: Total of 66 patients (39 girls, 59%) fulfilling sJIA ILAR and/or PRINTO criteria were identified, majority (97%) were followed from SJIA onset. Number of new cases per year ranged between 2-4 with outbreaks of 6 in 2018, 2021 and 2022. Mean follow-up (F/U) time was 6.2 years (SD 4.3), mean age at diagnosis was 7.4 years (SD 4.7). In 44 patients (66,7%) only mild oligoarthritis or no arthritis was ever present. Initial systemic manifestation score (SMS) was 4.4 (SD 1.7). Macrophage activation syndrome (MAS) developed in 25/66 (38%) patients, in 18/66 (27%) at sJIA onset, in 6/25 (24%) it had chronic or relapsing course. All MAS patients had hepatopathy (2 liver failure), respiratory and gut failure occurred in 2 patients each, severe CNS involvement in one. SJIA lung disease (LD) has been identified since 2017 in 7 patients, pulmonary hypertension in one, all had also MAS. One patient (with recurrent MAS and LD) died 3 years from onset. Until 2016 all patients initially received corticosteroids (CS), in majority with methotrexate. From 2017, 59 patients were treated with anakinra, total of 28 patients received it as a first-line therapy, in 16 cases as monotherapy. Within 6 months, 18/28 reached clinical inactive disease (CID) without or with <0.2mg/kg/day CS, from 16 patients who received anakinra as monotherapy 14 had CID. Canakinumab was used in 17 patients as a 2nd or 3rd line biologic, 21 received tocilizumab (15 within 6 months from diagnosis). TNF inhibitor was prescribed to 11 patients, 2 received abatacept. Haematopoietic stem cell transplantation was performed in 3 patients (1 autologous), 5 received emapalumab for MAS, one was treated with MAS825. Total of 9/66 (13.6%) difficult-to-treat patients received 3 or more different biologics. Other treatments used included JAK inhibitors (n=8), Cyclosporin A (n=14), etoposide (n=2), mycophenolate mofetil (n=3), cyclophosphamide (n=1). CID without CS at 6 months from the diagnosis was achieved in 32/66 (48.5%) patients, 26/32 were treated after 2017 in contrast to 6/32 patients treated in "pre-anakinra era". At the last F/U total of 49/66 (74.2%) patients had CID without CS, 30 (45.5 %) were in full (drug-free) remission.
Conclusion: SJIA therapeutic algorithms have rapidly evolved over the past 2 decades when IL-6 and later IL-1 blocking agents became available. Their introduction as a first-line therapy that has been advocated in the past few years seems to have targeted the "window of opportunity" to reach disease inactivity early while significantly reducing CS toxicity burden. Number of our patients reaching the recommended therapeutic target of CID without CS by 6 months from diagnosis has grown more than 4-times in the past 7 years. Nevertheless, over 10% of patients whose disease is often complicated with chronic MAS and/or LD confer difficult-to-treat disease management of which remains a challenge.
Acknowledgments: Supported by the Czech Health Research Council (AZV CR) grant NU21-05-00522
Disclosure of Interest: A. Kozáková: None declared, K. Šingelová Speaker bureau of: Pfizer, N. Husáková: None declared, P. Šeferna: None declared, Š. Fingerhutová Speaker bureau of: Sobi, P. Doležalová Speaker bureau of: Novartis, Sobi, Pfizer, Medac

Identifier: PO046

ADULT PATIENTS WITH UNCLASSIFIED SYSTEMIC AUTOINFLAMMATORY DISEASE - A SINGLE CENTER CASE SERIES

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Introduction: Autoinflammatory Diseases (AID) have been traditionally conceptualized as monogenic conditions presenting in early childhood. It is now increasingly recognized that AIDs may present in adulthood. Moreover, many patients with autoinflammatory phenotypes do not fit any specific diagnostic criteria, nor carry variants classified as Likely/Pathogenic. At our adult center, most patients actually fall into this category as having Unclassified Systemic Autoinflammatory Disease (USAID). Due to the significant proportion of our patients having this syndrome, we herein report their findings.

Objectives: Describe the clinical and genetic characteristics of patients with USAID at an adult autoinflammatory clinic.

Methods: Patients 18 years or older were recruited from an Autoinflammatory Clinic in Toronto. Inclusion criteria were unexplained signs of recurrent or chronic inflammation. These signs included fevers, serositis, peritonitis, pharyngitis, mucocutaneous ulceration, skin lesions, elevated CRP, response to colchicine or IL-1 blockade. Patients were excluded if there was an explanatory infection, or if they fit the diagnostic criteria for any specific AID. Gene panel testing was performed at the Division of Genome Diagnostics, Hospital for Sick Children. Variants classified as Likely/Benign were not reported. All patients provided written consent to be included in a case series.

Results: A total of 35 patients were included (89% female). The ethnic composition was diverse, including Caucasian (63%), South Asian (17%), East Asian and African (both 9%). The median age at enrollment was 39 years, and first symptom onset at 25 years. A family history of similar symptoms was present in 14% of patients. Prior to the first onset of symptoms, an antecedent event was recalled in 34% of patients. The most common were viral infections, and concussion (both in 14% of patients). The most common manifestations were joint pain/swelling (80%), recurrent fevers >38c and dermatologic lesions (both in 26 patients, 74%, each). The most common dermatologic manifestations were mucocutaneous ulcerations (15/26) and urticaria-like lesions (10/26). 7 patients received skin biopsy, with neutrophilic infiltration found in four. CRP was not available in all 35 patients. 16/27 patients (59%) showed elevated CRP during flares, while 8/32 (25%) were elevated at baseline. Colchicine was beneficial in 20/27 patients. 5/5 patients treated with IL-1 inhibitor showed clinical and biochemical improvement. Autoinflammatory gene panel testing was available in all but one patient. 29/34 patients (85%) carried a variant. *MEFV* variants were present in 13/34 (38%) for which the most common was E148Q (8/13, 61%). *NOD2* variants were present in 9/34 (26%), the most common being L1007fs (4/9, 44%). *NLRP3* variants were present in 3/34 (9%), with two patients carrying V200M.

Conclusion: The etiology of USAID remains elusive but should be prioritized as an important area of investigation given the large numbers of patients with autoinflammation that lack a monogenic explanation. It is unclear if USAID patients have a monogenic disease in a yet unknown gene, or a multifactorial condition with genetic susceptibility factors. Indeed, a '2 hit hypothesis' appears plausible given that many in our cohort described an external triggering event, and/or carried variants in known autoinflammatory genes. There was only one patient whom neither reported an antecedent triggering event, nor carried an autoinflammatory variant. The overwhelming female predominance may also suggest additional hormonal or X-chromosome related factors.

Our study was limited by the restricted access to clinical exome sequencing and functional studies for all patients. Future studies using these tests as well as larger multicenter cohorts with greater statistical power may shed further light on the role of AID variants in USAID patients.

Disclosure of Interest: None declared

Identifier: PO047

CUTANEOUS MANIFESTATIONS IN A CHILEAN COHORT WITH SYSTEMIC AUTOINFLAMMATORY DISEASES

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Introduction: Systemic Autoinflammatory Diseases (SAIDs) are a heterogeneous group of disorders arising from innate immune dysregulation. These disorders are defined by chronic systemic or localized tissue inflammation occurring in the absence of infection or malignancy. Their clinical presentation is diverse and often includes recurrent episodes of fever, intense systemic inflammation with macrophage activation, and persistent inflammation affecting the skin, bones, or other tissues. Despite the critical diagnostic value of skin involvement in SAIDs, cutaneous manifestations associated with autoinflammatory syndromes remain understudied. This study highlights the diverse cutaneous manifestations associated with SAIDs that can be associated to different underlying molecular mechanisms.

Objectives: To characterize the cutaneous manifestations in a cohort of patients with SAIDs.

Methods: Patients of all ages with SAID of probable or confirmed genetic origin were invited to participate. Included patients (n=74) underwent a medical assessment involving a review of their prior medical records and a physical examination. Cutaneous manifestations were clustered into 16 groups. If these manifestations were not present during the evaluation, photographic evidence was used. In cases where no photographic records were available, the patients were excluded from the study (n=10).

Results: Among patients with SAID included, 78% (n=58) had a history of cutaneous manifestations. Of these, 48 patients had objectively identifiable skin lesions and were included in the study. The age range of the included patients was 0 to 47 years and 54% were male. 37 % had mucosal or cutaneous ulcers, 20% pustules, 16% erythematous squamous papule or plaques, 16% had urticaria, 16% erythematous plaque, 12% nodules, 8% livedo reticularis, 8 % calcinosis, 4% panniculitis, 4% hyperpigmentation, 4% alopecia, 4% lipodystrophy, 2% atrophic plaque, 2% necrosis and 2% erythema pernio-like lesions. Among 48 patients included, 33% had confirmed genetic diagnosis, most presented with cutaneous lesions classically associated to their genetic diagnosis: 3 patients had Cryopyrin-Associated Periodic Syndromes (CAPS/*NLRP3*) and all had urticaria as the main cutaneous manifestation; 2 with DADA2, had livedo reticularis; one with SAVI (*TMEM173*) had necrotic and pernio like lesions; one with HA20 (*TNFAIP3*) and one patient with trisomy 8 presented with mucocutaneous ulcers, another patient with trisomy 8 had hidradenitis suppurativa. Other patients with variants in *MEFV, MVK, XIAP, XLPDR* and *STAT1* had heterogenous cutaneous phenotypes. Interestingly, two twin brothers with CTLA4 haploinsufficiency showed erythematous squamous papules, plaques and lipodystrophy, which have not been classically associated to this disease.

Conclusion: Our observations confirm clustering of cutaneous lesions among different SAIDs. Inflammasome-driven AIDs, such as Cryopyrin-Associated Periodic Syndromes (CAPS), manifest with urticarial or maculo-papular erythematous exanthems. Histopathological findings have revealed neutrophilic infiltrates and cytokine-driven inflammation, emphasizing the role of IL-1β and IL-18. Non-inflammasome-mediated diseases like STING-associated vasculopathy with onset in infancy (SAVI) exhibit violaceous pernio-like lesions and progressive necrosis, linked to Type I interferonopathies. Livedo reticularis is an additional distinctive pattern in SAIDs, such as ADA2. Recognition of these dermatologic signs, combined with an understanding of the underlying cytokine dysregulation can facilitate an early diagnosis and targeted therapies. This study underscores the importance of interdisciplinary approaches to improve patient outcomes in these complex conditions.

Acknowledgments: We would like to thank all the patients and their families for participating in this study. This work was funded by Jeffrey Modell Foundation and FONDECYT Project No. 1221802, ANID, Chile.

Disclosure of Interest: None declared

Identifier: PO048

WORLDWIDE ASSESSMENT OF CLINICAL PRACTICE STRATEGIES (CLIPS) IN STILL'S DISEASE TREATMENT THROUGH THE JIR-CLIPS NETWORK: A COST ACTION

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Introduction: Although evidence- or consensus-based recommendations exist for treating Still's disease, their implementation in real-world settings remains challenging.

Objectives: To gather real-life clinical practice strategies (CliPS) from physicians worldwide who treat Still's disease, aiming to create appropriate management plans that support physicians in decision-making processes.

Methods: This research was conducted as part of the CliPS project, funded by COST (European Cooperation for Science and Technology), using online questionnaires distributed since September 2022. The study analyzed treatment options for the first, second, and third lines according to the phenotypic presentation (mainly systemic, mainly articular) and disease severity (presence of serositis or MAS). Participants' choices were also compared based on country income levels. Statistical analysis was performed with SPSS® software version 27 with significance set at $\alpha=0.05$

Results: By December 2024, 326 physicians had responded to the survey. Most were pediatric specialists (68.4%, n=223), 25.5% were adult specialists (n=83), and 5.2% were both pediatric and adult specialists (n=17). Respondents were from 54 countries across Europe, Asia, Africa, South America, North America, and Oceania. A preliminary analysis of 278 responses revealed distinct treatment strategies based on patient phenotype and disease severity.

For patients with *mainly systemic symptoms*, the most popular first-line treatment was steroids (71.9%), predominantly as intravenous methylprednisolone pulses, followed by biologics (50.3%), particularly anakinra. In cases of non-response, switching within IL-1 inhibitors or introducing IL-6 inhibitors were the most common second and third-line treatments. Physicians in high-income countries prioritized biologics (anti-IL-1 > anti-IL-6 agents) as first-line treatment, while physicians in medium- and lower-income countries more frequently opted for steroids or methotrexate.

For patients with *mainly articular symptoms*, methotrexate (51.3%) remained the most popular first-line treatment, with or without steroids and NSAIDs, followed by biologics (31%), particularly tocilizumab and anakinra. In non-responsive cases, physicians preferred to add or switch to biologics, with JAK inhibitors emerging as third-line options.

For patients with *serositis*, steroids (76.5%) were the most commonly selected first-line treatment, often in combination with biologics (53.9%, mainly anakinra). In refractory cases, switching to a different biologic, particularly IL-1 or IL-6 inhibitors, was the most common second-line approach, while third-line strategies included the addition of immunoglobulins, further steroid adjustments, or the introduction of JAK inhibitors.

For patients with *MAS*, intravenous steroids (93.2%) were the cornerstone of first-line treatment, followed by biologics (51.2%, mostly anakinra) and cyclosporin (26.7%). In cases of non-response, the addition of cyclosporin or switching to a different biologic, such as tocilizumab, were the most common second-line approaches. Etoposide, plasma exchange, and JAK inhibitors were included among third-line strategies in more severe or refractory cases.

Conclusion: This study underscores the diverse approaches used by physicians globally, highlighting variations based on patient phenotype and country income levels. These findings emphasize the need for tailored management plans to optimize patient outcomes and address challenges in implementing evidence-based recommendations.
Disclosure of Interest: None declared

Identifier: PO049

CHRONIC RECURRENT MULTIFOCAL OSTEOMYELITIS AND LUNG INVOLVEMENT: REPORT OF TWO CASES

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Introduction: Chronic recurrent multifocal osteomyelitis (CRMO) is a chronic inflammatory condition of the bone. Except for cutaneous involvement, extraskeletal manifestations are rare, in particular lung lesions.
Objectives: To report two CRMO pediatric cases with extensive lung consolidations.
Methods: We describe the clinical picture, imaging and outcome of two children with CRMO and pulmonary disease, followed by our rheumatology and autoinflammatory diaseases unit.
Results: Case 1. A 10-year-old Caucasian girl was followed by our tertiary referral center for an aggressive steroiddependent SAPHO syndrome, characterized by PPP and severe bone involvement; the patient underwent treatment with different DMARDs, without complete control of the clinical picture. Three years after disease onset, while on treatment with salazopyrin and adalimumab, a radiological follow up showed stability of the bone lesions and the appearance of a large parenchymal consolidation of the right superior lobe on whole body-MRI. Histologic analysis detected an inflammatory infiltrate consistent with subacute organizing pneumonia. Salazopyrin was withdrawn. Due to the absence of symptoms, no other therapeutic changes were introduced. The lung consolidation resolved within three months and no more pulmonary anomalies were found in the following years.
Case 2. An 11-year-old Caucasian boy with CRMO was initially treated with ibuprofen, then withdrawn for disease remission. Due to the onset of chest pain, he underwent a chest X-ray showing a retrocardiac oval shaped image of the lung. Acute phase reactants were within normal range. A WB-MRI revealed a posteroinferior left lobe consolidation with pleural effusion and hilar lymphadenopathy, in absence of bone lesions. Bioptic findings showed an inflammatory infiltrate consistent with chronic organizing pneumonia. Non-necrotizing granulomas were also detected, despite of Quantiferon, Ziehl-Neelsen coloration and ANCA antibodies negativity. The boy was treated with NSAIDS and symptoms resolved within a few days of onset. No further treatment for CRMO was started. Radiological findings disappeared in a few months.
Conclusion: CRMO is an idiopathic inflammatory disorder of the bone, which is predominant among pediatric population.
In contrast to skin manifestations, lung disease associated with CRMO was rarely described. The diagnostic workup of pulmonary disease may be challenging, as lung manifestations may be silent and detected occasionally. Moreover, radiological features could mimic a large variety of diseases, hence histopathology is pivotal. The evolution of the disease was benign with spontaneous disappearance in all cases. These findings suggest that lung lesions may be part of CRMO clinical picture. However, the spontaneous remission of the parenchymal consolidation, makes a direct link between the pulmonal manifestations and the disease activity still unclear.
Disclosure of Interest: None declared

Identifier: PO050

MACROPHAGE ACTIVATION SYNDROME IN A PATIENT WITH CLERICUZIO-TYPE POIKILODERMA NEUTROPENIA SYNDROME

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Introduction: Poikiloderma is a chronic skin disease with macular pigment changes (hypopigmentation, hyperpigmentation), epidermalatrophy and telangiectatic lesions (1). Clericuzio type of autosomal recessive poikiloderma neutropenia (PN) syndrome was first described by Clericuzio in 1991 in the Navojo tribe of Native Americans. It is characterized with recurrent sinopulmonary infections, poikiloderma, chronic neutropenia, hyperferritinemia, palmoplantar hyperkeratosis, and paronychia (2).

Macrophage activation syndrome (MAS) is a life-threatening complication can accompany especially rheumatological conditions such as systemic juvenile idiopathic arthritis, infections and malignancies. It is typically characterized by persistent high fever, hepatosplenomegaly, lymphadenopathy, serositis, cytopenia, hyperferritinemia, elevated liver enzymes, elevated LDH, and elevated triglycerides (3).

Objectives: We present a case of MAS developing in a patient with PN, a rare syndrome.
Methods: Case: A 14-year-old female patient was being followed up with the diagnosis of PN in our center. Hgb:12.7 g/dL, WBC: 2350/mm³, neutrophil: 310/mm³, lymphocyte: 1770/mm³, PLT: 227000/mm³, ferritin: 1179 ng/mL were range in the patient's routine blood tests. The patient presented with the complaint of cough that has been present for 5 days at the last visit. Generalized poikiloderma, distal phalanx autoamputation of the hand fingers, pachyonychia, flattening of the nasal root, hepatosplenomegaly, bilateral diffuse rales in the lung were detected in the physical examination. Piperacillin tazobactam and teicoplanin treatments were started with the diagnosis of pneumonia in the patient with diffuse bilateral infiltration on chest X-ray. On the 10th day of his hospitalization, laboratory tests were performed due to persistent fever at 40ºC. Hgb: 8.6 g/dL, WBC: 820/mm³, lymphocyte: 280/mm³, neutrophil: 390/mm³, PLT: 81000/mm³, ferritin: 13494 ng/mL , LDH: 2103 IU/L, AST: 105 IU/ L, ALT: 26 IU/L, ESR: 100 mm/h, CRP: 87 mg/L, Procalcitonin >100 ng/mL were detected. No hemophagocytic and blastic cells were observed in the bone marrow aspiration. The patient was given IVIG and pulse methylprednisolone treatments with the diagnosis of macrophage activation syndrome. Anakinra was started due to persistence of hyperferritinemia and pancytopenia while under maintenance methylprednisolone therapy. Ferritin values gradually decreased with anakinra treatment.
Results: We presented here a case with PN developed macrophage activation syndrome in her follow up. She was treated with IVIG, pulse methylprednisolon and anakinra. Poikiloderma neutropenia syndrome is a rare genodermatosis. Poikiloderma and recurrent infections at early ages are important findings. Cases presenting with recurrent infections and skin findings have been reported in the literature. But the development of MAS in PN has not yet been reported. This is the first case report of MAS in a patient with PN according to our knowledge.
Conclusion: Hyperferritinemia is an expected laboratory finding in PN syndrome. If a patient with PN presents with persistant fever, pancytopenia, elevated acute phase reactants and a significant hyperferritinemia MAS always be kept in mind. Early diagnosis and treatment of MAS are important, because MAS may result in death if not treated timely.
Disclosure of Interest: None declared

Identifier: PO051

CLINICAL AND RADIOLOGICAL FEATURES OF MANDIBULAR CHRONIC NONBACTERIAL OSTEOMYELITIS (CNO): A RETROSPECTIVE CASE SERIES

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Introduction: Chronic Nonbacterial Osteomyelitis (CNO) is a rare, autoinflammatory bone disorder that primarily affects children and young adults. It Commonly involves the long bones, clavicles and vertebrae. Mandibular involvement though infrequent is significant as it may mimic infectious or other dental pathologies leading to diagnostic delay and unnecessary interventions.
Objectives: To analyse the clinical and imaging features of mandibular CNO in our cohort of pediatric patients diagnosed with CNO.
Methods: A retrospective review was conducted on patients diagnosed with CNO from September 2020 to December 2024 at our centre. Demographic, clinical, laboratory, and imaging data were analysed to elucidate the presentation and diagnostic challenges in mandibular involvement.
Results: Out of 49 cases of CNO, 6 (12.2%) demonstrated mandibular involvement (3 males, 3 females). The median age at diagnosis was 9 years (range: 4-14 years) with a median diagnostic delay of 9 months (range: 3-18 months).The patients were referred from infectious disease specialist (n=1), pediatric orthopaedics (n=1), pediatricians (n=3) and oral and maxillofacial surgeon (n=1).

Five patients presented with isolated mandibular symptoms, such as swelling and pain, while one patient initially had lower limb pain that progressed to mandibular involvement. Notably, one patient developed clavicular swelling three years after mandibular symptoms. All cases involved unilateral mandibular pathology, and systemic symptom (fever) was noted in 1 case. Prior to referral, five patients underwent invasive dental procedures (tooth extraction: n= 3, root canal: n= 1, curettage n= 1).

Imaging (CT scan: n=6, MRI: n=5, one excluded due to cochlear implant) revealed osteolysis (17%), osteosclerosis (33%), a combination of both (50%), periosteal reaction (33%), soft tissue oedema (33%). Whole body MRI(WB-MRI) performed on five patients (83%) identified multifocal bone lesions in four patients (symptomatically silent) while one had a solitary mandibular lesion.Bone scan was conducted for the patient with cochlear implant which showed a mixed osteolytic/ sclerotic lesion.

Inflammatory markers were elevated in most cases (ESR 40-123 mm/hr, CRP 0.5-49 mg/L). Biopsy, performed in one patient, confirmed sterile inflammation. In three cases, initial misdiagnosis of fibrous dysplasia was made based on imaging.

Conclusion: Mandibular involvement occurred in 12 % in our series. It can be the presenting feature of multifocal CNO or can present as an isolated finding in mandible. CT and MRI findings including lytic and sclerotic lesions, periosteal reaction, and soft tissue oedema were consistent across patients. WB-MRI proved pivotal in identifying silent lesions in asymptomatic sites, thus confirming multifocal involvement, thereby eliminating the need for invasive biopsies, as seen in five of our patients. Three patients were initially misdiagnosed as fibrous dysplasia, again underscoring the importance of WB-MRI in detection of silent multifocal lesions to confirm the diagnosis of CNO.
Acknowledgments: none
Disclosure of Interest: None declared

Identifier: PO052

DISPENSED PRESCRIPTIONS OF ADHD MEDICATIONS TO CHILDREN WITH PFAPA

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Introduction: In clinical practice, we are often asked by parents if Periodic Fever, Aphthous Stomatitis, Pharyngitis and Adenitis syndrome (PFAPA) is connected to activity and attention disorders. Previous studies have shown an increased prevalence of ADHD and neuropsychiatric symptoms in children with familial Mediterranean fever, but data for children with PFAPA are lacking.

Comprehensive register data on ADHD diagnoses are unavailable in Sweden, but by accessing nationwide prescription data, dispensed prescriptions of drugs used for ADHD can be used as a surrogate marker for ADHD diagnosis.

Objectives: To investigate the rate of dispensed prescriptions of ADHD drugs to children and adolescents with PFAPA.
Methods: ADHD medications were defined as ATC codes N06BA: centrally acting sympathomimetics excl. modafinil, and C02AC02: guanfacine. Data on dispensed prescriptions of these drugs to 333 individuals with PFAPA in a previously described cohort (Rydenman et al 2022) from 2006 to 2021 and corresponding data for the general population in Region Västra Götaland were obtained from the Swedish National Prescribed Drug Register. The χ^2 test was used for comparison of ADHD drug prescription rates to PFAPA patients who had gone through tonsillectomy or not. Fisher's exact test was used for analysis of prescription of ADHD drugs in the PFAPA cohort compared to the general population.

The study was approved by the Swedish Ethical Review Authority.

Results: Of the 333 patients with PFAPA in the cohort, 29 (9%) had ≥1 dispensed prescription of an ADHD drug during the follow-up period, which ranged from 15 to 5 years as data were available from 2006 and the youngest person in the cohort was born in 2016. Median age at the time of the first prescription was 12 years (range 6-17). More boys (20/29, 69%) than girls (9/29, 31%) were prescribed ADHD medications. The number of PFAPA patients with ADHD medications were similar in the subgroup that had gone through tonsillectomy and in the subgroup that had not (8/116 (7%) vs 21/218 (10%); OR 0,69, p=0.4). All except 2 patients were prescribed methylphenidate as first line treatment, 18 patients received ≥1 other substance and 7 patients received 3 different substances during the follow-up period.

The proportion of patients with ≥1 dispensed prescription of an ADHD drug each year increased over time in the PFAPA cohort from 0/147 (0%) in 2006, when patients in the cohort were aged 0-17 years, to 23/292 (7.9%) in 2021, when the age span was 5-32 years, as the patients aged but also mirroring increased prescription rates of ADHD drugs in the general population in Region Västra Götaland (from 0.4% in 2006 to 2.3% in 2021 in ages 0-34 years). Data for 2021 in different age groups are shown in Table 1. There was a tendency to higher rates of ADHD drug prescription rates in the PFAPA cohort, with significant differences in some subgroups.

Table 1. Children and adolescents aged 5-19 years with dispensed ADHD drugs in the PFAPA cohort and general population in Region Västra Götaland in 2021

Ages	PFAPA cohort, (*n*=292)	General pop.	*P*	PFAPA cohort, males (*n*=154)	General pop., males	*P*	PFAPA cohort, females (*n*=138)	General pop., females	*P*
5-9 years									
	0/51 0%	1,130/102,711 1.1%	1.0	0/28 0%	861/52,825 1.6%	1.0	0/23 0%	269/49,886 0.5%	1.0
10-14 years									
	11/135 8.1%	4,427/103,182 4.3%	**0.05**	10/71 14.1%	3,231/53,284 6.1%	**0.01**	1/64 1.6%	1,196/49,898 2.4%	1.0
15-19 years									
	10/106 9.4%	4,617/94,394 4.9%	**0.04**	5/55 9.1%	2,700/48,679 5.5%	0.2	5/51 9.8%	1,917/45,715 4.2%	0.06
Total 5-19 years									
	21/292 7.2%	10,174/300,287 3.4%	**0.02**	15/154 9.7%	6,792/154,788 4.4%	**0.04**	6/138 4.3%	3,382/145,499 2.3%	0.14

Conclusion: These findings suggest that a notable proportion of children with PFAPA are treated with ADHD drugs, and tonsillectomy did not affect prescription rates. The proportion treated with ADHD drugs tends to be higher among patients with PFAPA than in the general population. This warrants further studies of ADHD symptoms and diagnoses in children and adolescents with PFAPA.

Disclosure of Interest: None declared

Identifier: PO053

MONITORING COLCHICINE EFFECTIVITY IN CHILDREN WITH PFAPA BY USING AUTOINFLAMMATORY DISEASES ACTIVITY INDEX (AIDAI) SCORES

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Introduction: Periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) syndrome is a prevalent form of periodic fever syndrome in pediatric populations. During these episodes, pharyngitis, cervical lymphadenopathy, and/or aphthous stomatitis may be observed. Between febrile episodes, children exhibit no symptoms or signs, and have normal linear growth and development.
Objectives: In our study, we aimed to evaluate the efficacy of prophylactic colchicine treatment on disease activity PFAPA syndrome using Auto-Inflammatory Diseases Activity Index (AIDAI). We also aimed to identify demographic, clinical and genetic factors that may predict response to colchicine treatment.
Methods: 76 patients who were started prophylactic colchicine treatment with a diagnosis of PFAPA in our tertiary center and followed up for at least 3 months were included in the study. AIDAI scores were calculated for one month before colchicine, one month after colchicine, and three months after colchicine treatment. Those with no symptom from one month after the treatment until three months after the treatment were classified as complete responders and patients were divided into two groups according to their complete response status. These two groups were compared in terms of demographic and clinical characteristics as well as Mediterranean Fever (*MEFV*) gene analysis results.
Results: The mean age of 76 patients with PFAPA syndrome was 4.4 ± 2.13 years and 65.8% (n=50) were male. The median age at the first episode was 2.5 (0.25-7.5) years. Heterozygous MEFV gene mutation was detected in 42.1% (n=32) of patients. Median AIDAI scores showed a significant decrease from 1 month before to 3 months after prophylaxis ($p<0.001$). Having lymphadenitis during an attack was found to be a risk factor when comparing patients who achieved a complete response with those who did not (aOR: 0,225, %95 C.I.: 0,053-0,951, p=0,043). Another analysis focused on the difference in AIDAI score between 1 month before treatment and 1 month after treatment, when the decline was most pronounced. The decline in AIDAI score was significantly lower in patients with a family history of tonsillectomy ($F(1.402, 22.427) = 5.308$, $p = 0.021$, partial $\eta^2 = 0.249$). The time-genotype interaction was also significant, with carriers of the M694V mutation showing a smaller decrease in AIDAI scores ($F(2, 24) = 4.153$, $p = 0.028$, partial $\eta^2 = 0.257$). Multivariate linear regression showed that the M694V mutation had a negative significant effect on the maximum AIDAI score decline ($B = -0.399$, $p = 0.018$).
Conclusion: This is the first study evaluating the possible factros may affect the AIDAI decline pattern in PFAPA patients. Our study shows that the M694V mutation has a negative impact on treatment response by reducing the post-treatment AIDAI score difference. The presence of lymphadenitis was determined as a significant clinical finding that decreased treatment success.
Disclosure of Interest: None declared

Identifier: PO054

ATTITUDES TOWARD GENETIC TESTING IN PFAPA SYNDROME: UNVEILING CLINICAL TRENDS FROM THE JIR-CLIPS SURVEY

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Introduction: PFAPA syndrome (Periodic Fever, Aphthous Stomatitis, Pharyngitis, and Cervical Adenitis) is a frequent autoinflammatory recurrent fever syndrome. While its exact cause remains unclear, genetic testing is increasingly used to rule out monogenic autoinflammatory diseases. Clinicians' views on genetic analysis in PFAPA vary, with some questioning its necessity and cost-effectiveness, as the diagnosis is primarily clinical. A better understanding of current used clinical strategies could enable the development of useful recommendations, minimizing unnecessary testing.
Objectives: This study aims to formulate Clinical Practice Strategies (CliPS) regarding genetic testing in patients suspected of PFAPA that reflects real-life experience of physician in the field.
Methods: This study is part of the Juvenile Inflammatory Rheumatisms (JIR)-CliPS project, an international cross-sectional online survey led by the JIR-network (www.jircohorte.org) and conducted on 5 JIR medical conditions by a consortium of pediatric and adult rheumatologists and immunologists from Europe and beyond. The current analysis focused on 14 questions on genetic testing in patients suspected of PFAPA. We analyzed the responses according to the participant's professional profile and geographical origin. Based on the results, we propose a decision algorithm for genetic testing in patients suspected of PFAPA.
Results: As of May 2024, a total of 130 participants (95 female, 35 male) from 43 countries provided responses on genetic testing questions. Half of the participants came from the five most represented countries (Turkey, France, Brazil, Germany, and Switzerland). The majority cared for pediatric patients (n=111), 80 worked at university hospitals, 92 were pediatric rheumatologists, 73 had more than ten years of experience. Two thirds of the participants reported occasionally performing genetic tests, 15% never, 8% always, and 12% often. Sixty-one percent favored autoinflammatory gene panels, and 20% preferred single-gene tests The choice of the test did not significantly differ according to the country's GDP. Physicians with < 10 years of experience preferred single-gene tests compared to those with > 10 years (21 vs. 7, $p<0.001$). Atypical presentation was the most reported reason for performing a genetic test. A variant of unknown significance (VUS) was considered as a causative variant in 73% of the responders, mainly based on expert opinion and compatible clinical findings. Based on the results we have drawn a flowchart representing the different strategies used by the participants.

Table. Genetic tests in PFAPA diagnosis

		Which genetic test? *Q2*
How often do you use genetics? *Q1*	Always (n=11)	Single n=7 Panel n=7 WES n=2 WGS n=0
	Often (n=16)	Single n=4 Panel n=10 WES n=2 WGS n=0
	Occasionally (n=85)	Single n=16 Panel n=60 WES n=13 WGS n=3
	Never (n=18)	
In which clinical situation? *Q3*	Atypical presentation n=115 Family history n=73 Consanguinity n=55 Long evolutionary time n=45 Needing more intensive treatment n= 44	

Conclusion: Examining physicians' genetic testing practices can provide valuable information for improving the management of patients with PFAPA syndrome.

Disclosure of Interest: H. Sönmez Grant /Research support from: This article/publication is based upon work from COST Action CA21168 – Improving outcome of Juvenile Inflammatory Rheumatism via universally applicable clinical practice strategies (JIR-CliPS), supported by COST (European Cooperation in Science and Technology) - www.cost.eu., C. Vinit: None declared, N. Toplak: None declared, O. Boyarchuk: None declared, M. Gattorno: None declared, G. Ozomay Baykal:

None declared, K. Pateras: None declared, E. D. Batu: None declared, F. Hofer: None declared, C. Jurcut: None declared, M. Rodrigues: None declared, O. Gillaux: None declared, K. Laskari: None declared, M. Santos Faria: None declared, R. Craveiro da Costa: None declared, R. Craveiro da Costa: None declared, M. Hofer: None declared

Identifier: PO056

CARD8-FS VARIANT IN SLOVAK COHORT OF PFAPA PATIENTS

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Introduction: PFAPA syndrome is the most frequent periodic fever syndrome in children. Last studies demonstrated a higher frequency of *CARD8-FS,* which product loses CARD8 activity and activates the NLRP3 inflammasome. This variant was also reported in patients with PFAPA syndrome and Kawasaki disease recently.

Objectives: The aim of our study was to investigate the presence of *CARD8-FS* variant in our PFAPA patients and how the presence of the variant affects the clinical picture.

Methods: We included 90 PFAPA patients and 30 controls (age and sex-matched). We performed a complete clinical examination and blood sampling for selected markers focused on inflammation. *CARD8-FS* was determined in PFAPA patients and controls by High Resolution Melt Analysis (HRMA). The results were evaluated and statistically processed.

Results: Priemerný vek nástupu symptómov bol 2,31 + 2,02 roka, priemerný záchvat trval 2,8 + 1,2 dňa s intervalmi 4 + 1 týždeň. Počas záchvatu bola prítomná signifikantná elevácia CRP, IL-6, alfa-1 glykoproteínu, SAA, výrazná leukocytóza, neutrofília, mierna anémia v krvnom obraze. Variant *CAPD8-FS* bol prítomný v 13,54 % probandov a 6,64 % kontrol . Pacienti s PFAPA s *CARD8-FS* mali významne skorší nástup ochorenia (1 (0,5-1,125) rok oproti 2 (1,06-3) rokom). Významne vyššia koncentrácia IL-6 v sére bola pozorovaná v období bez ataku u nosičov variantu *CARD8-FS* .

Conclusion: Our study confirmed the importance of *CARD8-FS* variant in pathogenesis of PFAPA syndrome. The presence of *CAPD8-FS* seems to modify clinical picture and inflammatory parameters. More data are needed in the future to confirm our findings.

Disclosure of Interest: None declared

Identifier: PO057

EVALUATION OF SECOND-LINE TREATMENTS IN CHRONIC RECURRENT MULTIFOCAL OSTEOMYELITIS

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Introduction: Chronic recurrent multifocal osteomyelitis (CRMO) is an inflammatory bone disorder, of unknown etiology, that affects children and adolescents. There is no real consensus regarding treatment, NSAIDs are recommended as first-line therapy. After NSAIDs failure, a second-line treatment can be initiated, using bisphosphonates or TNF inhibitors.
Objectives: The aim of this study was to evaluate the clinical practices in the management of CRMO.
Methods: A multicenter retrospective study of patients with CRMO from January 2008 to July 2022 at the University Hospital of Montpellier and Nîmes. The clinical characteristics, and responses to treatment were analyzed.
Results: Thirty-one patients were diagnosed over this period. The median age at diagnosis was ten years, with 61% females. Seventeen patients received second-line treatment, amounting to 54% of our cohort. Of these, 16 patients received bisphosphonates, with a very good efficacy for the single locations, and remission in 31% of cases. Eight patients received TNF inhibitors, and we found a response to treatment in 75% of cases but an inability to stop the treatment in 50% of cases. In our study, 62.5% of the patients who have now reached adulthood are in complete remission.
Conclusion: A better understanding of this disease and the clinical characteristic of these patients could reduce the delay in diagnosis, improve therapeutic management and, therefore, their quality of life. Half of our patients received a second-line treatment, which reinforces the notion that studies regarding the effectiveness of treatments should be carried out to establish international guidelines.
Acknowledgments: I would like to express my sincere gratitude to Professor JEZIORSKI for his invaluable assistance and insightful guidance throughout the development of this work. My heartfelt thanks also go to Dr. Carbasse for his active participation in the study and for his valuable advice. I am deeply grateful to Dr. Ludwig and Dr. Delpont for their contribution through the participation of their patients. Most importantly, we wish to extend our special thanks to the families of the patients and the children who kindly agreed to take part in this study.
Disclosure of Interest: None declared

Identifier: PO058

USE AND SAFETY OF DIFFERENT BISPHOSPHONATES IN CHRONIC RECURRENT MULTIFOCAL OSTEOMYELITIS AND A COMPARISON OF THE SAFETY PROFILE: GOSH EXPERIENCE

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Introduction: Bisphosphonates were first used successfully in children with osteogenesis imperfecta, later expanding to secondary osteoporosis and inflammatory bone diseases where side effects and acute phase responses may be variable.
Objectives: We aimed to examine the side effects of pamidronate and zoledronate in patients with chronic recurrent multifocal osteomyelitis (pwCRMO) and compare the side effects of zoledronate between pwCRMO and patients with different underlying diagnoses.
Methods: pwCRMO diagnosed between April 2019-December 2024 were included. In pwCRMO, pamidronate was used between 2019-August 2023, and zoledronate was used from August 2023-December 2024. Patients with different diagnoses who received zoledronate over a 10-month period were included. Parents of pwCRMO were interviewed via telephone regarding the side effect profile. All medical reports were reviewed from electronic patient files, including pre-and post-infusion electrolytes, vitamin D, CRP, bone and renal profile.
Results: Thirty-five patients with CRMO and 25 with other diagnoses treated with bisphosphonates were included. Of the CRMO patients, 15 received zoledronate, 20 received pamidronate, and all non-CRMO patients received zoledronate (Table 1).

In pwCRMO, significant reductions in calcium and phosphorus were observed after both pamidronate and zoledronate (for all $p<0.05$). CRP increased significantly only in the pamidronate group ($p=0.02$), whereas zoledronate significantly increased alkaline phosphatase ($p=0.01$). There were no significant differences in the side effect profile of pamidronate and zoledronate in pwCRMO. The most reported adverse events were flu-like symptoms (pamidronate: 65%; zoledronate: 66.7%) and fever (pamidronate: 50%; zoledronate: 63.6%) (Table 1).

When comparing pwCRMO treated with zoledronate and other patients, calcium levels decreased significantly in both groups ($p<0.01$). However, phosphorus levels decreased significantly only in the CRMO group ($p<0.001$). Regarding side effects, fever was significantly more frequent in pwCRMO ($p=0.008$), and hypophosphatemia was higher in this group (60% vs. 5%, $p=0.002$). Flu-like illness was similar in both groups.

Table 1: Demographics, Diagnosis, and Side Effects of Bisphosphonate Treatments in CRMO and Other Diseases

	CRMO patients Total (n=35)	**CRMO patients Pamidronate** (n=20)	**CRMO patients Zoledronate** (n=15)	**Other diseases** (n=25)	**p value[1]**	**p value[2]**

Age (months)	164.7± 38	175.1±36.1	150,8±37,2	119.1±47.3	0.06	0.03
Age at the infusion (months)	137.8±33.6	136.1±33.3	140±34.9	105.5±46.7	0.73	0.01
Gender (females)	26 (74.3)	15 (75)	11 (73.3)	9 (36)	0.91	0.02
Diagnosis Inflammatory Diseases *CRMO* *JIA* *Vasculitis (Takayasu A)* Neuromuscular Diseases *Duchenne MD* *Spinal Muscular Atrophy* *Congenital MD* *Global Developmental Delay* Skeletal Dysplasia's *Osteogenesis Imperfecta* *Other SD's* Other Diseases *Bone tumor* *Other secondary osteoporosis*	 35 (100) - - - - - - - - - -	 20 (100) - - - - - - - - - -	 15 (100) - - - - - - - - - -	 - 1 (4) 1 (4) 7 (28) 2 (8) 1 (4) 1 (4) 8 (32) 1 (4) 1 (4) 2 (8)	-	-
Side effects Flu-like illness Fever Hypocalcemia (symptomatic)	 	 13/20 (65) 10/20 (50)	 8/12 (66.7) 7/11 (63.6)	 13/25 (52) 4/25 (16)	 0.92 0.46	 0.39 0.008

Hypocalcemia (laboratory)		2/20 (10)	1/13 (7.7)	1/25 (4)	0.82	0.62
Hypophosphatemia (laboratory)		6/11 (54.6) 2/11(18.2)	6/10 (60) 6/10 (60)	10/25 (40) 1/20 (5)	0.800.08	0.48 0.002

Conclusion: Zoledronate and pamidronate have been used in CRMO treatment with similar side effect profiles. Checking renal functions, bone profile and vitamin D levels before infusion and prescribing calcium supplementation post-infusion is essential to prevent side effects. Fever and flu-like symptoms were observed in over half of bisphosphonate-naïve pwCRMO, hence regular paracetamol use for 24-48 hours after the first infusion might help alleviate side effects.

Disclosure of Interest: None declared

Identifier: PO059

YAO SYNDROME IN CHILDREN: A PEDIATRIC CASE SERIES FROM AUTOINFLAMMATION REFERENCE CENTER TÜBINGEN

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Introduction: Nucleotide-binding oligomerization domain containing 2 (NOD2) genetic variations are associated with diseases such as Crohn's disease (CD), Blau syndrome (BS), and recently Yao syndrome (YAOS) which is a multisystem autoinflammatory condition characterized by recurrent fever, dermatitis, arthralgias, gastrointestinal and sicca-like symptoms, distal leg and eyelid swelling. YAOS is considered to be a Genetically Transitional Disease (GTD) and hypothesized that a complex interaction of genetic variants in NOD2 and other innate immune sensor genes, in combination with environmental triggers cause the clinical presentation. Yao syndrome is a rare disease affecting mainly adult female patients. In literature approximately 250 cases, 9 with juvenile onset, from USA, Greece and China were reported.

Objectives: To present the genetical and clinical characteristics of our pediatric patients with Yao Syndrome.

Methods: This is a retrospective analysis of pediatric patients with features of systemic autoinflammatory disease (SAID) and NOD2-variants in whole exome sequencing by next generation sequencing with suspect of SAID fulfilling the clinical criteria suggested by Yao et al.

Results: In total 8 patients (F/M= 4/4) fulfilling the criteria of Yao Syndrome were detected. Two patients carry IVS8+158 and one patient carry G908R variant. All patients presented with periodic fever, since minimum 6 months of age with duration of 3-15 days. The other clinical findings consist of skin rash including nonspecific dermatitis, eyelid and leg swelling (n=8), arthralgia and myalgia (n=6), abdominal pain (n=5), recurrent tonsillitis(n=5), oral ulcers (n=3), neurological symptoms with headache and febrile seizures (n=3) with elevated inflammatory markers. Notably two patients had failure to thrive and one patient was diagnosed as primary polydipsia at the age of 5. The initial clinical diagnosis was Periodic Fever, Aphthous Stomatitis, Pharyngitis, Adenitis (PFAPA) (4/8), systemic juvenile idiopathic arthritis (3/8) and Muckle-Wells Syndrome (1/8). The family history was positive for Yao syndrome in one patient, 4 patients have family history of other inflammatory diseases. Four patients were treated with biologicals including anti-IL1 and anti-IL6 therapies showing variable response.

Conclusion: This is the first pediatric case series presenting the clinical characteristics of pediatric patients with Yao Syndrome. Similar to adult cases reported in the literature, the pediatric cases have also recurrent inflammatory attacks with skin, joint and abdominal pain mimicking relatively common SAID, requiring biological treatments and affecting the growth and psychosocial development of the children.

Disclosure of Interest: None declared

Identifier: PO060

CHRONIC MACROPHAGE ACTIVATION SYNDROME IN STILLS DISEASE: A CASE REPORT OF SUCCESSFUL TREATMENT WITH JAK AND INTERLEUKIN-1 INHIBITORS

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Introduction: Systemic juvenile idiopathic arthritis (sJIA), or Still's disease, is a rare pediatric inflammatory condition with a severe complication known as macrophage activation syndrome (MAS). While acute MAS is well-documented, chronic or refractory MAS remains exceedingly rare and presents significant therapeutic challenges.
Objectives: To demonstrate a young patient with chronic refractory MAS, who responded well to a combination therapy with tofacitinib and canakinumab.
Methods: Case presentation.
Results: We report the case of an 18-month-old girl who presented at 9 months of age with prolonged fever and erythematous rash. She was diagnosed with Still's disease after excluding other potential causes and initially responded to anakinra. However, her disease relapsed with features of MAS, including persistently elevated inflammatory markers, hyperferritinemia, and severe rash with Kobner's sign. Despite multiple treatment modalities, including corticosteroids and biologics, her MAS features persisted. A novel combination therapy of Tofacitinib (JAK inhibitor) and Canakinumab (IL-1 inhibitor) was introduced, leading to significant clinical improvement, normalization of inflammatory markers, resolution of the rash, and successful tapering of corticosteroids. Furthermore, no significant infections or side effects have been observed with this treatment.
Conclusion: This case highlights the efficacy of combining JAK inhibitors with IL-1 inhibitors in the management of refractory MAS. Tofacitinib targets the JAK-STAT pathway, reducing cytokine-driven inflammation, while Canakinumab neutralizes IL-1β, a key cytokine in the inflammatory cascade of Still's disease and MAS.
Disclosure of Interest: None declared

Identifier: PO061

DIAGNOSIS, TREATMENT AND MONITORING OF PEDIATRIC BEHCET'S DISEASE (BD) AND BD-RELATED PHENOTYPES ON IDENTIFIED MONOGENIC MIMICS: A SYSTEMATIC REVIEW PROTOCOL

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Introduction: Behçet's disease (BD) is a polygenic condition with a complex immunopathogenetic background and challenging diagnostic and therapeutic concepts. Treatment options ought to be evaluated in a multidisciplinary setting, given the complexity and diverse organ involvement. Despite the presence of diagnostic criteria, the diagnosis of pediatric BD is still difficult due to atypical findings and the heterogeneity of the disease.

Objectives: The focus of this systematic review is to summarise the current knowledge of the clinical presentation, immunopathogenetic associations, management approach and monitoring in patients with paediatric BD and BD-related phenotypes on identified monogenic mimics.

Methods: An international steering committee (SC) was established and decided a task force including pediatricians, rheumatologists, neurologists, geneticists, immunologists and ophthalmologists. The SC developed search terms and clinical questions to guide systematic literature review and data extraction.

The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) recommendations were followed during the systematic review. For retrieving the relevant literature, an online search was conducted on Medline, PubMed, EMBASE, the Cochrane Database of Systematic Reviews CENTRAL and CINAHL with the help of a librarian. The search included, MeSH/Emtree and title/abstract search for "Behcet's Disease","Pediatric" and their synonyms without any date and language restriction.

Two reviewers screen the articles independently for full text review. Any discrepancies will be resolved by a third reviewer. Ful text screening will be done again by two reviewers and final included articles will be decided. Data on study characteristics, clinical findings, investigations, treatment, monitoring and complications will be collected.

Results: In total 7677 articles retrieved for title and abstract screening after removing duplications. Steering committee developed 82 clinical questions related with diagnosis, organ-specific involvement, management and monitoring. Some of the questions are listed in Table 1. Also, BD-related phenotypes on identified monogenic mimics consensus were obtained to include the genes; *TNFAIP3, RELA, Trisomy 8, NFKB1, ELF4*.

Table 1. Example for clinical questions

When to suspect a genetic cause (monogenic, constitutional)?

Is Pathergy test recommended in the diagnosis of PBD?
Which pattern of articular (axial/peripheral)/involvement is more frequent in the PBD?
For pediatric Behcet uveitis, what is the frequency of anterior/intermediate/posterior/panuveitis and retinal vasculitis?
Which types of vascular involvement are the most characteristic of PBD?
Which neurological manifestation are frequent in CNS involvement?

Conclusion: Due to rarity of BD in children, heterogeneity of disease expression, BD-related phenotypes on identified monogenic mimics, lag of time between the first symptoms and fulfilling the diagnostic criteria and lack of randomized control studies in pediatrics, there are currently no consensus management guidelines for pediatric BD. We will collect all treatment data in detail according to the organ system involvement (dosage, frequency.) on Azathioprine, Methotrexate, Cyclosporine A, biologic DMARDS, anticoagulants/aspirin and other treatments. SLR will provide extensive data synthesis about the diagnosis, management based on organ system involvement and monitoring about pediatric BD and BD-related phenotypes on identified monogenic mimics.

Disclosure of Interest: None declared

Identifier: PO062

NEUROLOGIC PRESENTATIONS IN ELDERLY PATIENTS WITH YAO SYNDROME

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Introduction:

Introduction: Yao syndrome (YAOS, OMIM #617321) is an autoinflammatory disease affecting multi-organ systems and is associated with Nucleotide-binding Oligomerization Domain containing protein 2 (NOD2) mutations. This disease primarily affects White people aged 20-40s with a female to male ratio of 3-4;1. The disease is increasingly reported worldwide. We recently reclassified it a Genetically Transitional Disease (GTD), where a gene mutation is necessary but not sufficient to cause disease alone, highlighting the pervasive impact of genetic background with environment.

Objectives: This study aimed to report the clinical features of a case series of elderly patients with YAOS.
Methods: We conducted a retrospective analysis of a case series of elderly patients with YAOS.

All patients underwent extensive workup to rule out systemic autoimmune, infectious, malignant and other neurologic diseases. They had testing for a periodic fever syndrome gene panel and were identified to carry *NOD2* variant.

Results: In total, three patients were included in this study and all were self-reported White. There were two men and one woman. Mean age was 65 at disease onset and 71 at diagnosis. They all had autoinflammatory symptoms such as episodic fever. All were frequently hospitalized prior to the diagnosis of YAOS. All patients carried the NOD2 variant, heterozygous V955I and responded well to glucocorticoids for their symptoms. Case 1 was a 76-year-old man and presented with headaches, photophobia, neck stiffness and oral ulcers. An MRI of brain and lumbar punctures were normal, but meningitis-like disease was suspected. His symptoms were well controlled with methylprednisolone with taper dose daily. Case 2 was a 68-year-old female and had recurrent high fever and delirium. An MRI of brain was normal. Case 3 was a 68 year-old-male and presented with recurrent low-grade fever, headaches, neck pain and disorientation. An MRI/MRA of brain was normal. Lumbar puncture showed neutrophil elevation with suspicion of meningitis or encephalitis. His symptoms responded well to short courses of prednisone. The demographic, clinical and laboratory data will be presented in a Table in detail.
Conclusion: YAOS primarily affects patients of early adulthood, and can occur in elderly who may present with central nervous symptoms. A proper molecular testing for *NOD2* gene may aid in diagnosis and prompt therapy

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Acknowledgments: None
Disclosure of Interest: None declared

Identifier: PO063

DE NOVO TGFBR1 MUTATION ASSOCIATED WITH ATYPICAL AUTOINFLAMMATORY AND PERIOSTEAL INVOLVEMENT: DIAGNOSTIC CHALLENGES AND THERAPEUTIC APPROACHES

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Introduction: Loeys-Dietz syndrome (LDS) is a connective tissue disorder caused by mutations in genes involved in transforming growth factor-beta (TGF-β) signaling . It is characterized by cardiovascular, craniofacial, skeletal, and neurocognitive abnormalities. While some reports in the literature describe inflammatory phenotypes of LDS with inflammatory bowel disease like symptoms, systemic and bone inflammation have not been documented.
Objectives: To outline the diagnostic process and therapeutic approach in a patient with refractory inflammation, skeletal involvement, and a de novo ***TGFBR1*** mutation.
Methods: Evaluation of clinical history, laboratory and radiological exams, and response to therapy
Results: A 12-month-old girl presented with pain and functional impairment in the left arm, along with edema and tenderness of the ipsilateral lower limb. X-rays revealed atraumatic fractures, periosteal thickening, and bone irregularities, prompting hospitalization for suspected collagenopathy. Genetic testing (trio WES) identified a de novo heterozygous c.696G>C, p.Lys232Asn variant in *TGFBR1*, absent in gnomAD v4 and All of Us and predicted to be deleterious (CADD 25.5, Revel 0.834) associated with LDS . The patient's phenotype is characterized by grey sclerae, velvety skin, ligamentous hyperlaxity, however, the inflammatory phenotype with periostosis had not been previously described in LDS.
Her condition worsened, with increasing pain, functional limitation, fever, and elevated inflammatory markers. Whole-body MRI revealed extensive bone edema and periosteal thickening. Bone biopsy excluded neoplasms, instead indicating chronic osteomyelitis with osteoclastic bone resorption. Cytokine profiling showed elevations in IL-18, IL-6, IL-1Ra, and TNFR1, while the interferon signature was negative.
Antibiotic therapy was ineffective and discontinued. High-dose methylprednisolone initially improved symptoms, but relapses occurred during tapering, necessitating repeated intensification. Biological therapies were initiated: anakinra showed no advantage, and also therapy with etanercept was not beneficial.
Trio exome sequencing did not detect any other candidate variants potentially explaining the autoinflammatory manifestations. Bisphosphonate therapy was also added to address bone modeling, but showed no impact on pain or inflammation.
Weekly adalimumab plus methotrexate brought an initial improvement in pain and inflammation, enabled gradual steroid tapering. Canakinumab was added, without any clear improvement in inflammation control.
Following steroid tapering, the patient experienced worsening suggesting the development of new lesions. X-rays and whole-body MRI confirmed worsening periosteal thickening in the arms and new lesions in the shoulder and ribs. Canakinumab was discontinued, and infliximab was introduced at the time of reporting, with slight initial improvement.
Conclusion: The correlation between the patient's *TGFBR1* mutation and this atypical autoinflammatory presentation remains unclear. TGF-β is a key cytokine in bone matrix regulation, and mutations in TGF-β-related genes have been implicated in inflammatory periosteal diseases such as Camurati-Engelmann disease. This underlines the role of this pathway in bone remodeling. However, no previous *TGFBR1* mutations associated with LDS have been associated with this type of inflammatory bone involvement.
Unresolved questions remain regarding both diagnosis and therapy. Anti-TNF agents currently provide the best pain control but fail to halt disease progression. Further investigation is essential to elucidate the role of this mutation in driving systemic inflammation, its cytokine pathways, and skeletal manifestations, as well as to identify more effective targeted therapies

Disclosure of Interest: None declared

Identifier: PO064

A NOVEL CASE OF P2XR7 ASSOCIATED AUTOINFLAMMATORY DISEASE SUCCESSFULLY TREATED WITH ANTI-IL1 THERAPY

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Introduction: Autoinflammatory diseases were originally defined as a family of disorders characterized by a genetic predisposition to excessive inflammation, mainly reflecting over-activation of innate immune responses, not involving the acquired immune system, such as high autoantibody titers or the presence of antigen-specific T cells, with recurrent/periodic fever as the main manifestation. The P2X7 receptor is a well-known activator of the NLRP3 inflammasome, with studies focusing on its role in innate myeloid cells (monocytes, macrophages, and dendritic cells). Among the different signaling pathways induced by P2X7, the most significant events leading to NLRP3 activation are a decrease in intracellular K+, an increase in intracellular Ca2+, ROS production, depolarisation of mitochondria, and destabilization of lysosomes.
Objectives: We present the case of a patient presenting with severe myalgia, rash, and arthritis, who displayed distinct clinical features consistent with a P2RX7 mutation.
Methods: The clinical and laboratory characteristics of the patient have been delineated.
Results: Case presentation: A previously healthy 10-year-old girl presented to the pediatric rheumatology clinic with a history of recurrent episodes of rash. These episodes were often accompanied by fever, arthralgia, and severe myalgia. There is no consanguineous marriage in her parents, and she has a healthy 2-year-old brother. Laboratory parameters demonstrated elevated acute phase reactants, including an erythrocyte sedimentation rate of 78 mm/h and a C-reactive protein level of 105 mg/l in attacks. Renal and liver function tests were within normal ranges, and no cytopenia was observed. The family reported that the patient had similar attacks for two years, with an average frequency of once a month and a duration of approximately ten days. It was learned that she used antihistamines and steroids without any clinical and laboratory response. MEFV gene analysis revealed a heterozygous K695R variant. In another center, the patient was commenced on colchicine treatment with suspected FMF. However, despite the administration of the maximum dose of colchicine, the attacks remained uncontrolled. In the whole exome analysis performed on the patient due to recurrent attacks, c.532C>T (p.Arg178Trp) variant change was detected in P2RX7. Consequently, anti-IL-1 treatment was initiated for the patient, resulting in the achievement of complete clinical and laboratory remission
Conclusion: The patient's recurrent episodes of rash, fever, myalgia, and arthralgia were suggestive of an autoinflammatory disease. The attacks were notably accompanied by elevations in acute-phase reactants. The activation of the P2X7 receptor (P2X7R) by adenosine triphosphate (ATP) has been demonstrated to be a critical element in the inflammatory response. The activation of this pathway results in the release of pro-inflammatory cytokines, particularly interleukin-1β (IL-1β), which further propagates the inflammatory response. Furthermore, P2X7R activation has been demonstrated to stimulate the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling pathway, thereby contributing to the transcription of proinflammatory mediators. These findings underscore the pivotal role of P2X7R in orchestrating and amplifying inflammatory responses through both the NLRP3 inflammasome and NF-κB pathways. P2X7 polymorphism has been documented in the literature regarding cases of chronic nonbacterial osteomyelitis. The P2XR7 gene has not previously been associated with autoinflammatory diseases in the literature, although its role in the inflammasome pathway is well known. Our case represents the first report of this association and this unique case demonstrates the efficacy of anti-IL1 therapy in achieving clinical and laboratory remission.
Disclosure of Interest: None declared

Identifier: PO065

A PATIENT WITH VERY EARLY ONSET INFLAMMATORY BOWEL DISEASE (VEO-IBD), HEPATITIS, SPECIFIC ANTIBODY DEFICIENCY AND A VARIANT OF UNCERTAIN SIGNIFICANCE IN PIK3CD

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Introduction: Heterozygous gain-of-function variants in the *PIK3CD* gene, that encodes for p110δ catalytic subunit of Phosphoinositide 3-kinase δ, result in activated Phosphoinositide 3-kinase δ syndrome (APDS1). APDS1 is an inborn error of immunity (IEI) associated with a spectrum of clinical manifestations, including lymphoproliferation, hypogammaglobulinaemia, and inflammatory features such as VEO-IBD.
Objectives: We report a patient born to non-consanguineous parents who presented with VEO-IBD and subsequently developed recurrent pneumonia and liver inflammation. She has a variant of uncertain significance (VUS) in *PIK3CD*.
Methods: Retrospective case records of the patient were reviewed.
Results: A 21-year-old Malay female born to non-consanguineous parents first presented at age 4 with bronchopneumonia, along with a 1-year history of intermittent bloody diarrhoea and failure to thrive. Initial biochemistries revealed anaemia, lymphopaenia, raised transaminases, and extensive work-up for an infectious cause of diarrhoea was negative. The endoscopy showed active colitis but normal ileal mucosa, with histology of acute-on-chronic pancolitis with cryptal destruction, drop-out and distortion, and areas of surface ulceration. Dense mixed inflammatory infiltrate in the lamina propria and focal pericryptitis, cryptitis and crypt abscesses were seen, and no definite granulomas were appreciated. She was diagnosed with Crohn's disease but was non-adherent to sulfasalazine, resulting in multiple attendances for Crohn's flares throughout childhood and adolescence.

At age 9, she was diagnosed with autoimmune hepatitis. A percutaneous liver biopsy performed to evaluate persistently raised transaminases showed a moderate inflammatory infiltrate of lymphocytes and plasma cells consistent with interface hepatitis. ANA was elevated (1:800), but Anti-M2, LKM, SLA/AP, LC-1 and SMA were negative. She was treated with azathioprine.
She had numerous hospitalisations for pneumonia (including Pneumococcus and *Moraxella catarrhalis*) growing up, often unrelated to immunosuppression as she was non-adherent. She eventually developed bronchiectasis and restrictive lung disease. On flow cytometry, she had almost no B cells, and low percentage of total T cells, but normal percentage of CD4 and CD8 T cells. However, naive CD4 and CD8 cell percentages were low and central memory CD4 T cells and central/effector CD8 T cells were increased. PD1 as a marker of T cell activation was also increased on memory and Tfh cells. Lymphocyte proliferation with PHA/ConA/Anti-CD3 was normal. IgG, IgA, and IgM were in the normal range. She had a normal vaccination response to tetanus toxoid but an abnormal pneumococcal-antigen vaccination response indicative of specific antibody deficiency.

Genetic testing with a NGS panel (Fulgent) for Primary Immunodeficiency revealed a heterozygous VUS in NM_005026.4(PIK3CD):c.1367C>T (p.Thr456Met). This variant has been observed at a frequency of <0.01%, with no known homozygous control individuals. The physiochemical difference is considered to be of moderate change (Grantham's Distance 81). Amino acid conservation data in primates and mammals suggest that the mutation may be damaging. We were unable to perform functional testing or segregation testing of family members. She is now being treated with sirolimus, low-dose prednisolone and monthly IVIg replacement. This has helped to control her VEO-IBD and liver inflammation.

Conclusion: We describe a case of VEO-IBD, liver inflammation and specific antibody deficiency with an associated variant in *PIK3CD* of uncertain significance. She has no lymphoproliferative manifestations. The pathogenicity of this variant cannot yet be upgraded despite a clinically suggestive phenotype.
Disclosure of Interest: None declared

Identifier: PO066

TRNT1 RELATED AUTOINFLAMMATORY SYNDROME IN A PATIENT WITH PRIMARY CILIARY DYSKINESIA

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Introduction: TRNT1 mutation is associated to an autoinflammatory syndrome (SAID) presenting with a wide clinical heterogeneity. The clinical phenotypes ranged from severe infantile forms to milder forms diagnosed in adolescence as in our case reported.
Objectives: This case reported underlined how, although this SAID could be diagnosed also in adolescence, the recognition of this condition is essential to establish a right diagnostic and therapeutic approach.
Methods: Here we describe the case of a 19-year-old girl affected by Primary ciliary dyskinesia (PCD) referred at our Centre with a history of recurrent episodes of fever and arthralgias. Her past medical history started at the age of 2 days of life, when she underwent surgery repair for intestinal malrotation and jejunum atresia. At the age of 10, she was diagnosed with PCD due to chronic sinusitis, recurrent pneumonia and bronchiectasis, confirmed by genetic analysis. In the following years, she presented recurrent episodes of fever identified as respiratory exacerbations and some episode of arthralgia and arthritis, which showed a good response to short courses of corticosteroids. So, she was referred at our Centre at 19 years old. Her clinical examination was unremarkable, except for wheezing and mild facial dysmorphisms. No signs of arthritis were detected. The lung disease resulted moderately controlled. Laboratory investigations revealed a remarkable increase of the serum amyloid A (SAA 587 mg/l), few days after a febrile episode. An isolated splenomegaly was found at the abdomen ultrasound. A next generation sequencing panel for SAIDs was performed, showing the homozygous pathogenetic mutation c.1246A>G (p.Lys416Glu) in the TRNT1 gene. The immunological, ophthalmological, audiometric and cardiologic assessments resulted normal. After starting Etanercept at the weekly dose of 50 mg, the patient presented the resolution of fever and arthralgias episodes and reported an improvement in lung symptoms.
Results: The presence of recurrent fever associated with elevation of inflammatory indexes and joint symptoms, presenting a good response to corticosteroids, led to consider the diagnosis of an autoinflammatory syndrome. Currently, only about fifty cases of TRNT1 mutation-related autoinflammatory syndromes have been reported. This disorder was firstly associated to congenital sideroblastic anaemia with immunodeficiency, fevers, and developmental delay (SIFD) (1,2) but over the years a wide phenotypic heterogeneity was described. This heterogeneity was attributed to the different mutations found, observing that homozygous loss of function mutations was associated to a lethal phenotype while, on the other side, missense mutations could be associated to a reduced enzyme activity and to a milder phenotype (3). Of note, other 2 patients with TRNT1 related SAID are followed at our Centre (4) and they have been effectively and safely treated with Etanercept for more than 10 years.
Conclusion: The disease onset in our patient, which is also affected by PCD, occurred in adolescence, a later onset compared with literature**.** It was probably due to a milder phenotype and to the concomitant other disease so that some fever episodes in infancy were attributed to respiratory disease. Phenotypic heterogeneity is one of the leading features in this disorder. In this case, as in others described in literature, Etanercept was effective in controlling autoinflammatory episodes. This case shows that an early diagnosis would allow patients to promptly access to therapies.
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Disclosure of Interest: None declared

Identifier: PO067

NEMO-NDAS: CLINICAL DIVERSITY AND THERAPEUTIC CHALLENGES IN PEDIATRIC CASES

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Introduction: Nemo-NDAS is a rare syndrome, with fewer than 30 reported cases worldwide, recently classified as part of the systemic autoinflammatory diseases (SAIDs). It results from mutations in the NF-κB essential modulator (NEMO), encoded by the X-linked IKBKG gene. NEMO is a key component of the NF-κB inhibitor complex, leading to disruptions in both innate and adaptive immune responses, as well as pro-inflammatory pathways.
Objectives: We present three cases of Nemo-NDAS to highlight the diverse clinical manifestations and therapeutic challenges associated with the disease.
Methods: We report three French pediatric cases of Nemo-NDAS, each confirmed by genetic diagnosis identifying mutations in canonical IKBKG splice sites.
Results: Patients 1 and 2: Both girls, aged four and two years, presented with recurrent episodes of erythematous subcutaneous nodules involving the entire body since infancy, accompanied by systemic inflammation (maximum CRP : 129 mg/L for Patient 1 and 229 mg/L for Patient 2), fever, and severe failure to thrive. Initial skin biopsies revealed diffuse lobular panniculitis. Systemic corticosteroids initially improved their symptoms but led to corticosteroid dependence. Methotrexate was ineffective in Patient 1. After diagnosis, both patients received TNF inhibitors, which partially controlled inflammation. The addition of a JAK inhibitor (Baricitinib) allowed corticosteroid tapering but did not enable full discontinuation in Patient 1. The efficacy of Baricitinib in Patient 2 is currently being investigated.

Patient 3: A 17-year-old boy presented with a distinct clinical picture. His symptoms began at 1 month of age with recurrent fever and moderate inflammatory syndrome (CRP: 20-30 mg/L). Unlike the other patients, he did not experience panniculitis. Initially treated for undifferentiated recurrent fever syndrome (SURF) with on-demand corticosteroids, he later developed lymphocytic meningitis, which progressed to chronic pachymeningitis with persistent headaches. At age six, he experienced gastrointestinal necrosis of unclear origin, and by age seven, he developed severe panuveitis and retinal vasculitis, leading to a diagnosis of pseudo-Behçet's disease. Treatment with corticosteroids and anti-TNF agents controlled the ocular damage, but relapses of uveitis and meningitis occurred whenever corticosteroids were reduced. Despite this immunosuppressive therapy, the patient also developed recurrent arthritis. The combinations of anti-TNF agents with azathioprine and then methotrexate proved ineffective, necessitating regular corticosteroids to control fever and pain. Over time, he developed antibodies against infliximab and adalimumab. Dual therapy with a JAK inhibitor (Baricitinib) and another TNF inhibitor (Golimumab) was initiated in September 2024, showing promising results with clinical disease control. Since 2018, the patient is also noted to have karyotype-confirmed Klinefelter syndrome.

Conclusion: These cases underscore the diagnostic complexity of SAIDs in young patients due to their diverse clinical manifestations. They also highlight therapeutic challenges, particularly in young children, including corticosteroid dependency and immunization against anti-TNF agents.
Disclosure of Interest: None declared

Identifier: PO068

HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS DURING A RELAPSE OF A VEXAS SYNDROME

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Introduction: VEXAS syndrome is a rare adult onset autoinflammatory disease caused by a somatic mutation of the UBA1 gene on the X chromosome of haematopoietic progenitors. VEXAS is responsible for multi-system auto-inflammatory manifestations and cytopenia. Haemophagocytic lymphohistiocytosis (HLH) is rarely described in the literature as a complication of VEXAS syndrome. A few cases of Epstein-Barr virus (EBV)-HLH have been reported in the context of immunocompromised VEXAS patients.
Objectives: Case report
Methods: To report a patient with VEXAS syndrome who presenting with HLH during a relapse of the disease successfully treated with methyl prednisone and etoposide.
Results: A 69-year-old male patient without any medical history except prostate cancer was diagnosed one year ago as a VEXAS syndrome with a rare UBA1 mutation (p,Ser56Ph). He presented with inflammatory syndrome, fever, cutaneous (sweet syndrome) and muscle involvement (lower limb myalgia and trismus). His blow count including the mean corpuscular volume (MCV) was within the range.

He was successfully treated with glucocorticoids (GCs) but remain dependent of 20mg equivalent prednisone. He underwent a 2nd-line treatment with tocilizumab (anti IL-6 receptor) with no laboratory or clinical improvement and received a JKAk inhibitor, ruxolitinib as a 3trd-line treatment without improvement.

He was admitted in our department in November 2024 for a diagnostic procedure. He presented for 4 weeks, loss weight, reappearance of trismus and a futher drop in blood count (anaemia, thrombocytopenia). Laboratory findings revealed major hepatic cytolysis (20N), hyperferitinemia (ferritin 25 000µg/l). His haemoglobin level had fallen to 9g/L (*vs.* 12g/L usually), MCV was normal (95 fl) and his platelets have decreased 110G/L, leucocytes were within the range 5 G/L. The H-score (to evaluate the HLH hypothesis) was high 208 (probability of HLH between 88-93%). Bone marrow aspiration revealed typical haemophagocytic findings. Etiological work-up for HLH was negative including infectious disease. Medullary biopsy found no myelodysplastic syndrome nor lymphoproliferation. No solid neoplasm including prostatic cancer relapse was shown on the CT -scan. A pharmacovigilance study rules out any drug related to HLH.

After having ruled-out the classical causes of HLH and in the context of relapsing VEXAS, the diagnosis of HLH secondary to VEXAS syndrome was performed. A treatment with solumedrol and etoposide led to complete and rapid regression of HLH findings including rapid decrease of the hepatic cytolysis and normalization of the ferritin level within one week. A chemotherapy with azacytidine was then started and one month after the patient is well.

Conclusion: This case highlights VEXAS syndrome as a possible cause of HLH. Further observations are need to confirm HLH as a potential life-threatening complication of VEXAS syndrome.
Disclosure of Interest: None declared

Identifier: PO071

A RETROSPECTIVE ANALYSIS OF THREE PATIENTS WITH A VEXAS-LIKE SYNDROME LACKING DETECTABLE UBA1 MUTATIONS

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Introduction: VEXAS syndrome is an acquired autoinflammatory condition characterized by somatic mutations in the UBA1 gene. Affected patients present with a broad spectrum of systemic inflammatory manifestations, including macrocytic anemia, fever, chondritis, pneumonitis, and cutaneous eruptions. Although diagnostic scoring systems have been proposed to improve recognition, cases have been reported in which the clinical suspicion of VEXAS syndrome is high, yet no UBA1 mutations are detectable.

Objectives: This study aimed to elucidate the clinical features of patients who exhibited a VEXAS-like phenotype but did not harbor detectable UBA1 mutations in their peripheral blood.

Methods: A retrospective review of medical records at Osaka University Hospital was conducted for the period 2022–2024. Patients were included if they were clinically suspected of having VEXAS syndrome but did not have detectable UBA1 mutations. Data on laboratory findings, imaging results, therapeutic interventions, and clinical outcomes were collected and analyzed.

Results: Three patients met the inclusion criteria. The UBA1 gene mutation was analyzed at Yokohama City University Graduate School of Medicine. All showed evidence of myelodysplastic syndrome (MDS) and macrocytic anemia, accompanied by elevated inflammatory markers. Two patients demonstrated radiologically confirmed multifocal chondritis, and two presented with cutaneous lesions. Of these, one case was histologically diagnosed as histiocytoid Sweet's syndrome. All three patients received high-dose corticosteroid therapy. However, none could be successfully tapered to a stable dose below 10 mg/day. Two patients also received biologic agents—adalimumab and tocilizumab—without achieving sustained disease control or successfully reducing corticosteroid requirements to low doses.

Conclusion: Our findings confirm the existence of patients with a VEXAS-like clinical picture who lack detectable UBA1 mutations. Current treatment strategies, including high-dose corticosteroids and biologics, remain suboptimal in controlling inflammation and reducing steroid dependence in these populations. Further research is warranted to clarify the underlying pathogenesis, refine diagnostic criteria, and identify more effective treatment strategies for this challenging subset of patients.

Disclosure of Interest: None declared

Identifier: PO072

CHRONIC RECURRENT WHEALS AND APHTHOUS ULCERS ASSOCIATED WITH AN MEFV K695R MUTATION

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Introduction: Patients initially presenting with recurrent wheals are frequently diagnosed with chronic spontaneous urticaria and less frequently with urticarial vasculitis and autoinflammatory diseases. The latter ones include within others cryopyrinopathies, Still's disease, Schnitzler syndrome and more rarely pyrin-associated autoinflammatory diseases (PAAD) such as familial Mediterranean fever (FMF). Dermatological manifestations of FMF also include erysipelas-like skin lesions, diffuse palmoplantar erythema, erythema nodosum, Raynaud-like phenomena and purpuric exanthema.

Objectives: The aim of this case report is to highlight diagnostic challenges and therapeutic management of a patient with chronic recurrent wheals, aphthous ulcers, and laboratory signs of systemic inflammation.

Methods: The patient underwent a detailed medical history and physical examination at our center. Laboratory values were determined, including ANA titer, differential blood count, immunofixation, C-reactive protein (CRP), serum amyloid A (SAA) and S100A8/9. Lesional skin biopsy was taken for histological analysis. Molecular genetic examinations of the autoinflammatory periodic fever syndrome genes *ADA2, COPA, IL1RN, IL36RN, MEFV, MVK, NLRC4, NLRP3, NOD2, PLCG2, TMEM173* and *TNFRSF1A* were performed.

Results: A 66-year-old female of German origin presented in our outpatient clinic in 2021 with a decade-long history of chronic recurrent wheals (daily occurrence, single wheals lasting <24h, accompanied by pruritus) and recurrent aphthous ulcers. She reported rare episodes of joint stiffness. Apart from osteoporosis, no other comorbidities were reported. The patient's family history was negative for autoimmune or autoinflammatory diseases. Prior laboratory and histological findings where ambiguous and suggested chronic urticaria, urticarial vasculitis, undifferentiated connective tissue disease and subacute cutaneous lupus erythematosus as diagnoses and extensive prior treatments, including second generation H1-antihistamines in up to four fold-doses, intravenous methylprednisolone pulse therapy, several immunosuppressants (methotrexate, azathioprine, hydroxychloroquine, dapsone, cyclosporine and mycophenolate mofetil) and JAK-inhibitor baricitinib, showed no efficacy.

Laboratory findings revealed elevated CRP (67.4 mg/L, Ref. <0.5 mg/L), SAA (120 mg/l, Ref. <6.4 mg/l) and S100A8/9 (10.16 µg/mL, Ref. <1.75 mg/L) with leukocytosis and neutrophilia. Immunofixation was unremarkable. ANA titer was 1:320 (Ref. <1:160). Skin biopsies demonstrated dermal neutrophilic infiltration. Genetic testing revealed a heterozygous c.2084A>G variant in exon 10 of the *MEFV* gene (K695R mutation). Treatment with colchicine had to be discontinued due to gastrointestinal side effects. Subsequently, treatment with IL-1 receptor antagonist anakinra was initiated and resulted in complete control of chronic recurrent wheals and partial response of aphthous ulcers.

Conclusion: We identified a heterozygous K695R mutation in a patient with chronic recurrent wheals and aphthous ulcers. The K695R variant has previously been reported in patients with FMF-like clinical symptoms and patients with IgA vasculitis. The case underscores the importance of considering autoinflammatory syndromes and performing genetic testing timely in patients with chronic recurrent wheals and signs of systemic inflammation despite a negative family history.

Disclosure of Interest: L. S. Herzog Conflict with: LSH received travel grants from: CSL Behring, Celltrion Healthcare, K. Krause Conflict with: KK received research support and/or consultant/speaker fees from: Bayer, Beiersdorf, CSL Behring, Moxie, Novartis, Roche/CHUGAI, SOBI, Takeda., P. Kolkhir Conflict with: PK was a speaker/consultant and/or advisor for and/or has received research funding from BioCryst, Merus, Novartis, ValenzaBio and Roche outside of submitted work,

H. Bonnekoh Conflict with: HB received research support and/or consultant/speaker fees from: AbbVie, Biocryst, Celltrion, Granular, Novartis, Sanofi Aventis and ValenzaBio.

Identifier: PO073

CHALLENGING DIAGNOSTIC AND THERAPEUTIC JOURNEY IN VEXAS SYNDROME: A CASE REPORT

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Introduction: VEXAS syndrome, a recently recognized autoinflammatory disorder characterized by multi-organ involvement, is associated with the UBA1 gene mutation. It presents with symptoms such as fever, rash, cytopenias, and various inflammatory markers elevation. We report a case of a 30-year-old male programmer with a complex clinical course, highlighting the diagnostic and therapeutic challenges in managing this rare condition, particularly the pulmonary involvement and hematological aspects.

Objectives: This case report aims to delineate the clinical presentation, diagnostic evaluation, and treatment challenges of a patient with VEXAS syndrome, with a focus on the pivotal role of genetic testing in establishing the diagnosis and the necessity for a personalized management approach.

Methods: The patient presented with recurrent fever, conjunctivitis, polychondritis, and significant pulmonary infiltrates. The diagnostic evaluation encompassed comprehensive laboratory tests, imaging studies, bronchoscopy with alveolar lavage, and genetic testing. Treatment strategies included corticosteroids, immunosuppressants, and targeted therapies tailored to clinical manifestations and disease activity.

Results: The patient exhibited a steroid-dependent clinical trajectory, characterized by recurrent fever and extensive pulmonary infiltrates. Despite multimodal therapy with tacrolimus, ruxolitinib, and upadacitinib, disease exacerbations persisted. The patient's condition was further complicated by anemia, glucocorticoid-induced diabetes mellitus, and osteoporosis. Genetic analysis confirmed a UBA1 mutation, establishing the diagnosis of VEXAS syndrome. The patient responded to tocilizumab, an anti-IL-6 receptor humanized monoclonal antibody, administered at a dosage of 480mg intravenously every 3-4 weeks, equating to 8mg/kg based on the patient's weight. Post-initial administration, the patient's fever and auricular-nostril swelling resolved. Hemoglobin levels rose from 62g/L to 88g/L, erythrocyte sedimentation rate decreased from >140mm/h to 17mm/h, hypersensitive C-reactive protein levels dropped from 146.97mg/L to 1.78mg/L, and IL-6 levels fell from 209.53pg/ml to 9.6pg/ml. A subsequent chest CT scan demonstrated marked improvement in the previously noted diffuse bilateral ground-glass opacities. After three courses of treatment, the patient's hemoglobin continued to recover, with the most recent level at 98g/L, and the patient remained afebrile, symptom-free, and returned to normal work and life activities.

Conclusion: VEXAS syndrome, with its pronounced clinical heterogeneity, poses significant challenges in diagnosis due to a high rate of misdiagnosis. The syndrome's varied clinical manifestations often lead to diagnostic dilemmas, and treatment remains a quandary, with few effective ongoing therapeutic options beyond high-dose corticosteroids. This case illustrates the importance of a personalized treatment approach, which is crucial for addressing the multifaceted clinical features and complications inherent to VEXAS syndrome, especially the pulmonary and hematological manifestations. The shared inflammatory pathway is underscored by the concurrent improvement in both inflammatory and hematological parameters following tocilizumab therapy, emphasizing the importance of targeted treatment in this complex disease. The necessity for tailored therapies is further emphasized by the lack of a one-size-fits-all treatment strategy. Genetic testing is pivotal in the diagnostic workup of patients with unexplained inflammatory diseases, and ongoing research is imperative to develop more effective and sustainable treatment strategies that can be individualized to each patient's unique needs and response profile.

Acknowledgments: Special thanks are due to Dr. Tian Xinlun from the Respiratory Department, Dr. Mao Yueying from the Hematology Department, and Dr. Xu Tingting from the Pharmacy Department for their invaluable contributions.

Disclosure of Interest: None declared

Identifier: PO074

AN UNUSUAL CASE OF WRISTS AND ANKLES "BOGGY SYNOVITIS": AUTOINFLAMMATION LINKING AUTOIMMUNITY?

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Introduction: We describe a child presenting with a Blau-like phenotype (e.g. symmetric knee and elbow arthritis, boggy synovitis of wrists and ankles, annular skin lesion of forearm) lacking genetic confirmation in NOD2 but unveiling overlapping autoimmune features

Objectives: To increase awareness of an undefined autoinflammatory disease by describing the clinical course, response to treatments and potential putative genotype in patient with unsolved “boggy synovitis”

Methods: Complete blood count, lymphocyte subpopulations, serum Ig, IgG subclasses and response to vaccines were assessed. Underlying autoimmune vasculitis was explored by evaluating inflammatory markers, serum protein electrophoresis, ANA, ENA profiles, C3/C4, Coombs test, urine analysis as well as nail capillaroscopy. Blau’s syndrome was investigated both clinically (ACE levels, joint and eye exam) and by genetic test (in silico WES), and identified variants were confirmed by Sanger sequencing. The isolated cutaneous lesion was investigated by skin biopsy to rule out granuloma and/or lupus specific stain (i.e. mucins). Boggy synovitis was investigated by MRI. Multiorgan involvement was assessed by RFTs, thorax X-ray, abdomen/lymph nodes US, echocardiogram and Whole body MRI

Results: A Caucasian 9.8 years old girl with unremarkable family and personal history started to experience asymptomatic swelling of ankles without any constitutional symptoms. She later suffered of painful boggy swelling of ankles and wrists, worsening with use and not featured by morning stiffness. At the same time, appearance of an annular shape, not macroscopically inflamed skin lesion, resembling scleroderma-like features, was observed on right forearm. After a few months, symmetric knee, elbow and wrist pain occurred without limping nor limitation in daily activity. Blau syndrome was suspected. Laboratory tests were unremarkable except for mild CRP elevation associated with hypergammaglobulinemia, ANA positivity (1/160, granular pattern) and persistent ACE elevation. Chitotriosidase levels were withing normal range. Slight persistent positivity of dsDNA was not confirmed by WB ENA profiling. Neither cytopenia or C3/C4 decrease, nor Coombs test positivity were observed. Joint US unveiled mild synovial effusion only in elbows and knees in absence of doppler signal. Boggy synovitis in wrists and ankles was featured by tenovaginitis without arthritis. Ocular involvement was absent at onset and follow-up visits. Skin biopsy excluded cutaneous lupus and addressed morphea like-features without granuloma. Multiorgan involvement was excluded. Knee synovial fluid was enriched with mononuclear cells, mostly (96%) lymphocytes. While waiting for genetic tests, provisional diagnosis of JIA and morphea were formulated, intraarticular steroid treatment of affected joints was performed, and therapy with methotrexate was attempted. The latter had partial benefit, with clinical amelioration but persistent US signs of inflammatory activity of ankle synovitis and only transient reduction of wrists synovitis. First-line systemic treatment failed to induce arthritis remission with persistent subclinical disease activity at 6 month follow-up visit. Whole body MRI was repeated without signs of disease progression while target wrist MRI confirmed diffuse tenosynovitis. Surprisingly, in silico WES was negative for NOD2 variants but identified unforeseen VUS in POMP gene (c.358+3_358+6del)

Conclusion: The peculiar clinical picture may be consistent with an overlap syndrome in which autoimmunity and autoinflammation co-exist. Given the inconclusive genetic NOD testing, wrist synovial biopsy has been planned in order to better characterize the peculiar articular involvement before step up therapy with potentially confounding strategy

Disclosure of Interest: None declared

Identifier: PO075

CASE REPORT: IDENTIFICATION OF POST-ZYGOTIC MOSAICISM WITH A PATHOGENIC TNFRSF1A VARIANT IN A PATIENT WITH ELEVATED INFLAMMATORY MARKERS

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Introduction: TNF receptor-associated periodic syndrome (TRAPS) is an autosomal dominant disorder caused by gain-of-function variants in the *TNFRSF1A* gene, which encodes TNF receptor type I (TNFR1). It is characterized by episodic fever with severe abdominal pain, arthralgia, myalgia, rash, chest pain, and conjunctivitis. Laboratory findings during flares typically include elevated Erythrocyte Sedimentation Rate (ESR), and C-reactive protein (CRP), leukocytosis, and thrombocytosis, indicating systemic inflammation. The use of next-generation sequencing (NGS) has highlighted the role of post-zygotic mosaicism in systemic autoinflammatory diseases, adding complexity to the understanding of monogenic disorders. The first TRAPS case involving post-zygotic mosaicism, due to a novel 24-nucleotide deletion, was described in 2015, with only three additional cases reported since.
Objectives: We present the case of a 56-year-old female patient with recurrently elevated CRP levels (10–100 mg/L), elevated ESR and serum amyloid A (333 mg/L) for several years. Extensive evaluations, including cardiological, rheumatological, hematological, and infectious workups, revealed no significant findings. Additionally, a whole-body PET-CT scan and autoantibody diagnostics yielded no notable results.
Methods: For further clarification, a panel of 24 genes associated with autoinflammatory diseases was analyzed using NGS. Coding exons and conserved splice regions were enriched via hybridization (Twist Bioscience) and sequenced on the NovaSeqX platform (Illumina) with a minimum coverage of 500x. Data analysis was performed using the Illumina® DRAGEN Bio-IT Platform, followed by analysis with Varseq® (GoldenHelix). The identified variant was subsequently confirmed through targeted amplicon sequencing with a coverage depth of 7000x.
Results: The variant NM_001065.3:c.236C>T p.(Thr79Met) was identified in the *TNFRSF1A* gene, with a variant allele fraction of 23% (NGS panel) and 20% (targeted amplicon) in the patient's DNA extracted from whole blood. Based on current variant classification guidelines, it was determined to be pathogenic for TRAPS. This variant is one of the first identified germline variants in TRAPS and is among the most common *TNFRSF1A* variants. The substitution disrupts a non-covalent hydrogen bond within the cysteine-rich domain 1 (CRD1). Functional studies indicate that this alteration leads to improper protein folding, increased cytoplasmic accumulation of the TNFR1 receptor, and reduced TNF binding efficiency.
Conclusion: We report the fifth documented case of a patient with post-zygotic mosaicism for a pathogenic variant (VAF 20-23%). The Thr79Met variant is located at the end of the CRD1 domain of the receptor, in proximity to other variants previously described, supporting the hypothesis of a hotspot region for mosaic variants. Notably, this patient shows no evidence of typical clinically overt TRAPS, and abdominal fat aspiration revealed no signs of amyloidosis. In contrast, all previously reported patients with VAFs ranging from 1.3% to 30% in whole blood experienced recurrent fever episodes, erythematous rashes, plus various additional symptoms, and responded well to treatment with Anakinra or Canakinumab. These findings suggest that the phenotypic severity of TRAPS in patients with post-zygotic mosaicism is not directly correlated with the specific TNFRSF1A variant or VAF. Further, as yet unidentified factors, appear to influence the onset and severity of the inflammatory phenotype.
Disclosure of Interest: None declared

Identifier: PO076

AN UNUSUAL KIDNEY PRESENTATION IN GENETICALLY-CONFIRMED FAMILIAL MEDITERRANEAN FEVER

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Introduction: Amyloid-related damage represents the typical kidney presentation in autoinflammatory diseases (AID). However, IgA nephropathy (IgAN) is anecdotally reported
Objectives: To increase awareness on unusual kidney involvement in a patient with genetically-confirmed FMF
Methods: NGS panel covering TNFRFS1A, MEFV, MVK and NLPR3 was firstly employed and variants confirmed by Sanger. WGS was used to rule out other variants
Results: A 6-years-old girl, born to non-consanguineous Albanian parents, was admitted with swelling of the right ankle and foot without (w/o) a clear trauma history. Family and perinatal history was unremarkable. Neurodevelopmental genetic disease had been suspected as MBD5 haploinsufficiency. Interestingly, CGH-Array unveiled the presence of duplicated CHRFAM7A which has no clear pathological significance but it has been implicated in IL1-mediated inflammatory responses. Fifteen months earlier the child had been admitted for severe abdominal pain and myalgias associated with inflammatory indices increase despite absence of fever or signs of joint/skin involvement, serositis or hyperferritinemia. Procalcitonin was steadily negative consistent with unremarkable microbial cultures. Hypergammaglobulinemia and isolated transient c-ANCA slight positivity were observed, w/o signs of vasculitis (brain angio-MRI, thorax-abdomen angio-CT). Given the discrepancy between elevated ERS and negative infectious and inflammatory foci, malignancies were investigated and ruled out. Whole body MRI failed to report bone and other organ localization. Upper and lower gastroenterological endoscopy (including video capsule) plus biopsies were carried out with no pathological findings. Wide-spectrum antibiotic treatments and 6 months clinical surveillance were completed, with disappearance of clinical signs and inflammatory markers. Nine months later, the child was admitted again for suspected right ankle and foot cellulitis, after traveling to Albania. Antibiotics were started with initial improvement. However, during hospitalization fever spikes and abdominal pain occurred along with migrating, spontaneously resolving soft tissue swellings and arthromyalgias. Unfortunately, concomitant worsening of the behavioral disorder hampered clinical assessment. Increase of neutrophils, platelets, ESR and CRP was observed w/o evidence of current infection or malignancy. Autoimmune profiling was unremarkable. Underlying ADA2 deficiency and interferonopathy were ruled out by ADA2 activity and IFN signature, respectively. Joint and abdomen US surveillance was carried out and found isolated transient thickening of intestine walls. Cardiac and neurological involvement was excluded. While waiting for ongoing tests, intravenous (i.v.) immunoglobulins (2 gr/Kg) were started with partial clinical benefit. Meanwhile, progressive proteinuria, macrohematuria and transient bloody diarrhea appeared. Given the worsening proteinuria, kidney biopsy was performed, unveiling underlying IgAN. Methylprednisolone pulses were immediately started, followed by oral prednisone with immediate response. However, symptoms, inflammatory markers and proteinuria were partially controlled during steroid tapering. In light of the unexplained previous episode, evocative for autoinflammation, and the anectodical report of IgAN in AID, TRAPS syndrome was suspected and investigated. Surprisingly, homozygous c.2040G>C (p.Met680Ile) (M694I) MEFV mutation was unveiled in the child with asymptomatic parents being heterozygous for M694I. WGS confirmed the absence of other variants
Conclusion: This unusual presentation of M694I/M694I variant with IgAN as manifestation at onset rather than late damage outcome should raise awareness. Whether or not CHRFAM7A duplication may have played a role is unclear
Disclosure of Interest: None declared

Identifier: PO077

EVALUATION OF A DOMINANTLY INHERITED MEFV VARIANT IN A FAMILY WITH FMF-LIKE PHENOTYPE

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Introduction: Familial Mediterranean fever (FMF) is a systemic autoinflammatory disease resulting from recessively inherited mutations in the *MEFV* gene, presenting typically with recurrent fever, serositis, and erythema. There are also reports of dominantly inherited *MEFV* pathogenic variants linked to distinct inflammatory phenotypes. Given this complex inheritance pattern and *MEFV* tolerance to gene variants (Z score = -1.61), identifying novel or ultra-rare missense variants in this gene requires functional validation.
Objectives: To describe clinical, genetic, and functional findings for an undiagnosed family with four affected members presenting with an FMF-like disease presentation.
Methods: A detailed clinical history was collected from the family. Targeted Sanger sequencing of *MEFV* was completed on the proband, sibling, mother, and maternal grandfather. Exome sequencing (ES) was completed on the maternal grandfather and mother. REVEL, CADD, and AlphaMissense scores were collected by Ensembl VEP. U-937 cells were retrovirally transfected with *MEFV* overexpression constructs generated by site-directed mutagenesis. IL-1β and pyrin were quantified by ELISA and western blot.
Results: A three-generation family was referred to our center for genetic testing. The proband is a 27-year-old male with a history of recurrent fevers, erythema, neurogenic bladder, developmental delay, and hypersensitivity to insect bites and vaccinations. Currently, he is managed with colchicine 2-3 times a day; however, breakthrough flares continue to occur. His affected mother has a history of recurrent fevers, febrile seizures, hypersensitivity to insect bites, oral ulcers, and abdominal pain during flares. She is currently taking canakinumab following breakthrough flares on colchicine. His sister and grandfather reported similar symptoms, typically flaring under stress, and are both successfully managed under colchicine.

Targeted genetic sequencing for *MEFV* revealed an ultra-rare (AF < 0.000001) heterozygous p. Thr767Arg variant (CADD 10.97; REVEL 0.236) in the proband, sibling, and mother, but not in the affected maternal grandfather. We performed ES for the mother and grandfather, which did not yield pathogenic variants in other autoinflammatory-related genes. The functional study using U-937 cells retrovirally transfected with the mutant *MEFV* Thr767Arg construct showed elevated IL-1β levels when stimulated with PMA and LPS. This aligns with the observation that they respond positively to colchicine and canakinumab.

Conclusion: The current functional data support our hypothesis that the p.Thr767Arg variant is contributory to the FMF-like phenotype. However, further functional studies utilizing primary samples are critical in determining the molecular pathogenesis of the phenotypes observed in this family. Given that the maternal grandfather was found to be negative for the p.Thr767Arg variant, despite the positive response to colchicine treatment, suggests involvement of the pyrin inflammasome-mediated pathway, which will need to be elucidated to provide a diagnosis for this family.
Disclosure of Interest: None declared

Identifier: PO078

FATAL RHEUMATOID VASCULITIS ASSOCIATED WITH ANTIPHOSPHOLIPID ANTIBODY POSITIVITY LEADING TO CRITICAL LIMB ISCHEMIA

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Introduction: Rheumatoid vasculitis can affect small to medium-sized vessels of any organ system, thus is extremely heterogeneous in clinical presentation. It has a vast array of clinical manifestations with a predilection for the skin (peripheral gangrene, deep cutaneous ulcers) and the peripheral nervous system (mononeuritis multiplex)(1). Less frequently vasculitis affects the central nervous system, the eyes, the heart, the lungs, the kidneys, and the gastrointestinal system(2). This case report discusses a patient who developed critical limb ischemia requiring amputation due to multiple arterial involvement and thrombus formation.
Objectives: To report a rare case of a rheumatoid arthritis (RA) patient with stable disease activity who suddenly developed rheumatoid vasculitis (RV) leading to critical limb ischemia and ultimately death.
Methods: Case report.
Results: A 75-year-old female presented with numbness in both hands and feet, along with bilateral leg pain. She had been diagnosed with RA 30 years ago, with a recurrence of symptoms 6 years prior to admission, treated with methotrexate and leflunomide, and had a DAS28 ESR of 1.36 indicating remission several months prior. However, one month before admission, she experienced a worsening of arthritis, leading to increased steroid therapy. Two weeks prior to admission, she developed numbness and pain in both legs and hands. Physical examination revealed left ankle arthritis and livedo racemosa in the knee and elbow regions. On the second day of hospitalization, cyanosis progressed to the tips of both fingers and the great toes. In the following 1-2 days, ischemia progressed to mid-phalanx in five of her fingers, and the right leg developed ischemia below the knee while the left leg below the ankle, leading to the onset of rhabdomyolysis (HOD 3, CK 13,079 IU/L). Laboratory results showed Anti-CCP antibodies at 258 U/mL and Anti-cardiolipin IgM at 82.2 MPL U/mL, while other autoantibodies, including anti-nuclear antibodies, MPO, and PR-3, were negative. Nerve conduction velocity indicated multiple mononeuropathy, echocardiography showed minimal pericardial effusion, and p-angiography demonstrated total occlusion of the right deep superficial femoral artery. Mechanical thrombectomy was performed, revealing severe stenosis with slightly resolved flow. A biopsy could not be performed due to anticoagulation, but the patient met Scott and Bacon's 1984 diagnostic criteria for rheumatoid vasculitis, demonstrating mononeuritis multiplex and active extra-articular disease (pericarditis), leading to a diagnosis of rheumatoid vasculitis and R/O catastrophic anti-phospholipid antibody syndrome. Subsequently, the patient was treated with methylprednisolone 1g/day for three days, followed by 500 mg of cyclophosphamide and high-dose steroids, along with plasma exchange. Anti-cardiolipin IgM became negative, and although limb ischemia persisted, its extent did not worsen, indicating a partial treatment effect. The patient stabilized overall, and amputation was planned. However, on the 8th day of hospitalization, she suddenly developed a 22 cm massive retroperitoneal hematoma in the left psoas muscle, along with ischemia in the small and large bowel, liver, and spleen, leading to liver failure and death.
Conclusion: This case highlights an uncommon presentation in a rheumatoid arthritis patient, detailing the course and treatment of rheumatoid vasculitis, and prompting discussion on the potential for other underlying conditions.

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Disclosure of Interest: None declared

Identifier: PO079

EFFICACY OF HIGH DOSES INTRAVENOUS ANAKINRA IN TWO PAEDIATRIC CASES OF TAFRO SYNDROME

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Introduction: TAFRO syndrome, characterized by thrombocytopenia, anasarca, fever, reticulin fibrosis, renal insufficiency, and organomegaly, is a rare and potentially life-threatening inflammatory condition. It can complicate infectious diseases, neoplasms, connective tissue disorders, and, classically, idiopathic multicentric Castleman disease (iMCD). While interleukin-6 (IL-6) inhibitors have been the primary treatment for many cases, refractory cases necessitating alternative therapies have been reported

Objectives: To present two paediatric cases of TAFRO syndrome treated with anakinra and to perform a literature review of paediatric TAFRO cases.

Methods: Patients' medical records were reviewed. The concentration of inflammatory cytokines of the two patients was measured in plasma of patients.

Results: We present two patients with life-threatening clinical condition consistent with TAFRO syndrome with acute onset and aggressive progression, successfully treated with the interleukin-1 (IL-1) receptor inhibitor anakinra. Both patients exhibited persistent fever and multiorgan involvement. Anakinra was initiated, associated with ongoing corticosteroid treatment, resulting in significant clinical improvement and sustained remission.

In both cases, lymph node biopsies were performed, which were compatible with multicentric Castleman disease. In the second case, positivity for anti-SSA antibodies and lymphocytic infiltration were found in the minor salivary gland biopsy, although without typical symptoms or positivity for the diagnostic criteria for Sjögren's syndrome.

The literature review confirmed the rarity of TAFRO syndrome in the paediatric population; IL-6 inhibitors, considered the treatment of choice in this condition, appear to be fully effective in approximately half of the patients.

Conclusion: TAFRO syndrome is an inflammatory condition which may present in overlap or complicate rheumatologic diseases. Our report suggests the potential efficacy of anakinra in paediatric TAFRO syndrome, particularly in patients refractory to corticosteroids. Anakinra's ease of administration and favourable safety profile make it a suitable option, especially in emergency situations and/or in patients with severe liver dysfunction. Further studies are needed to establish if IL-1-blockade should be preferred to IL-6 inhibitors for the treatment of TAFRO syndrome, particularly in paediatric populations.

Acknowledgments: Not applicable.

Disclosure of Interest: S. Palmeri: None declared, J. Ferro: None declared, V. Natoli: None declared, C. Matucci-Cerinic: None declared, R. Papa Conflict with: Speaker fee from SOBI, S. Rosina: None declared, S. Sorrentino: None declared, S. Volpi Conflict with: Speaker fee from SOBI., V. G. Vellone: None declared, M. Gattorno Consultant for: from Boheringer, Fresinius-Kabi, Kiniksa, Novartis and SOBI., Conflict with: Speaking fee from Boheringer, Fresinius-Kabi, Kiniksa, Novartis and SOBI., R. Caorsi Consultant for: from SOBI., Conflict with: Speaker fee from SOBI.

Identifier: PO080

A RARE CONDITION THAT CAN BE MISTAKEN FOR VASCULITIS: PROLIDASE ENZYME DEFICIENCY

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Introduction: Prolidase enzyme deficiency is an autosomal recessive disorder characterized by chronic, painful, treatment-resistant skin lesions on the lower extremities, telangiectasias on the hands and face, recurrent infections, dysmorphic facial features, intellectual disability, organomegaly, and cytopenias. This case report presents two siblings diagnosed with prolidase enzyme deficiency.
Objectives: The objective of this case report is to present two cases of prolidase enzyme deficiency in siblings to illustrate the clinical presentation, diagnostic challenges, and the importance of considering this rare condition that can be mistaken for vasculitis.
Methods: This case report details the clinical course, physical examination findings, laboratory results, and imaging results of two siblings: a 42-year-old male and a 40-year-old female. Both were diagnosed with prolidase enzyme deficiency at age 14. Diagnostic investigations included physical examination, laboratory analysis of blood, radiographic imaging, and tissue cultures.
Results: *CASE 1:* A 42-year-old male was admitted to our clinic with ulcerative lesions on both feet and ankles (Figure 1). He had been diagnosed with prolidase enzyme deficiency at age 14, following the onset of painful ulcers on his feet, ankles, and legs, which gradually deepened and expanded. Upon admission, the patient's vital signs were stable. Laboratory results revealed anemia and thrombocytopenia, with negative autoantibodies. Physical examination revealed a dysmorphic appearance similar to that of his sister and aunt, including crowded, small teeth, hypertelorism, a prominent nasal arch, a cleft hard palate, and hyperkeratotic, hyperpigmented areas on the patella (Figure 2). Angiographic tomography, performed with a preliminary diagnosis of vasculitis, showed no evidence of vascular stenosis or aneurysms. Given findings of chronic osteomyelitis on lower extremity MRI and Pseudomonas aeruginosa growth in tissue cultures, antibiotic treatment was initiated.

CASE 2: A 40-year-old female, with clinical features similar to those of Case 1, was diagnosed with prolidase enzyme deficiency at age 14. Unlike Case 1, her lower extremity lesions led to joint deformities (Figure 1). She presented with foul-smelling, purulent lesions on the dorsum of both feet. Based on MRI findings suggesting chronic osteomyelitis in the lower extremities and the growth of Pseudomonas aeruginosa in tissue cultures, the patient was started on a prolonged course of antibiotics.

Conclusion: Prolidase enzyme plays a critical role in the cell cycle, inflammation, angiogenesis, and carcinogenesis. Deficiency of this enzyme is closely associated with dermatologic lesions, dysmorphic facial features, cytopenias, and recurrent infections. Diagnosis is confirmed through the detection of low prolidase enzyme levels in erythrocytes, leukocytes, or fibroblasts, or by measuring elevated proline levels in urine. Treatment options include proline-containing oral supplements, ascorbic acid, and hyperbaric oxygen therapy to promote wound healing. Additionally, apheresis, bone marrow transplantation, and enzyme replacement therapy may be considered in management. This case report underscores the need to consider prolidase enzyme deficiency in patients with the aforementioned constellation of symptoms to ensure proper diagnosis and management.
Disclosure of Interest: None declared

Identifier: PO081

A RARE PRESENTATION OF OPTIC DISC EDEMA DIAGNOSIS OF CRYOPYRIN-ASSOCIATED PERIODIC SYNDROMES (CAPS): A CASE REPORT

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Introduction: Cryopyrin-Associated Periodic Syndromes (CAPS) are a group of hereditary and rare autoinflammatory diseases associated with mutations in the NLRP3 gene. CAPS comprises three subtypes: Familial Cold Autoinflammatory Syndrome type (FCAS), Muckle-Wells Syndrome (MWS), and Chronic Infantile Neurological Cutaneous and Articular (CINCA) / Neonatal-Onset Multisystem Inflammatory Disease (NOMID). The NLRP3 gene encodes the cryopyrin protein, which plays a key role in inflammation. Mutations in this gene lead to increased IL-1 production, resulting in an inappropriate inflammatory response characterized by periodic episodes of skin rash, fever, and joint pain.
Objectives: In this case report, we present a patient who was previously evaluated for arthralgia and rash and later diagnosed with CAPS after the detection of optic disc edema
Methods: case report
Results: A 12-year-old male patient presented to our clinic with complaints of prolonged urticarial rashes and joint pain. He is the third child of a healthy mother, and his father has been diagnosed with sarcoidosis. There was no history of consanguinity in his family. His medical history revealed urticarial rashes since the neonatal period and migratory arthralgia starting two years ago, which resolved with non-steroidal anti-inflammatory drugs (NSAIDs). His symptoms were accompanied by hot- or cold-induced rashes, that spreads across the entire body, but his urticarial episodes were not associated with fever.

Physical examinations revealed growth and developmental delay, maculopapular rashes on face, arms and torso, and bilateral preorbital edema and hyperemia. Ophthalmologic examination identified bilateral optic disc edema. Given the recurrent urticarial episodes, arthralgia, and optic disc edema.

Laboratory investigations showed elevated inflammatory markers (C-reactive protein:19mg/mL, erythrocyte sedimentation rate:59 mm/hr, serum amyloid A: 1080 mg/L). Genetic testing for periodic fever syndromes were performed.

To evaluate the optic disc edema, cranial imaging and lumbar puncture were conducted. Cranial magnetic resolution imaging (MRI) and cranial magnetic resolution angiography were normal. However, lumber puncture revealed elevated cerebrospinal fluid (CSF) pressure (52cmH20).

A skin biopsy was performed to investigate the prolonged urticarial rashes. Histopathological findings revealed superficial perivascular dermatitis with neutrophilic and eosinophilic infiltration Corticosteroid therapy was started, resulting in resolution of the rashes and gradual improvement in optic disc edema.

Despite corticosteroid treatment, follow-up ophthalmologic evaluation one month later revealed worsening optic disc edema and new bilateral vitritis. Anakinra, an IL-1 receptor antagonist, was added to the treatment regimen. Subsequent ophthalmologic assessments showed significant improvement in optic disc edema following the initiation of anakinra.

Genetic testing confirmed a heterozygous mutation in the ***NLRP3*** gene (NM_004895.5: c.1049C>T), which established the definitive diagnosis of CAPS. The patient is currently under follow-up with continued anakinra therapy.

Conclusion: CAPS is characterized by underdiagnosis and underreporting due to its rarity. This leads to an unknown incidence and delays in diagnosis, as it is often overlooked in the differential diagnosis of suspected cases. The prognosis of CAPS, an autoinflammatory disease, depends on the severity of the phenotype and the initiation of effective

treatment at an early stage. Early and aggressive treatment is crucial to improving quality of life and preventing organ damage. With this case report, we aim to highlight the characteristic clinical presentation of Cryopyrin-Associated Periodic Syndromes and increase awareness for timely diagnosis of this rare condition.

Acknowledgments: none

Disclosure of Interest: None declared

Identifier: PO082

RECURRENT MAS-HLH IN A 68-YEAR-OLD WOMAN WITH ADULT-ONSET STILL'S DISEASE AND STXBP2 MUTATION

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Introduction: A 68-year-old female with a history of hypertension, dyslipidemia and provoked PE was diagnosed with AOSD in June 2023, presenting with a fever, rash, arthritis and hepatitis. She was treated with prednisone 40 mg, leading to clinical and laboratory response, Shortly after, following tapering of prednisone she was admitted with fever, chills, and a productive cough, testing positive for COVID-19.

Objectives: .

Methods: During hospitalization, she developed HLH/MAS (macrophage activation syndrome) with high ferritin (45,000 ng/ml), low fibrinogen (61 mg/dL), elevated triglycerides, and cytopenias. She was treated with Remdesivir, Dexamethasone, Solu-Medrol, Tocilizumab, and cryoprecipitate, yet she experienced multiple relapses, with fluctuating ferritin levels and abdominal pain attributed to HLH/MAS. Hematologic neoplasms, solid malignancies and other HLH-related infectious diseases were excluded, and S.C. Anakinra 200 mg/day was initiated along with 60 mg prednisone daily. Genetic testing revealed a heterozygous splice-site variant in the STXBP2 gene, which affects cytolytic granule release. A degranulation assay confirmed a deficiency in CD107a expression (2%, compared to a normal control of 38.5%). she continues to be treated by anakinra 100mg o.d. and is in continuous remission.

Results: Learning points for clinical practice

Familial HLH is caused by genetic defects affecting cytotoxic T-cells (CTL) and NK cells, primarily involving mutations in genes such as PRF1, UNC13D, STX11, and STXBP2, and present usually in early life. These genetic defects impair the exocytosis of cytotoxic granules, crucial for apoptosis in target cells, leading to uncontrolled T cell-mediated immune responses. Interestingly, a previous report indicated a prevalence 14% of germline genetic mutations associated with familial HLH in adult-onset HLH cases. It has been suggested that pts with hypomorphic mutations may not develop HLH until later in life, often triggered by viral infections or environmental stresses.

Conclusion: This case highlights the necessity of a comprehensive approach in managing complex cases of MAS-HLH. Genetic and functional testing should be considered in adult patients with atypical presentations or poor response to conventional therapies, as these tests can uncover underlying genetic predispositions that may guide more targeted and effective treatment strategies. High-dose Anakinra has shown promise in treating refractory HLH, but further studies are needed to establish optimal dosing guidelines.

Disclosure of Interest: None declared

Identifier: PO083

AN ATYPICAL PRESENTATION OF ANTISYNTHETASE SYNDROME

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Introduction: Antisynthetase syndrome (ASS) is an idiopathic inflammatory myopathy characterised by the presence of anti-aminoacyl-tRNA synthetase autoantibodies, combined with various phenotypic associations, which may include myositis, arthritis and interstitial lung disease.[1] We describe an atypical presentation of ASS in a 7-year old girl.
Objectives: It is hoped a description of this case will highlight possible atypical disease characteristics of ASS and foster shared learning.
Methods: A chronology of the clinical presentation and key details of the case is described. This was correlated with a literature review to identify atypical characteristics of the case.
Results: A 7-year old female was referred following a ten-month history of intermittent lower limb myalgia. Initial investigations had revealed elevated muscle enzymes and an MRI of her thighs revealed muscle oedema, in keeping with myositis. She had raised anti-PL12 myositis antibodies, and was negative for other autoantibodies.

At the point of our assessment, her symptoms had resolved and her examination was unremarkable. A repeat MRI scan of her thighs was normal. Repeat myositis antibodies showed persistent anti-PL12 positivity, and serum amyloid A levels were also elevated (346 mg/L).

Her past medical history revealed a diagnosis of idiopathic bronchiectasis diagnosed at 1-year of age. She retained an acceptable pulmonary function test. However, interval CT imaging revealed progressive interstitial lung disease.

The constellation of myositis with positive myositis antibody, interstitial lung disease and raised serum amyloid A raised the suspicion of an underlying inflammatory process. Subsequent genetic testing revealed a genetic variant of unknown significance in the TNFAIP3 gene.

She was discussed at a national panel and a diagnosis of atypical ASS was made.

This case highlighted a number of curious aspects, which were felt noteworthy:

- The young age of presentation of ASS in this case is unusual, as disease onset typically occurs in older children.[2]
- The interstitial lung disease preceded the onset of myositis by some years; an underlying autoimmune process was not initially identified.
- The presence of extra-muscular manifestations in this case were limited to interstitial lung disease. Whilst not a requisite for diagnosis, the involvement of other signs (including cutaneous disease and inflammatory arthritis) in ASS are relatively common,[3] though the data on isolated extra-muscular disease is limited.

Conclusion: The features of this case may represent a *forme fruste* of ASS, or may highlight the broad spectrum of a generally under-researched area. Further, the rare and heterogeneous nature of juvenile myositis makes classification even more challenging.[4]

The following learning points are therefore proposed:

1. Highlighting such cases such may help other clinicians in the recognition of possible atypical manifestations of musculoskeletal disease.
2. Repeating interval investigations or widening differential diagnoses and seeking advice from other clinical teams, particularly with the persistence or progression of symptoms, may be useful.

3. Underpinning this, more data into the phenotype and underlying autoimmune profiles of patients presenting idiopathic inflammatory myopathies is needed.

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Disclosure of Interest: None declared

Identifier: PO084

CASE REPORT OF A FEMALE PATIENT WITH OVER 25 YEARS OF RECURRENT FEVER - STILL MORE QUESTIONS THAN ANSWERS

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Introduction: So far, no diagnostic standards have been developed for adults with suspected autoinflammatory disease. It is not clear what the scope of testing should be to determine that a monogenic defect has been excluded. Currently, in centers providing care for adults, the percentage of patients diagnosed with an unclassified form of autoinflammatory disease may reach 40%.

Objectives: To present a broad approach to diagnose a complex form of autoinflammatory syndrome in an adult female patient

Methods: We analysed medical history, diagnostic and treatment attempts over 25 years.

Results: A 29-year-old woman was referred with suspicion of autoinflammatory syndrome. Since she was 6 mo. old, she had recurrent fevers (14-21 days, 39-40 C, every 2 month). Since she was 5 yo. she had recurrent skin lesions like erythema nodosum and since she was 19 -psoriatic like. Sustained elevated ESR, CRP, SAA was reported, which suggested a chronic inflammatory response. At the age of 12 the abdominal pain (colitis suspected in endoscopy) and transient oligoarticular arthritis (knees, ankles and wrists) had appeared. In adolescence growth delay was observed. Her family history of chronic diseases was unremarkable. Initially JIA was diagnosed. Therapy included: methylprednisolone pulse and chronic oral corticosteroids, sulfasalazine, methotrexate, cyclophosphamide, azathioprine, IVIG, cyclosporine A, secukinumab. All were ineffective. Partial response was achieved with anti-TNF treatment (infliximab, adalimumab) however neutropenia was observed. Histopathology of skin biopsy revealed slightly thickened epidermis with focal parakeratosis in the stratum corneum. In the papillary layers, there are dilated, thin-walled blood vessels surrounded by few inflammatory cells. No signs of vasculitis. The image has no specific features

Immunologic evaluation revealed: IgG 936 mg/dl (ref. 700-1600), low IgG4 0.5 mg/dl (ref. 3.0-201), high IgA 794 mg/dl (ref. 70-400), low IgM 24 mg/dl (ref. 40-230). Several populations of immune cells were monitored to evaluate the immunological status, however the main feature was lymphopenia (cells/uL): T CD3+: 692, CD4+: 278, CD8+: 322, NK: 108, B CD19+: 144 (cells/uL), whereas proportion of cells, including Treg, were mainly preserved.

Whole exome sequencing (with copy number variation analysis) was performed to identify known pathogenic and likely pathogenic variants described in the ClinVar database with the detailed analysis of variants (pathogenic/likely pathogenic/variation of uncertain significance (VUS) in 578 genes associated with autoinflammatory diseases and inborn errors of immunity. The analysis did not reveal any pathogenic variants. Among VUS two variants might be of interest: NLRP1 c.3221C>T p.Thr1074Met and NFKB2 c.1760C>T p.Pro587Leu However, they did not support the diagnosis of autoinflammatory syndrome. Never less we decided to administer the interleukin 1 (IL-1) inhibitor anakinra 100 mg sc/day, again without effect.

Conclusion: Despite the progress of medical knowledge and extensive diagnostics, we still have not clarified the cause of the disease and the choice of further treatment remains empirical.The main first open question is if this disease could be an inflammasomopathy or other complex autoinflammatory condition. In the next step should we measure the main biomarkers of inflammasome activation or to search other biomarkers or pathways. The second is how to treat patient and preserve the proper balance between benefit and risk. Should we during potential immunosuppressive/immunomodulatory treatment provide infection prevention as she had not received preventive vaccinations since the age of 4.

In conclusion recent discoveries highlight the importance of reevaluation of diagnosis in adult patients with inflammation which persisted from childhood or is refractory for treatment. However, achievement of proper diagnosis is still a challenge.

Disclosure of Interest: None declared

Identifier: PO085

A PATIENT WITH A VARIANT OF UNKNOWN SIGNIFICANCE (VUS) ON AUTOINFLAMMATORY PHOSPHOLIPASE CG2 (PLCG2) GENE: NEW VARIANT WITH A RARE CLINICAL PRESENTATION?

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Introduction: Autoinflammatory phospholipase Cg2 (PLCg2)-associated antibody deficiency and immune dysregulation (APLAID) is a rare autoinflammatory disease caused by gain-of-function mutations in the PLCG2 gene
Objectives: To further investigate the phenotype of PLCG2-variants
Methods: Clinical data and laboratory tests
Results: We present a patient who came to our attentionat the age of 3 for a clinical picture featured by hypogammaglobulinemia, pneumonia, and associated pleuropericarditis. On physical examination: dermatitis. The immunophenotyping revealed a B-cell lineage differentiation defect, whereas the hypogammaglobulinemia observed at onset spontaneously resolved after 4 years of age. During follow-up, we observed other two episodes of pneumonia with pleuritis and pericarditis when he was 4 and 5 years old respectively. Intriguingly, the latter was associated with glomerulonephritis with hypocomplementemia. Colchicine therapy was started with following complete and persistent clinical control. The whole exome gene-trio showed a paternally segregated heterozygous VUSin the PLGC2 gene c.2966G>C (p.Gly989Ala). After this report we have gone deep again the father's pathological medical history and he told us that he suffered recurrences of even severe dermatitis on his hands and fever of unknown origin during infancy. We then e studied the VUS with functional tests: the Granule-Release-Assay (GRA) showed a partial defect and we detected a persistent (120 min) expression of PLCG2 protein on PBMCs of the patient compared to controls after stimulation with H2O2, but normal in the father.
Conclusion: This case report expands the heterogenic presentation associated with PLCG2-variants in particular the glomerulonephritis that was described only in one case report, but more accurate and specific functional validation is needed to confirm the disease-causing potential of this variant of unknown significance

Disclosure of Interest: None declared

Identifier: PO086

DEFICIENCY OF ADENOSINE DEAMINASE 2: A TALE OF TWO PATIENTS, ONE MUTATION

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Introduction: Deficiency of adenosine deaminase 2 (DADA2) is an autosomal recessive disorder caused by mutations in the ADA2 gene. First described in 2014, it manifests as a monogenic vasculopathy or vasculitis that primarily affects children. The condition resembles polyarteritis nodosa (PAN) and exhibits considerable clinical variability, ranging from mild symptoms to severe vasculitis and hematologic abnormalities.

Objectives: This case presentation aims to discuss two patients with the same genetic mutation in the ADA2 gene, but differing clinical manifestations of DADA2.

Methods: We analyzed the clinical and laboratory findings of both patients to highlight the variability in presentation of DADA2.

Results: *Case 1*:

A 13-year-old Azerbaijani male presented with fever, malaise, abdominal pain, weight loss, and diarrhea. Physical examination revealed pale skin, high blood pressure, and livedo racemosa on his abdomen and legs. Neurologic examination was notable for left eye esotropia (present since age 3). Abdominal tenderness was present, but no organomegaly or lymphadenopathy was observed. Laboratory tests showed neutrophilic leukocytosis, thrombocytosis, elevated C reactive protein (CRP), erythrocyte sedimentation rate (ESR), and mildly elevated ferritin. Abdominal CT angiography revealed multiple aneurysms in the renal, splenic, ileocolic, and jejunal arteries. Cranial MR angiography identified aneurysms in the external carotid and temporal arteries. These findings led to a prediagnosis of PAN.

The patient was started on pulse steroid therapy and antihypertensive medications, but no improvement was seen after five doses of steroids and one dose of cyclophosphamide. A seizure occurred on the sixth day, though MRI showed no intracranial hemorrhage. Splenic vein embolization was required due to hemorrhage from a splenic artery aneurysm. Suspecting DADA2, we tested ADA2 enzyme activity, which showed no enzyme function. Genetic testing revealed a pathogenic homozygous c.752C>T p.(Pro251Leu) mutation in the ADA2 gene, confirming DADA2. Treatment with anti-TNF therapy was initiated, and family members were advised to undergo genetic screening.

Case 2:

A 6-year-old female presented with a two-month history of prolonged fever and arthralgia, specifically in the wrists. There were no associated symptoms such as weight loss, night sweats, or cough. Physical examination showed a mild livedoid rash on the legs, and mild cervical lymphadenopathy, but no signs of arthritis or organomegaly. Laboratory tests revealed neutrophilic leukocytosis, mild microcytic anemia, thrombocytosis, and elevated CRP and ESR. Viral serologies, ANA, anti-dsDNA, and tuberculin skin tests were all negative, and C3, C4, and immunoglobulin levels were normal. Abdominal, renal, and portal vein Doppler ultrasonography were unremarkable. Bone marrow aspiration showed no signs of malignancy.

Despite starting colchicine therapy, there was no clinical improvement. Genetic testing revealed the same pathogenic c.752C>T p.(Pro251Leu) mutation in the ADA2 gene. DADA2 was diagnosed, and anti-TNF therapy was initiated. MR angiographies were planned to assess potential vasculitis. The patient's family was also referred for genetic counseling.

Conclusion: DADA2 presents a broad clinical spectrum, with significant variability between patients. It should be suspected in any child with a stroke, livedoid rash, unexplained cytopenias, or rheumatic symptoms. The heterogeneity of DADA2 cannot be fully explained by low ADA2 activity and genetic factors alone, suggesting the importance of

epigenetic factors in disease presentation. It is crucial to emphasise that DADA2 can manifest in a wide spectrum of clinical forms, and the same genotype can manifest in two very different phenotypes.

Disclosure of Interest: None declared

Identifier: PO087

DIFFICULT-TO-TREAT RARE DISEASES: A CHALLENGING CASE OF PASH SYNDROME REFRACTORY TO CONVENTIONAL THERAPY

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Introduction: PASH syndrome (Pyoderma gangrenosum or PG, Acne, and Suppurative Hidradenitis or HS) is an inflammatory skin disorder characterised by suppurative lesions in intertriginous areas and follicle epithelium. The etiology is still unknown and is based on the interaction of environmental and genetic factors (e.g., *MEFV, PSTPIP1* genes), however, the diagnosis remains clinical. The disease's progression is chronic and debilitating, and therapeutic approaches may not always be effective.
Objectives: We describe a severe and refractory case of PASH that partially benefited from a combination therapy with the IL-1 Ra anakinra and the Janus-kinases inhibitor (JAK-1) filgotinib.
Methods: A 24-year-old man, active smoker, arrived at our attention in 2022. Medical history: after being diagnosed with Crohn's disease in 2016 and having an ileocecal resection in 2019, anti-TNF-alpha (adalimumab) treatment was initiated in 2020, but it was discontinued after five months due to recurrent skin infections, skin abscesses, and the development of sterile anal fistulas. After developing a severe form of HS, he was treated with a variety of approaches (surgery, granulocyte apheresis, hyperbaric oxygen therapy, and transfusion support), with limited success. In 2021, he restarted adalimumab at 40 mg/week, then increased to 80 mg/week in combination with prednisone. Moreover, since mid-2021, suppurative acne appeared on the back confirming the diagnosis of PASH.
Results: A 70-gene NGS panel revealed no mutations in *MEFV* or *PSTPIP1*. In December 2022, the patient began taking anakinra at a dose of 100 mg daily. After one month, he was admitted to our Department due to severe anemia (Hb 63 g/L), fever, elevated inflammatory biomarkers (CRP 54 mg/L), and persistent pain (VAS 10/10). He was given anakinra 200 mg/day intravenously, along with the JAK-1 inhibitor filgotinib (200 mg/day) and prednisone (25 mg/day). Approximately six months after discharge, the patient showed significant clinical and laboratory improvement, necessitating a reduction in total analgesic intake. Two years later, the inflammation appears to be under control for prolonged periods, but occasional flares reccur and the patient's quality of life remains low; indeed blood transfusions are still required and infections still emerge occasionally, for which the patient is taking antibiotics as a prophylaxis measure.

Conclusion: The treatment is difficult due to the disease's rarity and multi-refractory clinical presentation. Based on encouraging findings from recent research that supports the use of JAK-I for moderate-to-severe types of HS, it was decided that it was suitable to introduce an IL-1 inhibitor linked to a selective JAK-1 in light of the failure of anti-TNF-alpha and other non-pharmacological approaches. Although this patient has a significant risk of infection, filgotinib's good safety profile and anakinra's short half-life enable fast modulation in case of infections. For the treatment of refractory patients, alternative therapeutic modalities, such as IL-36 inhibitors, are presently being investigated.
Disclosure of Interest: None declared

Identifier: PO089

PYODERMA GANGRENOSUM (PG) PRECEDING TAKAYASU ARTERITIS (TA) IN A PEDIATRIC PATIENT: AN ONGOING UNSOLVED SAGA - A CASE REPORT AND LITERATURE REVIEW

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Introduction: PG a neutrophilic dermatosis, presents as painful, ulcerative skin lesions, often on the lower extremities. TA is a rare large-vessel vasculitis affecting the aorta and its branches. The coexistence of TA and PG is extremely rare, with most reports in adults from Japan and only 11 pediatric cases documented. We report a pediatric case of TA with PG as the presenting feature with a history spanning 21 months and unsolved issues.
Objectives: To discuss a case of Takayasu arteritis presenting as pyoderma gangrenosum
Methods: An 11-year-old female presented with poorly localized left leg pain and painful purplish nodules on her toes. Examination showed normal vital signs, blood pressure at the 50th centile, and a non-palpable left dorsalis pedis artery. CT angiography of the abdominal aorta and below revealed near-complete occlusion of the left distal superficial femoral artery (SFA) with unremarkable aorta and renal arteries. MRI of left leg showed myofascitis with ill-defined lesions in the vastus lateralis, popliteus, gastrocnemius, and pre-tendo-Achilles regions. Initial investigations, including inflammatory markers, immunoglobulins were normal. ANCAs and ANA were negative. Cryoglobulins were absent. Lupus anticoagulant was however positive. She was started on low molecular weight heparin.

Skin lesions progressively worsened to become bilateral on both lower extremities, ulcerated and spread proximally thigh downwards. Skin biopsy confirmed PG. Initial therapies (hydroxychloroquine, anticoagulants, topical tacrolimus), followed by successive trials of adalimumab, methylprednisolone pulses, infliximab plus IVIG, mycophenolate mofetil, and methotrexate were unsuccessful. Partial skin improvement occurred with infliximab and IVIG, but she developed persistent chest and neck pain. Repeat imaging revealed intima-media thickening and severe stenosis of the aorta, carotid, subclavian, and renal arteries, confirming TA. Repeat inflammatory markers were raised. Whole exome sequencing (WES), performed for refractory PG with aorto-arteritis showed no pathogenic mutations.

Cytokine profiling indicated elevated IL-6 levels, prompting initiation of tocilizumab (200 mg fortnightly, @10mg/kg). PG lesions improved significantly after the first two doses. However, six months later, she developed intermittent post-prandial abdominal pain. Repeat angiography revealed severe stenosis of the celiac and superior mesenteric arteries, requiring celiac artery dilatation. Cyclophosphamide was added, but after 4 months she again developed intermittent severe leg pain with persistent itching. Nerve conduction studies at this point were normal. Inflammatory markers remained elevated, leading to the recent addition of tofacitinib.

Results: Questions-

We present a case of pyoderma gangrenosum (PG) preceding takayasu arteritis (TA)

1. Could OTULIN gene mutation or other undetected genetic abnormalities explain this presentation?

2. Best mode of treatment/ Are there alternative therapeutic strategies to consider in such refractory cases?

3.Any other thoughts?

Conclusion: The coexistence of PG and TA is exceedingly rare in children.This case highlights the rare coexistence of TA and PG in a pediatric patient, showcasing the diagnostic and therapeutic challenges. The sequential development of TA, approximately
after 1.5 years of PG onset, suggests a possible progression of autoimmune pathology.

Acknowledgments: None
Disclosure of Interest: None declared

Identifier: PO090

PERINATAL ENCEPHALOPATHY IN INFANT WITH TREX1 VARIANT

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Introduction: Interferonopathies are a group of genetic autoinflammatory conditions which are characterized by upregulation of type 1 interferon (INF) signaling leading to inflammation. Their diagnosis can be challenging especially at a very early age. Moreover, diagnosis is still difficult even with presence of concerning symptoms and high clinical suspicion. Genetic testing is one of the key diagnostic interventions, although results may not be decisive.
Objectives: To share our experience of a case of the 7-month-old male with perinatal encephalopathy and *TREX1* variant.
Methods: Case presentation
Results: The patient 30 2/7 weeks born to G2P2 mother with cystic fibrosis with birth weight 1619 g, Apgar score 5/7 and signs of cardiomegaly and hydrops fetalis on fetal US and severe cystic encephalomalacia of the supratentorial brain, subdural hemorrhages, hemorrhage/clot adjacent to the right cerebellar hemisphere, thrombosis of the sagittal sinus with mass effect on fetal MRI.

Lab work obtained on first day of life: Hgb 12.8 gr/L, ANC 0.9/mcL, WBC 12.8 10^9/L, Plt 358 10^9/L; AST 92 U/L, ALT 9 U/L; negative Rubella, Syphilis, HIV, GC/Chlamydia and Toxoplasma serologies; positive CMV IgG; negative qualitive urine CMV PCR and IgM. Brain MRI at 2 days of life confirmed severe perinatal encephalopathy: extensive, subacute/chronic stage cerebral injury affecting the cerebral hemispheres with areas of intrinsic T1 shortening/laminar necrosis, no definite parenchymal diffusion restriction to suggest ongoing injury, extra-axial hemorrhages with multifocal subpial hemorrhages, large holohemispheric subdural hemorrhage on the left, smaller volume subdural hemorrhages on the right; thrombosis of the right internal cerebral vein, right-sided cortical vein at the vertex, thrombosed medullary veins and severe right and mild left lateral ventriculomegaly. Main differential diagnoses at that moment were neonatal alloimmune thrombocytopenia, TORCH-infection and variant of COL4A gene.

Genetic testing was performed during 1st week of life. Duo whole exome sequencing of the patient and his mother was positive for heterozygous pathogenic variant c.341 G>A (p.R114H) of *TREX1* gene in patient but not his mother. Patient's older sibling is healthy.

The patient spent the first 3 months in NICU and was discharged home in stable condition. Encephalopathy was complicated by spasticity and developmental delay. At the age of 7 months ventriculoperitoneal shunt was placed due to progressive increase of intracranial pressure associted with persistent irritability and vomiting. CSF analysis after shunt placement showed no inflammatory changes.

At the age of 7 months was referred to pediatric rheumatology due to high association of patient's genetic variant with lupus. The neonatal form of Aicardi-Goutières syndrome (AGS) was suspected considering clinical presentation and genetic testing results. This is a common *TREX1* variant, and although the association of homozygous p.R114H with AGS is described in the literature, AGS has not been reported in heterozygous individuals.

Initial rheumatology work-up showed: normal inflammatory markers (CPR <0.4, ESR <1 mmHg), complement levels (C3 87 mg/L, C4 33.6 mg/L), negative ANA, ENA, and ITF-α level (<2 (IU/ml) and low IgG (162 gr/L) and IgM (10.4 gr/L). Repeated CBC was significant for developing persistent neutropenia with absolute neutrophile count ~ 500/mcL. Analysis of INF type I gene expression showed downregulation of genes associated with INF-α activity (-22.7, normal range > 0). Laboratory results raised concern for possible disease "burn out". Neopterin level in CSF and brain imaging are pending.

Conclusion: After initial evaluation, despite the presence of encephalopathy and positive genetic testing result, AGS could not be ruled in nor ruled out.
Disclosure of Interest: None declared

Identifier: PO091

MEVALONATE KINASE DEFICIENCY: AN UNDERDIAGNOSED CAUSE OF INFLAMMATION-RELATED ISCHEMIC STROKE – CASE REPORT AND NOVEL GENE MUTATION

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Introduction: Autoinflammatory diseases may cause thromboembolic complications. A single patient with ischemic stroke (IS) caused by mevalonate kinase deficiency (MKD) was reported.
Objectives: To report a second patient with MKD-related IS and a novel *MVK* variant.
Methods: Case report.
Results: One day following cold weather exposure, a 58-year-old man developed leg pain and finger cyanosis. He presented 2 weeks later with acute right-sided sensory-motor deficit. Brain MRI confirmed a small left thalamic infarct; no chronic changes. He had had intestinal ulcer surgery in his mid-thirties. He smoked cigarettes and cannabis. Being adopted, family history was limited to 4 healthy children, 1 healthy granddaughter, and 1 grandson with bilateral leg amputation from toxic shock in childhood. Cervicocephalic CT-angiography, cardiac ultrasound and monitoring, as well as thoraco-abdominal CT were unremarkable. Leukocytosis, thrombocytosis, normocytic anemia, increased C-reactive protein and interleukin-6 reflected systemic inflammation. Serum amyloid-A level was >50,000 ng/mL (normal <11524). Initial blood work-up was otherwise normal, including extensive prothrombotic, infectious and auto-immune tests. Immuno-electrophoresis found monoclonal gammopathy IgG-kappa, with no evidence of multiple myeloma or amyloidosis on bone marrow biopsy. Positron emission tomography documented diffuse lymph node hypermetabolism, but no evidence of cancer or vasculitis. Five months after presentation, he developed acute right leg pain. Vascular imaging was unremarkable. Electromyogram disclosed mononeuritis multiplex. Persistently high inflammatory markers were noted. Next-generation sequencing of 336 primary immunodeficiency genes revealed compound heterozygosity in the *MVK* gene for the pathogenic variant c.1129G>A (V377I) and a new variant of uncertain significance c.1049A>C (Q350P). The localization of the Q350P substitution at the highly conserved GMHP enzyme site and the computerized prediction of change in the three-dimensional conformation of the mevalonate kinase enzyme support pathogenicity of the c.1049A variant. His grandson was found to be heterozygous for the V377I variant, thus confirming that the variants occurred in *trans*. Initiation of canakinumab led to clinical remission and abolition of systemic inflammation. Despite late age at onset, we diagnosed probable MKD, as supported by neurologic manifestations including IS otherwise unexplained, systemic inflammation, compound heterozygosity in the *MVK* gene, and excellent response to anti-IL1 therapy. The patient has now remained asymptomatic on aspirin and canakinumab therapy for 1 year. Lymphocytic mevalonate kinase enzyme activity analysis is underway, as mevalonic aciduria could not be performed during his initial flare.
Conclusion: MKD is a rare cause of IS. The novel variant Q350P is likely pathogenic. The occurrence of two MKD-related IS patients from a single centre center suggests etiological underdiagnosis of this treatable condition.
Disclosure of Interest: None declared

Identifier: PO092

NEUROLOGICAL PHENOTYPES OF SOCS1 HAPLOINSUFFICIENCY: INSIGHTS FROM FUNCTIONAL AND HISTOLOGICAL INVESTIGATIONS

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Introduction: Suppressor of cytokine signaling 1 (SOCS1) haploinsufficiency is a recently described inborn error of immunity characterized by autoimmunity, inflammation, lymphoproliferation and increased susceptibility to infections. SOCS1 is a negative regulator of cytokine signalling through the inhibition of JAK/STAT cascade, accounting for its wide phenotypic variability. Single nucleotide polymorphisms in *SOCS1* have been associated with multiple sclerosis (MS) and *SOCS1* mimetics have been demonstrated to prevent or induce remission in MS animal models. To date, neurologic involvement of the disease has not been reported.

Objectives: In the present study we report a family carrying a heterozygous *SOCS1* variant, where neurological impairment, represented by multiple sclerosis, autoimmune encephalitis and recurrent complex regional pain syndrome, emerges as a novel feature.

Methods: Next-Generation Sequencing and segregation analysis on PBMC from patients and healthy donors were performed. Flow cytometry studies on PBMC were applied to functional and phenotypic studies. Type-I interferon (IFN) signature was analyzed by gene expression profiling. Intraepidermal nerve fiber density was analyzed on skin biopsy by immunohistochemistry.

Results: Genetic sequencing and segregation analysis confirmed the variant's inheritance pattern. Increased STAT5 phosphorylation and T cell proliferation in response to IL-2 was observed. Peripheral blood IFN signature was elevated during clinical relapse. Skin biopsy demonstrated reduced intraepidermal nerve fiber density.

Conclusion: Our report contributes novel insights into the understanding of SOCS1-related disorders, including neurological symptoms as part of its clinical spectrum and confirming the relevant role of SOCS1 in controlling inflammation in both central and peripheral nervous systems.

Acknowledgments: Not applicable.

Disclosure of Interest: S. Palmeri: None declared, I. Prigione: None declared, F. Schena: None declared, A. Bertoni: None declared, F. Penco: None declared, P. Bocca: None declared, S. Massucco: None declared, C. Venturi: None declared, A. Schenone: None declared, M. Lanciotti: None declared, M. Miano: None declared, C. Matucci-Cerinic: None declared, G. Viglizzo: None declared, R. Papa Conflict with: Speaking from SOBI. , R. Caorsi Consultant for: from SOBI, Conflict with: Speaking fee from SOBI, M. Gattorno Conflict with: MG received consultancy and speaker fee from Novartis, Sobi, Fresenius Kabi, Kiniksa, S. Volpi Conflict with: SV received speaker’s fee from SOBI and consultancies Boehringer.

Identifier: PO093

STEROID-SENSITIVE NEUROINFLAMMATION IN 2 SIBLINGS WITH AUTOIMMUNE LYMPHOPROLIFERATIVE SYNDROME

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Introduction: Autoimmune lymphoproliferative syndrome (ALPS) is characterized by defective lymphocyte homeostasis due to failure of Fas-mediated apoptosis: genetic variants leading to defects in the classic Fas-Fas ligand (FasL) pathway result in abnormal lymphocyte survival and cause both non-infectious chronic lymphoproliferation and autoimmune phenomena.

Objectives: Although neurologic manifestations have been rarely reported in ALPS, no psychiatric features have ever been described.

Methods: -

Results: A 35-year-old man was hospitalized for focal seizures, cognitive decline, hallucinations and delusions. Since the age of 2 years he suffered from recurrent fevers, arthralgia, oral ulcers, pharyngodynia, hepatosplenomegaly and persistent elevation of inflammatory markers without cytopenia. At 29 years, because of severe abdominal pain and fever, a colchicine trial was tried without benefit. The NGS panel for autoinflammatory syndromes was negative. At 32 years an increased number of double negative lymphocytes was found (11%) with Fas receptor assay after exposure to specific FasL antibodies showing 93% survival, which led to a diagnosis of ALPS. The interferon (IFN) signature demonstrated high IFN level (11%; n.v. <2). Focal epilepsy emerged at 34 years, while EEG showed left-sided anomalies and brain MRI right parieto-occipital oedema with T2/FLAIR hyperintensity and gyral/hippocampal contrast enhancement. Levetiracetam was started. One month after, a progressive cognitive decline with suicidal ideation emerged. Diagnosis of psychosis was established, requiring a combination of valproate, aripiprazole and haloperidol with poor benefit. Left homonymous hemianopsia and occasional transitory phosphenes were also referred. One year later, at 35 years, the patient presented confusion, cognitive/motor slowness and apathy; brain MRI showed T2/FLAIR hyperintensity of the left cerebral cortex with extension to the temporal lobe, insular region, external capsule, occipital regions and gyral/hippocampal contrast enhancement. A tissue-based assay demonstrated liquor immunoreactivity against rat brain tissue, but no specific neuronal antibody was ever accordingly detected. The patient did not present other signs of systemic involvement consistent with a mitochondrial pathology, as shown by negative lactate levels on both serum and cerebrospinal fluid, and negative muscle biopsy. Quantiferon test, the complete panel for autoantibodies, and thrombophilia screening were negative. A ttotal body CT scan excluded any neoplasm. A 5-day i.v. high-dose methylprednisolone treatment was started, leading to rapid benefit of cognitive/psychiatric symptoms and brain oedema on MRI.

Patient's sister, 20 years before, had similar features, being started at 10 years with recurrent fevers, elevation of inflammatory markers, hepatosplenomegaly, hypergammaglobulinemia, epileptic encephalopathy, and slowly progressive cognitive decline. Psychiatric symptoms with motor dysfunction were noted at around 30 years, but the patient died at 36 years due to infectious complications.

Conclusion: The clinical exome testing is currently ongoing to assess the different ALPS genes potentially involved in such disease.

These clinical reports show that an extensive autoimmune neurological involvement, including psychosis, epileptogenic encephalopathy, motor and visual involvement (with consistent impressive radiological images) may be present in some ALPS subtypes, without any role played by the known anti-neuronal antibodies.

Acknowledgments: -

Disclosure of Interest: None declared

Identifier: PO094

(MONO-) GENETIC MIMICS OF BEHÇET'S DISEASE

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Introduction: Various (mono)-genetic autoinflammatory diseases and primary immunodeficiencies may mimic Behçet's disease (BD). Data examining the spectrum of underlying genetic diseases and the diagnostic yield of multigene panel testing in patients with suspected BD are scarce.

Objectives: To identify the proportion of genetic forms of BD, describe their phenotypes and compare them with those without genetic diagnosis.

Methods: This is a retrospective multicenter study of consecutive children with clinically suspected BD who underwent next generation sequencing gene panel for autoinflammatory diseases at the laboratory of Rare and Autoinflammatory Diseases in Montpellier, France between 01/2015 and 02/2024. Patients were included if they presented at least one of the following features: oral aphtosis, genital ulcers, erythema nodosum, folliculitis, acne, uveitis, papillitis, vasculitis, stroke. Detailed clinical and laboratory data were collected for patients with underlying genetic diagnoses using a pre-specified data collection form completed by the referring physician. They were compared to those without genetic diagnosis by chi-square and Wilcoxon rank-sum test.

Results: Thirteen of 934 patients (1.4%) had an underlying (mono)-genetic disease: five with Haploinsufficiency of A20, two with RELA-associated autoinflammatory disease, one with WDR1-related PFIT, one with XMEN-Syndrome and four with Trisomy 8 mosaicism. They were mostly female (79%) with a median age of 17.6 (IQR 9.3-26.2) and median disease onset at 5 (IQR 2-9) years. In addition to oral (100%) and genital/perineal ulcers other common clinical features were fever (46%), arthralgia (46%), diarrhea (38%). skin lesions, neurological manifestations and fatigue (one third each). Compared to patients without genetic diagnosis, those with had significantly more genital ulcerations (79% vs 18%, $p<0.001$) They were also younger at disease onset, although this was not statistically significant (5 vs 9 years, $p=0.091$). 5/13 patients with genetic diagnosis fulfilled the PED-BD classification criteria.

Conclusion: Overall, diagnostic yield was low in this unselectioned cohort. Genital ulcers and younger age at symptom onset may be associated with higher pretest probability.

Acknowledgments: *FAA and GB contributed equally

Disclosure of Interest: None declared

Identifier: PO096

CENTRAL NERVOUS SYSTEM (CNS) VASCULITIS IN ACTIVATED PHOSPHOINOSITIDE 3-KINASE DELTA SYNDROME 1 (APDS1) TREATED WITH HEMATOPOIETIC STEM CELL TRANSPLANTATION (HSCT): A 39-MONTH FOLLOW-UP AND LITERATURE REVIEW

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Introduction: Activated Phosphoinositide 3-Kinase Delta Syndrome 1 (APDS1), also known as PASLI disease, is a rare primary immunodeficiency condition caused by gain-of-function mutations in the PIK3CD gene. It is characterized by immune dysregulation, recurrent infections, and lymphoproliferation. Vasculitis has been reported in only six cases of APDS. They were described as ANCA vasculitis, C1q deficiency, digital vasculitis, and cutaneous vasculitis. Their treatments included disease modifiers, steroids, and leniolisib. Whether bone marrow transplantation was performed in these patients has not been mentioned. We described the first case of CNS vasculitis in APDS1 at ISSAID 2023 (ISSAID23-ABS-1219).

Hematopoietic Stem Cell Transplantation (HSCT) is a recognized curative option for APDS1, capable of reversing immune dysregulation. However, its impact on associated vasculitis has not been thoroughly studied. We previously presented 15-month follow-up data on a child with CNS vasculitis secondary to APDS1 who underwent successful HSCT. Here, we report an extended 39-month follow-up of the same case.

Objectives: To present 39 months follow up of 'post hematopoitic transplant' child of APDS1 having CNS vasculitis

Methods: A 4-year-old girl presented with acute left-sided upper limb and facial weakness. Additional findings included growth stunting, recurrent respiratory infections, enlarged adenoids, rampant dental caries, and delays in cognitive and speech development.

Brain MRI revealed acute infarcts in the right frontoparietal and occipital regions, with severe narrowing of intracranial vessels, particularly the right middle cerebral artery (MCA) and posterior cerebral arteries (PCA). Collateral vessel formation was noted. Laboratory investigations showed reduced B, T, and NK cell counts with normal immunoglobulin levels. An autoimmune workup was negative. Genetic analysis confirmed a heterozygous pathogenic PIK3CD mutation (E1021K), establishing the diagnosis of APDS1.

With the availability of a 100% HLA-matched sibling donor, HSCT was performed four months after diagnosis. Pre-HSCT management included mTOR inhibition. Post-HSCT, the patient achieved full donor chimerism with significant clinical and radiological improvement.

Results: Over a 39-month follow-up, the patient demonstrated:

Absence of new infarcts or infections.

Stabilization of CNS vasculitis on serial MRIs, with marked vascular improvement and collateral formation.

Complete immunological reconstitution, with normalization of lymphocyte subsets and cytokine profiles.

Significant physical growth (weight gain: 9 kg; height increase: 32 cm), and achievement of cognitive, speech, and developmental milestones comparable to peers.

Residual left upper limb weakness persists but does not limit daily activities.

Conclusion: This case underscores CNS vasculitis as a rare phenotype in APDS1 and demonstrates that HSCT is effective in halting disease progression, stabilizing vasculitis, reversing lymphoproliferation, and restoring immunological function. HSCT also facilitated complete physical and developmental recovery in this child, achieving growth and cognitive milestones comparable to age-matched peers.

Disclosure of Interest: None declared

Identifier: PO097

AUTOINFLAMMATORY MANIFESTATIONS IN A PATIENT WITH TYPE II D2-HYDROXYGLUTARIC ACIDURIA

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Introduction: Type II D2-hydroxyglutaric aciduria (D2HGA) is a rare, autosomal dominant disorder caused by a gain-of-function mutation in the IDH2 gene, causing increased production of D-2-hydroxyglutarate (D2HG) from alpha-ketoglutarate (a-KG) in the mitochondria. Excess D2HG results in neurodevelopmental abnormalities, muscular hypotonia, epilepsy, and severe dilated cardiomyopathy.
Objectives: We report the first case of Type II D2HG presenting with vasculitis, arthritis and granulomatous skin rash. We investigated the underlying mechanisms of inflammation in D2HGA.
Methods: We performed a chart review, and functional studies on patient-derived immune cells.
Results: A 7-year-old Indian girl, born full term to non-consanguineous parents, was diagnosed antenatally with a structural brain abnormality. Follow up magnetic resonance imaging (MRI) revealed bilateral cystic changes in the periventricular and subependymal regions, absent septum pellucidum, and thinning of the corpus callosum. By 3.5 months of age, she had global developmental delay and refractory seizures. Metabolic, genetic, and infectious disease screening were unremarkable. Concurrently, she developed a papular rash that started on the abdomen and chest, which spread to the extremities and face. Corticosteroids were initiated, leading to rash resolution without significant improvements in seizures. After steroid tapering, the rash recurred.
At 1 year of age, whole exome sequencing identified a *de novo IDH2* c.419G>A (p.Arg140Gln) mutation confirming the diagnosis of Type II D2HG. By 22 months, she was found to have a patent ductus arteriosus (PDA). Cardiac catheterization for PDA closure revealed vasculitis, and tortuosity of the thoracic and abdominal aorta concerning for large vessel vasculitis. PET-CT and cardiac MRI showed vessel caliber abnormalities without significant inflammation, although her inflammatory markers were persistently abnormal. Skin biopsy revealed cutaneous granulomas, and whole-body MRI identified mild knee arthritis. Dihydrorhodamine (DHR) assay repeated twice revealed a reduction in the oxidative burst.
Treatment with corticosteroids and immunosuppressive agents, including infliximab and methotrexate, resulted in resolution of the rash and vasculitis. She had a flare due to developing anti-infliximab antibodies, necessitating change of treatment to adalimumab.
In late 2024, she was started on enasidenib, an off-label treatment initially approved for IDH2-mutant AML. This was based on reports in three patients with D2HGA, who were successfully treated with enasidenib, and demonstrated improvement in cardiomyopathy, and some development milestones. Our patient's autoinflammatory disease is in remission, and we are yet to see objective changes in her neurodevelopmental status.
Elevated production of pro-inflammatory cytokines TNFa, IL-1β, and IL-6 was observed in LPS-stimulated monocytes of the patient compared to healthy donors. Additionally, RNA sequencing of whole blood identified disrupted pathways including mitochondrial dysfunction, oxidative phosphorylation, Electron transport, neutrophil degranulation and others.
Conclusion: This case highlights a novel association between Type II D2HGA and autoinflammatory disease. Preliminary results suggest that mitochondrial dysfunction and altered cytokine signaling are critical in the pathogenesis of inflammation in patients with IDH2 mutations. Further mechanistic studies are needed to elucidate the origin of inflammation in these patients, understand the extent of inflammatory disease, and guide the development of targeted therapies for such rare disorders.
Acknowledgments: We thank our patient and family for participating in our study.
Disclosure of Interest: None declared

Identifier: PO098

A CROSS-SECTIONAL OVERVIEW OF BEHÇET'S DISEASE MANAGEMENT: A TUNISIAN EXPERIENCE

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Introduction: Behçet's disease (BD) is a systemic inflammatory vasculitis. The clinical manifestations are diverse, ranging from relatively minor cutaneous or mucosal involvement to more severe forms with a potential life-threatening complication (arterial aneurysm, neurological involvement) or functional impairment (ophthalmological involvement). Sometimes, management could be challenging mainly in emerging countries where access to biologic therapies is limited.

Objectives: The aim of our study was to describe the clinical spectrum of Behçet disease and treatment used for the management of BD.

Methods: We conducted a monocentric retrospective study including all patients dignosed with BD according to The International Criteria for Behçet's Disease (ICBD) between 2014 and 2024. We collected data on clinical presentation and treatment indication.

Results: Overall, 42 patients were enrolled. The mean age was 45± 12 years old. The sex ratio (M/F) was 2.5. Organ involvement was as follows: mucocutaneous lesions (N=39, 92%), articular involvement (N=19, 45%), ocular involvement (N=14, 33%, including 8 retinal vasculitis, 5 panuveitis, 4 posterior uveitis, 3 anterior uveitis), vascular involvement (N=10, 23%, including 8 venous thromboembolism, 1 pulmonary artery aneurysm and 1 arterial thrombosis), gastrointestinal involvement (N=6, 14%), and parenchymal central nervous system involvement (N=4, 10%).

All patients received colchicine. Thirty-two (72%) patients required the use of glucocorticoids. Twenty-seven (64%) patients received immunosuppressive therapy in addition to steroids. Fifteen (35%) patients received azathioprine mainly for vascular involvement. Cyclophosphamide was used in four cases, before switching to azathioprine in three cases and to infliximab (IFX) in one case. Interferon alpha was used in one case with ocular Behçet and failed to achieve remission.

Six (14%) patients received IFX treatment for a median period of 68 weeks, ranging from 30 to 180. IFX was administered at a standard dose of 5 mg/kg at 0, 2, and 6 weeks initially, then every 8 weeks as maintenance therapy. Refractory ocular involvement was the indication for all the patients. A remission was obtained in all the cases.
After receiving IFX for 82 weeks, one patient had a central nervous system tuberculosis and was switched to tocilizumab at a dose of 8mg/kg every 4 weeks with a partial control of the disease under IL6 blocker.

Conclusion: We report a series of predominantly male Tunisian patients. In this cohort, we frequently observed the presence of organ damage indicating the prescription of immunosuppressive treatment in addition to corticosteroid therapy (64%). Access to biologic therapies is possible but very difficult, with long waiting times for access to biotherapy leading to delays in treatment. Only 6 (14%) patients were able to benefit from anti-TNF, which remains the reference molecule in the treatment of MB, leading in our cohort to remission in 100% of cases. Further global efforts are needed to democratize access to biologics.

Disclosure of Interest: None declared

Identifier: PO100

THE PATHOLOGY OF THE SKIN, LYMPH NODES, LIVER, AND BONE MARROW AND RELATED CLINIC-BIOLOGICAL FEATURES IN PATIENTS WITH SEVERE SYSTEMIC JUVENILE IDIOPATHIC ARTHRITIS : A CASE SERIES OF 11 PATIENTS

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Introduction: Pediatric-onset Still's disease (pSD) is a chronic inflammatory disorder. Despite therapeutic advances, some patients present refractory disease with macrophage activation syndrome (MAS), severe hepatitis or atypical DRESS-like features after treatment with bDMARDs. Biopsies can help to characterize the underlying process and thereby better understand the disease mechanism in the affected organs. Histopathology has been reported in patients with adult-onset Still's disease (AOSD) but to date, specific pathologic findings in pSD are rare.

Objectives: To analyse pathological findings of the skin, lymph nodes, liver and bone marrow (BMB) and the associated clinico-biological findings in patients with pSD at onset or during follow-up and to assess the potential of pathological features to improve diagnostic accuracy and exclude differential diagnoses.

Methods: Eleven pSD patients, referred to Necker Hospital (Paris, France) between 2009 and 2024, were retrospectively included. They fulfilled the PRINTO classification criteria and underwent at least one tissue biopsy. Twenty-eight biopsies were reviewed. Related clinico-biological data were recorded. Patients were categorized into clinical subsets based on their predominant features (MAS, lymphoproliferative disorders (LPD), DRESS-like and hepatitis).

Results: Male-to-female ratio was 3:8. Median age was 4 years at onset and 7.5 years at the time of biopsy. Median maximum IL-18 blood levels (in 7 tested patients) was 50,000(2,000-400,000) pg/ml. Median number of administered treatment was 5. Clinical subsets at diagnosis or during follow-up were LPD (n=5), MAS (n=3), DRESS-like (n=4) and hepatitis (n=5) with 7 patients presenting 2 phenotypes. Lymph node biopsies (n=8) were performed in patients presenting persistent voluminous polyadenopathie. Such biopsies revealed immunoblastic proliferation, follicular hyperplasia, no evidence of lymphoma or hemophagocytosis even in patients with MAS episode. Varying degrees of vascular proliferation were observed and were prominent in 2 patients with fatal disease. Two biopsies showed circumscribed foci of apoptotic necrosis as observed in Kikuchi disease. BMB (n=5) showed moderately reduced to normal cellularity. Hemophagocytosis was observed in 2 patients including one without MAS episode. Skin biopsies (n=6) identified in half of the cases almost-pathognomonic dyskeratotic keratinocytes in the *stratum corneum* as found in AOSD. Two biopsies showed nonspecific interface dermatitis. Biopsies in patients with DRESS-like phenotype after bDMARDs treatment (n=5) did not show major lymphocytic infiltrate as observed in DRESS while eosinophilic infiltrate was observed in 2 biopsies. Finally, liver biopsies (n=9) revealed nonspecific fibrosis (mainly in perisinusoidal spaces) and portal inflammatory infiltrate. Four biopsies showed nodular regenerative hyperplasia. No specific evidence of hepatic toxicity was found in patients with suspected bDMARDS hepatic toxicity (n=7).

Conclusion: This is the first descriptive study that correlate pathologic and clinico-biological features in patients with severe pSD. Pathologic findings are not pathognomonic but provide valuable insights to help to differentiate pSD from other diagnoses. Skin biopsies with similar AOSD features highly suggest the diagnosis of pSD. Specific pathologic features of hepatic drug toxicity or DRESS were not seen in all biopsies when bDMARDs toxicity was suspected and might support the mechanism of cytokine dysregulation rather than classic drug toxicity. Major lymph node vascular proliferation in patients with fatal disease is interesting and could be involved in the physiopathology. Although nonspecific, the use of tissue biopsies might help to better understand severe phenotypes and guide the management of selected refractory patients.

Disclosure of Interest: None declared

Identifier: PO101

CLINICAL OUTCOME AND QUALITY OF LIFE IN PATIENTS WITH ARPC1B DEFICIENCY MANAGED CONSERVATIVELY OR WITH ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION - ON BEHALF OF THE ESID/EBMT INBORN ERRORS WORKING PARTY

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Introduction: ARPC1B deficiency leads to a combined immunodeficiency characterized by early clinical onset, recurrent infections and platelet abnormalities with bleeding tendency. Although most patients with ARPC1B mutations tolerate transplant conditioning, with a high rate of immunodeficiency resolution, there is a lack of studies comparing the clinical outcome and quality of life of patients undergoing transplantation or treated conservatively.
Objectives: The aim of the study is to compare ARPC1B patients managed conservatively and with HSCT assessing clinical outcome and quality of life.
Methods: The study was approved by ESID, EBMT, and CIS inborn error working parties. The inclusion criteria are patients with ARPC1B deficiency genetically confirmed treated conservatively or with HSCT. Clinical data including symptoms, genetics, IDDA 2.1 score at last follow-up, HSCT-related features were collected by local physicians and anonymized. Patients included in the study completed an age-related quality of life questionnaires: PedsQL 4.0 and SDQ for children and SF 12 for adults respectively.
Results: Thirteen centres from nine countries have been involved, collecting data from 20 patients. Clinical onset was early in all patients (median age 1 month [0-36]). The most frequent homozygous variant was c.311G>C (20%). Eight out of the 20 patients (40%) received allo-HSCT at a median age of 8.8 years (0,76-16,2). The main clinical features are summarized in Table 1. At last available follow-up, 17 out of 20 patients are alive (85%), with 3 out of 8 patients dead after transplant. The median age at follow up was 10,41 (1,58-36) for no-transplanted and 14,85 years (0,83-22,2) for transplanted patients. At the time of writing, 10 out of 17 patients (58.8%) had completed the QoL questionnaire (8/12 not transplanted, 2/5 transplanted. Total patient and proxy PedsQL 4.0 scale scores were significantly reduced in patients receiving conservative treatment compared to healthy controls ($p = 0.0094$, Mann-Whitney test).

Table 1

	Total (n=20)	**Non-HSCT (n=12)**	**Non-HSCT and pre-HSCT (n= 20)**	**Post-HSCT (n=8)**
Recurrent AOM	13 (65%)	9 (75%)	13 (65%)	1 (13%)
LRTI	11 (55%)	6 (50%)	11 (55%)	1 (13%)
CNS infections	3 (15%)	1 (8%)	1 (5%)	2 (25%)
Acute/Chronic CMV	7 (35%)	4 (33%)	6 (30%)	3 (38%)
Enterorrhagia	10 (50%)	7 (58%)	10 (50%)	0
ITP	**6 (30%)**	**3 (25%)**	**6 (30%)**	**0**
Severe eczema	**14 (70%)**	**8 (67%)**	**14 (70%)**	**1 (13%)**
IBD-like	**6 (30%)**	**4 (33%)**	**6 (30%)**	**0**
Last follow-up IDDA 2.1	**32.9 [4.1-174]**	**33.9 [6.9-66]**	**32.9 [1.1-66]**	**32.9 [4.1-174]**

HSCT: Hematopoietic Stem Cell Transplantation; **AOM**: Acute Otitis Media; **LRTI**: Lower Respiratory Tract Infection; **CNS**: Central Nervous System; **CMV**: Cytomegalovirus; **ITP**: Immune Thrombocytopenic Purpura; **IBD**: Inflammatory Bowel Disease; **IDDA**: Inflammatory Disease Damage Assessment

Conclusion: Preliminary results confirm that HSCT in ARPC1B deficiency is feasible and effective. Even if preliminary, QoL resulted significantly reduced in patients treated conservatively compared with healthy donors. Notably, there is a marked reduction in the frequency of bleeding, eczema, and autoimmune/autoinflammatory symptoms in the HSCT group. More data are needed to determine its impact on patient outcomes and quality of life.
Disclosure of Interest: None declared

Identifier: PO102

AN UPDATE ON THE CLINGEN MONOGENIC AUTOINFLAMMATORY DISEASES EXPERT CURATION PANELS: A FRAMEWORK FOR INTERPRETING GENETIC FINDINGS IN AUTOINFLAMMATORY DISEASES

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Introduction: As autoinflammatory diseases are becoming more recognized and evaluated, next generation sequencing (NGS) is increasingly being utilized in the evaluation of patients with suspected autoinflammatory conditions. Clinically available NGS panels often include a large number of genes, many of which may lack sufficient evidence to establish a clear link to disease causality. Moreover, many variants detected in both established and candidate genes are classified as variants of uncertain significance (VUS), and as such pose significant challenges for clinical interpretation.

Objectives: 1. To update on the progress of the ClinGen Monogenic Autoinflammatory Diseases Working Group
2. To increase the accuracy and efficiency of variant interpretation in autoinflammatory diseases

Methods: The Clinical Genome Resource (ClinGen) is an NIH-funded initiative dedicated to building a central resource that defines the clinical relevance of genes and variants for use in precision medicine and research. The ClinGen Monogenic Autoinflammatory Working Group was established in 2022 to provide expertise and develop a framework for assessing the monogenic autoinflammatory diseases. This group is a part of the larger Rheumatologic Autoimmune Disease Clinical Domain Working Group (RAD CDWG) and is composed of the Gene Curation Expert Panel (GCEP) and the Variant Curation Expert Panel (VCEP). The GCEP and VCEP are comprised of international experts in various clinical domains to create tailored guidelines for their areas of focus. Gene-disease curations are published on the ClinGen website. Variant interpretation guidelines are applied to variants that are submitted to the ClinVar and Infevers databases. Variants curated with ClinGen's validated protocols are recognized by the US Food and Drug Administration.

Results: The Monogenic Autoinflammatory Diseases GCEP was formally approved in April 2023 to curate the relationships between the numerous genes that have been implicated in autoinflammatory disease. Since its establishment the GCEP has published definitive curations for *MVK*/Mevalonate Kinase Deficiency and *LPIN2*/Majeed syndrome. Curations are currently underway and expected to be finalized in the coming months for *ALPK1, TNFRSF1A*, *PLCG2*, *RIPK1*, *PTSPIP1* and the proteosome deficiency-associated genes. We plan to complete curations for *NOD2, NLRP3, NLRP12, SHARPIN, TNFAIP3* and *RelA* in 2025. *MEFV* and *ADA2* have already been curated by other groups.

The VCEP is expected to be approved in early 2025. The VCEP will begin by developing variant curation guidelines for *MEFV, TNFRSF1A* and *ADA2*, and then will move on to the other genes. Guidelines will use evidence such as population frequency, computational predictors, functional studies, and clinical data. Existing data from the Infevers database will be used as a baseline to develop classification guidelines.

Conclusion: The Monogenic Autoinflammatory Diseases GCEP and VCEP will establish a standardized framework for curating gene-disease relationships and interpreting genetic variants in individuals with autoinflammatory diseases. This framework, along with the resulting variant classifications published to ClinVar and Infevers, will significantly enhance the ability of clinicians, diagnostic laboratories, and researchers to leverage genetic information, ultimately advancing the diagnosis and treatment of patients with these disorders.

Acknowledgments: We would like to thank to the greater ClinGen Rheumatologic Autoimmune Disease CDWG, and especially to co-Chair Louis Bridges, for their support.

Disclosure of Interest: None declared

Identifier: PO103

PREGNANCY OUTCOMES IN AUTOINFLAMMATORY DISEASES: A PROSPECTIVE STUDY OF 117 CASES, INCLUDING 79 WITH FAMILIAL MEDITERRANEAN FEVER.

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Introduction: Autoinflammatory diseases (AIDs) predominantly affect young patients who are likely to become pregnant. For many inflammatory diseases, pregnancy is known to destabilize the disease and may lead to complications for the mother or unborn child. There is a paucity of prospective large cohort data on pregnancy outcomes in patients with AIDs, especially in the most common of these, familial Mediterranean fever (FMF).
Objectives: to prospectively study pregnancies outcomes in patients with AIDs.
Methods: The French multicenter prospective pregnancy observational cohort (GR2 study) included patients with AIDs between 2016 and 2024. Disease activity, treatment, pregnancy outcome, delivery and neonatal health were analysed.
Results: 115 pregnancies, including 5 twin pregnancies, in 97 women followed for AID with, in descending order of frequency: FMF (n=79), Undifferentiated systemic autoinflammatory diseases (USAID) (n=21), Tumour necrosis factor (TNF) receptor-associated periodic syndrome (TRAPS) (n=5), cryopyrin-associated periodic syndromes (CAPS) (n=3), Still's disease (n=2), recurrent pericarditis (n=2), Mevalonate kinase deficiency (MKD) (n=1), A20 haploinsufficiency (HA20) (n=2), and pyogenic arthritis, pyoderma gangrenosum and acne (PAPA) syndrome (n=1). Patients had a median age at onset of pregnancy of 31 years [min 20-max 44] and a median BMI of 22.3 [min 16.4-max 35.8]. Pregnancies were achieved after assisted reproduction in 10.8% of cases, including only FMF. Patients had signs of disease activity in the year prior to pregnancy in 57.7% of cases and had flares during pregnancy in 59.1% of cases. Sixteen pregnancies were terminated before the 37th week of gestation: 2 foetal deaths in utero, 2 therapeutic abortions due to chromosomal abnormalities, and 1 spontaneous abortion.

In the USAID patients (n=21), the median age of disease onset was 14 years [0-32] and gestational age was 30 years [20-37]; half were receiving colchicine. Mean CRP at enrolment was 8.9 mg/dl [0-25]. Biotherapy was discontinued upon discovery of pregnancy (n=2: anakinra, tocilizumab). Three pregnancies (14%) were terminated prematurely due to late miscarriage, foetal death *in utero*, and medical abortion due to monosomy X. Of the newborns, only one had a birth weight <10th percentile.

For FMF patients, the median age at FMF symptom onset was 6 years and at pregnancy was 31 years. The median dose of colchicine was 2 mg/d [1.5-1.8]. Patients were carriers of 2 pathogenic variants of MEFV (79.4%) or only one (20.5%). They reported a mean of 4 attacks/year in the year prior to pregnancy. Mean CRP at enrolment was 22.5mg/L. At least one spontaneous miscarriage <22AW prior to this pregnancy was reported in 13.9% of patients, and 15% had undergone assisted reproduction for their pregnancy, 83% of them by in vitro fertilization. Inflammatory symptoms occurred during pregnancy in 65.7% of cases, including 3 prolonged febrile myalgia syndromes. Seven patients (8%) received anakinra on demand for persistent attacks. Pregnancy complications reported were one risk of preterm delivery in a twin pregnancy;

one anamios and one oligohydramnios in the same patient during both of her pregnancies. 17% of patients delivered before 37 AW, including 4 twin pregnancies, one miscarriage <22 AW and one unexplained foetal death *in utero* at 26 AW. Regarding the newborns: 22.4% had a birth weight below the 10th percentile, including none of the twins.

Conclusion: This national prospective study demonstrates the importance of monitoring inflammation during pregnancy. During FMF, there was more recourse to assisted reproduction, 17% preterm delivery and 22.4% intrauterine growth retardation, which are higher than the figures for the general French population (7 and 7.1% respectively).
Disclosure of Interest: None declared

Identifier: PO104

TRACKING COLCHICINE COMPLIANCE IN CHILDREN WITH FMF: CAN HAIR COLCHICINE DOSING PROVIDE USEFUL INFORMATION?

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Introduction: Familial Mediterranean fever (FMF) is a monogenic auto-inflammatory disease, clinically characterized by recurrent episodes of fever and/or serositis and severe complications such as AA amyloidosis. Colchicine, the primary treatment option, has been demonstrated to be effective in preventing inflammatory flares and reducing the risk of amyloidosis. However, compliance remains a significant challenge, particularly in children and adolescents. The current compliance assessment tools, which are primarily subjective, are unable to evaluate long-term intake. Recently validated in adults, measuring colchicine concentration in hair offers a non-invasive and objective method that holds potential for adaptation in children.
Objectives: The main aim of the study is to assess whether colchicine hair testing can be used as a measure of therapeutic compliance in children/adolescents with FMF. The secondary objective is to ascertain the influence of endogenous and exogenous factors on colchicine incorporation into hair.
Methods: The study population consisted of patients under the age of 18 with FMF who met the PRINTO/EUROFEVER classification criteria and were receiving regular colchicine treatment at 3 French pediatric tertiary centers. Following the provision of written consent by the patient and/or their legal guardian, an interview was conducted to assess the patient's adherence to the prescribed treatment. The patient was then classified into one of three categories based on their declared compliance: excellent, fair, or poor. Additionally, patients were asked to complete a self-report questionnaire regarding their hair care practices, which may impact colchicine hair concentration. This includes information on the use of hair dyes, bleaching, blow-drying, straightening, and other similar activities. A strand of hair was sampled from the top and back of the skull for analysis by liquid chromatography coupled to tandem mass spectrometery (LC-MS-MS). The analysis covers up to 6 cm from the root, reflecting colchicine intake over the previous six months assuming an average hair growth rate of 1 cm per month. Statistical analysis was performed with EasyMedStat (version 3.38; www.easymedstat.com).
Results: A total of 50 patients (31 girls and 19 boys) with a median age of 10.6 years (range 2-17 years) were included in the study. Of the 34 patients who exhibited two pathogenic *MEFV* mutations in exon 10, 29 were found to possess at least one Met694Val mutated allele. A total of 16 patients were heterozygous for a single exon 10 mutation. The median daily dose of colchicine was 1 mg/day, ranging from 0.25 to 2. Patients had been taking colchicine for a median of 4.30 years [0.52 -14.63]. According to adherence assessment interviews, 20 patients (40%) had excellent, 19 (38%) fair and 11 (22%) poor colchicine compliance. In all patients, colchicine was detectable in the hair with a median concentration of 5.42 pg/mg [0.1 -13.30]. However, there was no correlation between the daily dose of colchicine (either the total daily dose or the dose per kg) and hair concentrations. Similarly, no correlation was found between daily dose and hair concentrations, when the analysis was restricted to (i) patients with excellent compliance (ii) patients who did not have hair care habits that could interfere with drug incorporation into hair, (iii) patient older than 3 years.
Conclusion: Although hair analysis can effectively indicate whether a patient has been exposed to colchicine, significant inter-individual variability has been observed even among fully compliant patients receiving the same daily dose. This prevents the use of hair analysis as a reliable objective marker for assessing treatment adherence in children and adolescents less than 18 years.
Acknowledgments: We thank the Versailles Hospital for research assistance
Disclosure of Interest: None declared

Identifier: PO105

BREAKING THE CYCLE: IMPROVED OUTCOMES IN THE FIRST COHORT OF SECOND-GENERATION CAPS PATIENTS THROUGH EARLY DIAGNOSIS AND TREATMENT

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Introduction: Cryopyrin-associated periodic syndromes (CAPS) are a group of rare autoinflammatory disorders caused by mutations in the NLRP3 gene. Historically, CAPS diagnosis and treatment were often delayed, leading to significant disease complications and morbidity. However, advancements in genetic testing and disease awareness have enabled earlier identification and treatment of affected individuals, particularly in familial cases. This study focuses on the second generation of CAPS patients, who have been diagnosed and treated at a younger age due to their parents' prior diagnosis.

Objectives: We aim to determine whether early intervention in this cohort leads to reduced disease complications, better compliance and improved outcomes compared to their parents.

Methods: We conducted a retrospective review of medical records from the National Amyloidosis Centre at the Royal Free Hospital and Great Ormond Street Hospital for Children NHS Foundation Trust. Families with CAPS were identified, focusing on cases where both parents and their children were diagnosed. Data were collected on patient demographics, genetic mutations, age at diagnosis, age at treatment initiation, and disease-related complications. Comparisons were made between the first generation (parents) and the second generation (children) to evaluate the impact of earlier diagnosis and treatment on disease outcomes.

Results: We identified 29 children diagnosed with CAPS across 24 families, of whom 16 (55%) were female. The median age at the time of the study was 11.5 years (range: 6.1–17.0 years), with a median age of symptom onset at birth and a median age of treatment initiation at 3.2 years (range: 1.6–5.3 years). The most common genetic mutation was A439V, identified in 17/29 patients, while other mutations included L353P, R260W, D303N, R488K, T348M, L305P, Y859C, and T348M.

Among the children, 21 started treatment with canakinumab, while 7 began with anakinra, of which 5 were later transitioned to canakinumab. None of the children experienced hearing loss or ocular inflammation. Two notable complications were reported: one patient had refractory joint swelling requiring treatment escalation, and another developed depression and an eating disorder. No issues with treatment compliance were observed. The median follow-up period for this cohort was 4.5 years (range: 2.6–8.7 years).

In contrast, the affected parents had a median age of 37.4 years (range: 32.9–42.2 years) and started treatment at a median age of 28.6 years (range: 22.4–34.1 years). They had a median of 2 children (range: 1–2.5). Among the parents, 6/24 experienced hearing loss requiring hearing aids, 6/24 had ocular issues such as iritis or episcleritis, 6/24 reported musculoskeletal problems, and 3/24 were diagnosed with depression. Additional complications included hypertension and migraines/headaches. The median follow-up duration for the parents was 7.5 years (range: 4.7–10.8 years).

Conclusion: This study represents the first reported cohort of second-generation CAPS patients, providing unique insights into the impact of early diagnosis and treatment. Early intervention significantly reduced the prevalence of severe complications, including hearing loss and ocular inflammation, compared to their affected parents. Despite isolated cases of refractory joint swelling and mental health challenges, overall disease management outcomes were favourable. These findings underscore the importance of early identification and targeted therapy in mitigating the long-term disease burden in familial CAPS cases.

Disclosure of Interest: None declared

Identifier: PO106

LONG-TERM SAFETY AND EFFICACY OF COLCHICINE AND ANTI-IL-1 BLOCKERS IN FMF: RESULTS FROM THE EUROFEVER MULTICENTER OBSERVATIONAL STUDY

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Introduction: The majority of currently available data on patients with familial Mediterranean fever (FMF) are retrospective and based on single-center, national experiences.

Objectives: We present in detail the real-life data from the FMF cohort of the longitudinal, international registry of EuroFever.

Methods: The INSAID/Infevers classification to *MEFV* genetic variants were applied to the entire cohort. Patients fulfilling the current genetic and clinical Eurofever/PRINTO classification criteria (a suggestive clinical phenotype and carrying at least one pathogenic *MEFV* variant of two VUS) were considered as FMF+, while patients only diagnosed according to the clinical manifestations were considered as FMF- and analyzed as control group.

Results: In November 2024, 876 patients (466 M, 410 F) were enrolled. The median age at onset was 3.57 years (0 - 59.08), with a mean follow-up time of 2.9 ± 3.1 years. 349 (39.8%) patients carried a confirmatory *MEFV* genotype, with M694V being the prevalent variant (484, 55.3%). 730 (84%) patients were positive to FMF genetic and clinical criteria (FMF+), 146 (16%) did not display an informative *MEFV* genotype (FMF-). At baseline, the most frequently symptoms

were fever (778, 88.8%) and abdominal pain (731, 83.4%), with a global reduction of almost all the manifestations during the follow-up. FMF+ patients had shorter episode durations at baseline (3[2-3] vs 3 [3-5] days) and at the last follow-up -(2[1-3] vs 3 [2-3] days) than FMF-. At baseline, FMF+ patients had higher rates of chest pain (36.2% vs 24.7%, p=0.01) and pleuritis (13.7% vs 6.8%, p=0.032), while FMF− patients showed more aphthous lesions (39.7% vs 14.2%, p<0.001), latero-cervical adenopathy (36.3% vs 14.8%, p<0.001), and tonsillitis (31.5% vs 13.2%, p<0.001). At the last follow-up, the number of patients treated with colchicine (749, 85.5%), was similar to the baseline (724, 82.6%), without significant variations of dosage (median 1 [1-1.5] mg/day) between groups with different disease activity. Anti IL-1 treatment was ongoing in 133 patients (15.2%), mostly canakinumab (117, 13.4%), with a median dosage of 150 [73.3-150] mg/4 weeks. An optimal compliance (defined as taking > 90% of prescribed doses) was observed in 72.5% of visits for patients on colchicine, 48.2% for those on anakinra, and 80.7% for patients on canakinumab. At the last visit, 433 (50.6%) patients still had some disease activity, with FMF- patients showing a risk 1.6 greater than FMF + patients of having an incomplete clinical response rather than a complete clinical remission. Adverse events reported during the whole observational study were generally mild, mostly upper respiratory tract infections, abdominal pain or diarrhea. 22 adverse events were surely or possibly related to the ongoing treatment (20 for colchicine, 2 for anakinra, 0 for canakinumab).

Conclusion: Patients who lack genetic confirmation display significant differences in clinical features, duration of attacks, long term-outcome and a significantly less response to colchicine. Thus these patients should be considered as FMF-mimics and investigated for other causes. For FMF patients more than half reach complete remission with colchicine. Longitudinal data provides a detailed comprehension of the long-term burden of FMF and the impact of treatment on disease activity and patients' quality of life.

Acknowledgments: The Authors would like to thank Eugenia Mosci and Elisa Patrone for their commitment in the secretarial assistance for this study. The project has been funded by E-Rare-3 project (INSAID, grant 003037603). Eurofever was supported by the Executive Agency For Health and Consumers (EAHC, Project No 2007332). Novartis provided an unrestricted financial support to the study.

Disclosure of Interest: S. La Bella: None declared, M. Bustaffa: None declared, Y. Bayindir: None declared, G. Amaryan: None declared, R. Gallizzi: None declared, E. Papadopoulou-Alataki: None declared, G. Fabio: None declared, N. Assalia: None declared, G. Amarylio: None declared, M. Jesenak: None declared, L. Breda: None declared, J. Anton Grant /Research support from: Novartis, SOBI, Consultant for: Novartis, SOBI, Speaker bureau of: Novartis, SOBI, E. Legger Grant /Research support from: Novartis, SOBI, M. Alessio: None declared, G. Simonini: None declared, D. Rigante: None declared, L. Obici Consultant for: Novartis, J. Kuemmerle-Deschner: None declared, O. Kasapcopur Consultant for: Novartis, SOBI, Speaker bureau of: Novartis, SOBI, A. Insalaco: None declared, M. Glerup: None declared, J. Frenkel: None declared, J. Brunner: None declared, G. Horneff: None declared, J. Sánchez-Manubens: None declared, S. Bakkaloglu: None declared, L. Cantarini: None declared, A. Spagnolo: None declared, S. Alataki: None declared, M. Carrabba: None declared, A. Porreca: None declared, R. Caorsi: None declared, N. Ruperto: None declared, M. Gattorno Grant /Research support from: Novartis, Consultant for: Novartis, SOBI, Speaker bureau of: Novartis, SOBI, Fresinius-Kabi, S. Ozen Consultant for: Novartis, SOBI, Speaker bureau of: Novartis, SOBI

Identifier: PO107

COMBINATION OF BIOLOGICS AND JAK INHIBITORS IN THE TREATMENT OF REFRACTORY SYSTEMIC AUTOINFLAMMATORY DISEASES

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Introduction: Systemic autoinflammatory disorders (SAIDs) result from genetic defects in innate immunity, leading to excessive activation of inflammatory pathways such as IL-1, TNF, and JAK/STAT. Symptoms range from fever to life-threatening conditions like encephalitis and AA amyloidosis. Treatment focuses on controlling inflammation with glucocorticoids, colchicine, DMARDS, and advanced drug monotherapies (biologics and JAK inhibitors). Advanced combination treatment (ACT) refers to combining two or more biologics or a biologic and a JAK inhibitor to treat inflammatory diseases.

Objectives: To present our experience using ACT in difficult-to-treat SAID patients.

Methods: The charts of genetically confirmed SAIDs or undifferentiated autoinflammatory diseases (uSAID) who received two or more advanced treatments simultaneously were retrospectively reviewed. Collected data included patient demographics, clinical outcomes, prior therapies, and adverse events. The treatment responses were evaluated using a composite score that included steroid-sparing effects, improvements in C-reactive protein (CRP) levels, and the Clinical Global Impression-Improvement (CGI-I) scale. Treatment outcomes were categorized as non-response, partial response, or complete response, with the study evaluating the safety and efficacy of ACT in this patient cohort.

Results: The study included 38 patients with SAIDs who received ACT, with a median age of 30 years (range: 4–76). The most common conditions requiring ACT were pyoderma gangrenosum, pyogenic arthritis and acne syndrome, mevalonate kinase deficiency, and uSAIDs. Nearly all patients had complications such as joint destruction, skin disfigurement, retinopathy, and dependence on glucocorticoids or opioids. A total of 65 ACT regimens were trialed, with IL-1 and TNF inhibitor combinations being the most frequently used. ACT resulted in 22 complete responses, 29 partial responses, and 14 non-responses. Treatment was discontinued in 38 regimens due to inefficacy, secondary loss of efficacy, or adverse events. At the final assessment, 68% of patients remained on ACT, with a median treatment duration of 60 months (range: 11–186). Overall, ACT yielded significant clinical and laboratory improvements for most patients. Sixteen serious adverse events (all infections) were reported during 151.9 patient-years of follow-up, with no deaths attributed to ACT.

Conclusion: ACT demonstrates substantial clinical benefits for patients with refractory SAIDs, though challenges such as secondary loss of efficacy and infection risk persist.

Disclosure of Interest: None declared

Identifier: PO108

AA AMYLOIDOSIS RELATED TO MONOGENIC AUTOINFLAMMATORY DISEASES IN FRANCE: A COHORT STUDY OF 77 CASES

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Introduction: Amyloid A (AA) amyloidosis arises from persistent inflammation and represents the most severe complication of monogenic autoinflammatory diseases (AIDs).
Objectives: To describe AA amyloidosis in a cohort of patients with monogenic AIDs focusing on clinical characteristics, progression, and treatment outcomes.
Methods: We conducted a retrospective analysis of all patients diagnosed with AA amyloidosis who have been under follow-up since 2015 at the French center for AIDs and AA amyloidosis. Ethical approval was obtained from the Sorbonne University ethics committee, and patient consent for anonymous data collection was obtained.
Results: Among 258 patients with AAA, 89 (34.5%) had underlying AID, including 77 (29.8%) with monogenic AID, seven (2.7%) with Adult-onset Still's disease, four (1.6%) with undifferentiated AID, and one (0.4%) with Castleman disease. Familial Mediterranean fever (FMF) was the most common monogenic AID, accounting for 64 cases (83.12%), which represents 8.8% of the entire AA amyloidosis cohort. Other underlying diseases included cryopyrin-associated periodic syndromes (CAPS) (n=4), tumour necrosis factor receptor-associated periodic syndrome (TRAPS) (n=3), mevalonate kinase deficiency (MVK) (n=3), deficiency of adenosine deaminase 2 (DADA2) (n=1), pyogenic arthritis, pyoderma gangrenosum, and acne (PAPA) (n=1), and suspected pyrin-associated autoinflammation with neutrophilic dermatosis (PAAND) (n=1). Consistent with other studies, our data indicate a slightly higher prevalence of men, with 57.1% of participants being male and 42.9% female. The ethnic origins were Mediterranean (36.36%), Caucasian (35.06%), North African (22.01%), Sub-Saharan African and Asian (each 3.9%), and other (1.3%). The median age at AAA diagnosis was 38 years. The median duration of symptomatic monogenic AID before AAA diagnosis was 29 years, and the median time between monogenic AID and AAA diagnosis was 0.5 years. In our cohort, 49.2% of patients were diagnosed with a monogenic AID either concomitantly or following the diagnosis of AAA (n=65). Among these, 21 patients were FMF, with 17 receiving the diagnosis concurrently and four after the diagnosis of AAA. Two patients with CAPS were diagnosed simultaneously with AA amyloidosis. Among three patients with TRAPS, two were diagnosed concurrently, while one was diagnosed 11 years after the AAA diagnosis. Each patient with MVK was diagnosed 2, 13, and 16 years after the AAA diagnosis, respectively. Patients with DADA2, PAPA, and suspected PAAND were diagnosed one year, eight years, and six years after the AAA diagnosis, respectively. Most of the patients with FMF-associated AA amyloidosis had homozygous MEFV variants, predominantly M694V, highlighting the need for regular follow-up and therapeutic education within this population. During the follow-up period, 25% of patients (n=44) died. Among them, 10 patients were diagnosed with FMF, all of whom were homozygous for the M694V mutation, while one patient was diagnosed with MVK. The median age of death was 58 years (39-80). The median time between kidney transplantation and death was seven years (0-16).
Conclusion: AA amyloidosis remains a serious and potentially fatal complication in patients with monogenic AIDs. Early diagnosis, careful monitoring, and targeted treatment strategies are essential for reducing the burden of this condition. While Familial Mediterranean Fever is the most recognized monogenic disease, further efforts are still needed to improve early diagnosis and enhance monitoring. The objective should not only be to control symptoms but also to prevent silent inflammation that can lead to irreversible organ damage.
Disclosure of Interest: None declared

Identifier: PO110

"BALANCING IL-1 BLOCKADE IN DIRA: A TALE OF REMISSION, FLARE, AND THERAPEUTIC PRECISION"

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Introduction: Deficiency of Interleukin-1 Receptor Antagonist (DIRA) is a rare, life-threatening autosomal recessive autoinflammatory disorder caused by mutations in the *IL1RN* gene. This mutation results in the loss of functional interleukin-1 receptor antagonist (IL-1Ra), leading to unregulated activity of interleukin-1 (IL-1). IL-1 is a pro-inflammatory cytokine with two isoforms, IL-1α and IL-1β, both of which signal through the IL-1 receptor to drive systemic inflammation. The clinical manifestations of DIRA include systemic inflammation, pustular skin lesions, osteomyelitis, and failure to thrive, often presenting in the neonatal period. Without timely diagnosis and appropriate treatment, DIRA can result in severe morbidity and mortality. The cornerstone of DIRA management is IL-1 blockade.

Objectives: To illustrate the critical role of comprehensive IL-1 blockade in achieving and maintaining remission in DIRA . This case highlights the differential efficacy of anakinra and canakinumab in managing DIRA, underscoring the importance of understanding cytokine-specific mechanisms in treatment selection.
Methods: We conducted a detailed case review of a patient with genetically confirmed DIRA. Clinical presentation, laboratory findings, genetic analysis, and response to treatment were assessed.
Results: A male infant born term to consanguineous parents developed chronic diarrhea and poor feeding within the first week of life. He had 10-14 large watery mucoid stools per day. At two months of age, he presented with intermittent fever and irritability upon handling. In addition, he developed generalized extensive pustules on erythematous scaly plaques all over his body. On examination, he was failing to thrive and displayed extensive well-demarcated pustular plaques, dystrophic nails, hair loss, and a scaly scalp. Laboratory investigations revealed severe anemia (Hb 6 g/dL), hypoalbuminemia (26 g/L), and elevated inflammatory markers (CRP 98 mg/L). Imaging revealed osteomyelitis in the left tibia and widening of ribs.

Despite supportive measures, including antibiotics, nutritional support, and skin care, the patient's symptoms persisted. Whole-exome sequencing identified a homozygous pathogenic variant in the *IL1RN* gene (c.364C>T, p.Gln122Ter), confirming the diagnosis of DIRA.

Treatment with anakinra (2 mg/kg/day subcutaneously) resulted in rapid improvement. Within five days, diarrhea resolved, skin lesions cleared, and irritability subsided. Laboratory markers normalized within two weeks, and the patient achieved sustained clinical remission with no recurrence of symptoms over five years of anakinra therapy. Growth and development were normal, and regular monintoring showed no systemic complications.

To improve quality of life by reducing the burden of daily injections, the patient was switched to canakinumab (4 mg/kg/month). Within three weeks, he developed high-grade fever, generalized pustular rash, severe abdominal pain, leukocytosis (WBC 21 ×109 /L) and elevated inflammatory markers CRP (275 mg/L), ESR (75 mm/hr) and ferritin (589 ng/mL). Infectious causes were ruled out, and the disease flare was attributed to inadequate IL-1α inhibition by canakinumab. The flare was managed with corticosteroids and a return to anakinra, which restored remission.

Conclusion: This case emphasizes the importance of comprehensive IL-1 blockade in managing DIRA. Anakinra's ability to inhibit both IL-1α and IL-1β with was critical for achieving long-term remission. In contrast, canakinumab's selective

inhibition of IL-1β proved insufficient, leading to a disease flare. These findings highlight the need to tailor therapy based on disease pathophysiology, particularly in conditions like DIRA, where both IL-1α and IL-1β contribute to inflammation.
Disclosure of Interest: None declared

Identifier: PO111

EVALUATION OF PULMONARY INVOLVEMENT IN COLCHICINE RESISTANT FMF PATIENTS

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Introduction: Familial Mediterranean Fever (FMF) is characterized by self-limited episodes of fever and polyserositis, accompanied by a significant acute phase response. Approximately 40% of pediatric FMF patients experience pleuritic episodes, which lead to symptoms such as chest pain, breathlessness, and cough. Colchicine remains the cornerstone of FMF management, effectively reducing the frequency and severity of attacks while preventing organ complications. However, 5–10% of patients are colchicine-resistant. A recent study in adults reported pulmonary findings in 68.7% of cases, with apical fibrosis being the most common feature. Although pediatric data on radiological pulmonary findings are lacking, it is essential to monitor children for pulmonary involvement.

Objectives: To determine the prevalence and characterize the pulmonary involvement in pediatric patients with colchicine-resistant FMF.

Methods: This cross-sectional study included 31 colchicine-resistant FMF patients and 31 age- and sex-matched healthy volunteers who had undergone chest computerized tomography (CT) for trauma. Pulmonary function was assessed using spirometry, and chest CT scans performed during disease progression were evaluated. Demographic data, including age, gender, age at diagnosis, genotype, and medication history, were recorded, along with information on atopic status, respiratory symptoms, tobacco exposure, and attack characteristics.

Results: A total of 31 colchicine-resistant FMF patients were evaluated, including 20 girls (64.5%) and 11 boys (35.5%). The median ages at symptom onset and diagnosis were 55 months (6–115) and 66 months (18–144), respectively. The most common MEFV mutation was M694V/M694V (74.2%), followed by M694V/M680I (16.1%). The median attack frequency was 5 per year (4–12), lasting a median of 3 days (1–5). Abdominal pain (96.8%), fever (90.3%), and arthralgia (87.1%) were the most common symptoms. Chest pain occurred in 71% of patients, but none had amyloidosis. The median age at pulmonary evaluation was 11 years (5–20), with a median colchicine treatment duration of 36 months (12–192). Respiratory complaints included shortness of breath in 5 patients (16.1%), a history of atopy in 3 (9.7%), asthma in 2 (6.5%), and pneumonia in 3 (9.7%). Pulmonary function tests showed normal results in 18 patients (58.1%), an obstructive pattern in 2 (6.5%), and a restrictive pattern in 5 (16.1%), while 6 (19.4%) were unable to cooperate. Chest CT findings were normal in 8 patients (25.8%) but abnormal in 23 (74.2%), compared to 11 in the control group (p=0.002). Nodules, all solid in nature, were more common in patients, predominantly peri-lymphatic and located near the pleura, fissures, and bronchovascular tree (Table 1).

Table 1. Comparison of patients and controls.

	Patient group (n=31)	**Control group (n=31)**	**p value**
Sex, (Girls/Boys)	20/11	18/13	0.602
Age, median (min-max), years	11 (5–20)	11 (5-19)	0.977
Normal, n (%)	8 (25.8)	20 (64.5)	0.002

Apical fibrosis, n (%)	0 (0)	0 (0)	NA
Peri-lymphatic nodule, n (%)	14 (45.7)	6 (19.3)	0.03
Atelectasis, n (%)	5 (16.1)	1 (3.2)	0.195
Parenchymal fibrotic changes, n (%)	2 (6.4)	0 (0)	0.492
Focal air trapping, n (%)	1 (3.2)	3 (9.7)	0.612
Pleural changes, n (%)	3 (9.7)	0 (0)	0.238
Emphysema, n (%)	1 (3.2)	0 (0)	0.312
Mediastinal lymphadenopathy, n (%)	1 (3.2)	1 (3.2)	1
Bronchectesia, n (%)	0 (0)	0 (0)	NA
Pneumothorax, n (%)	0 (0)	1 (3.2)	1
Fracture, n (%)	0 (0)	2 (6.4)	0.492
Pleural effusion, n (%)	1 (3.2)	0 (0)	1
Bronchitis changes, n (%)	2 (6.4)	0 (0)	0.492
Pericardial calcification, n (%)	1 (3.2)	0 (0)	1
Honeycomb appearance, n (%)	1 (3.2)	0 (0)	1

Conclusion: In this study, increased peri-lymphatic nodules were observed in FMF patients, and it is hypothesized that this may be related to previous pleuritic attacks.

Disclosure of Interest: None declared

Identifier: PO112

GLOBAL MORTALITY OF FRENCH PATIENTS WITH SYSTEMIC AUTOINFLAMMATORY DISEASES

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Introduction: Systemic autoinflammatory diseases (SAIDs) are diseases considered to be non-benign due to the comorbidities they can cause, and their impact on patient's quality of life. However, to date, there is no data on overall mortality or life expectancy for these patients.

Objectives: The objective of this study is to obtain comprehensive mortality data in patients with FMF, MKD, CAPS and TRAPS, to compare them with each other and to relate them to general mortality data in France by age group.

Methods: We used data of patients with FMF, CAPS, TRAPS and MKD, included in the French National Rare Disease Registry (BNDMR). Patient's data originated from rare disease centers that are members of the FAI2R network, after study approval by the BNDMR institutional review board. Inclusion criteria were affected patients with confirmed diagnosis and with data collected between 01/01/2010 and 12/31/2023; healthy carriers were excluded. Dates of death were those entered in BAMARA and enriched with national publicly individual death data (INSEE), with verification of their coherence.

Results: In total, 2887 patients were selected. After exclusion of patients whose diagnosis was not certain and those who refused the reuse of their data, 2043 patients were included for analyses: 66 with MKD, 212 with CAPS, 1669 with FMF and 96 with TRAPS. Respective prevalence for these SAIDS were evaluated in 2022 as 0.9 per million for MKD, 2.5 per million for CAPS, 20.9 per million for FMF and 1.3 per million for TRAPS. A total of 31 deaths was observed during the period of observation, in which, 19 were patients with FMF. The number of deaths observed in the FMF cohort (19) was greater than the number of deaths expected according to INSEE life expectancy tables in France in a population of the same age and sex and followed over the same period, with 11 expected deaths. The number of observed deaths was below 10 in the three other cohorts.

Conclusion: It is the first study of mortality in rare SAIDs in France. It is a powerful study since it is based on a large database: the BNDMR cohort. However, it is exposed to some limitations, notably limited patients' follow-up and the small sample size).

The mortality rate in patients with FMF is high compared to other cohorts and data from the French general population. An in-depth analysis of the causes of these deaths could perhaps make it possible to better prevent them.

Disclosure of Interest: None declared

Identifier: PO113

BURDEN OF FATIGUE IN CRYOPYRIN-ASSOCIATED PERIODIC SYNDROMES (CAPS)

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Introduction: Cryopyrin-Associated Periodic Syndromes (CAPS) are rare hereditary autoinflammatory disorders caused by *NLRP3* gene mutations, leading to systemic inflammation with symptoms like fever, rash, arthralgia, and severe fatigue. While IL-1 inhibitors control inflammation, fatigue often persists, highlighting the need for further research to uncover its mechanisms and develop targeted treatments.
Objectives: To determine the burden of fatigue in cryopyrin associated periodic syndromes (CAPS), assess the relationship of fatigue with disease activity and explore factors associated with chronic fatigue in autoinflammation
Methods: A single-centre study of consecutive children and adults with CAPS followed between 2007 and 2024 was performed. Data including demographics, clinical features, inflammatory markers, treatment, disease activity, and fatigue scores were prospectively captured. The relationship of disease activity, treatment and fatigue scores was analysed. Putative predictors of chronic fatigue were tested.
Results: A total of 108 CAPS patients were included; 53 were female (49%). Median age at diagnosis was 11 years (range 0-73); median follow-up duration 7 years (range 1-18). Moderate CAPS was the most common phenotype (86%). At the time of diagnosis, hearing loss was present in 30%, aseptic meningitis in 6%. At enrolment, fatigue was the most common symptom, affecting 100 patients (93%), with a median fatigue score of 7 (0-10, VAS); high disease activity was present in 67%. At the last visit, fatigue remained prevalent, reported in 83 (77%), with a median score of 3 (range 0-10). Importantly, only 4% of patients had high disease activity, while 83% had inactive disease. Factors such as age at diagnosis, *NLRP3* mutation, disease activity, familial CAPS, and the COVID-19 pandemic influenced chronic fatigue in CAPS patients.
Conclusion: Fatigue remains a prominent problem in autoinflammatory diseases; even while disease activity is effectively controlled. Translational research is needed to uncover the underlying mechanisms and develop effective interventions for fatigue autoinflammation.
Disclosure of Interest: None declared

Identifier: PO114

TYPE I INTERFERON SCORE AS A BIOMARKER OF DISEASE ACTIVITY IN ADA2 DEFICIENCY

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Introduction: Deficiency of adenosine deaminase 2 (DADA2) is a rare systemic autoinflammatory disease with autosomal recessive inheritance caused by biallelic loss of function mutations in the ADA2 gene. The phenotypic spectrum of the disease is broad, including fever, early-onset vasculitis, stroke, immunologic and hematologic dysfunction. If not recognized and treated the disease can cause mortality and serious long-term sequelae. Although the exact mechanism involved in the pathogenesis of the disease is still unclear, in patients with DADA2 an increased type I IFN score (IS), correlated with disease activity and response to treatment, has been demonstrated. Recently an activity and damage score (DADA2AI and DADA2DI) have been developed[1] to aid in the longitudinal assessment of these patients, inter- and intra-patients comparisons and in the evaluation of long term outcome with different therapies

Objectives: To apply the recently published DADA2AI and DADA2DI in a bicentric cohort of DADA2 patients and to evaluate whether longitudinal follow-up of type I IS reflects disease activity and could potentially be used as a biomarker of the disease

Methods: ADA2 enzymatic activity was measured in a colorimetric assay adapted from Giusti et al (1974). An HEK293T overexpression system was setup to evaluate the impact of suspected pathogenic ADA2 variants on protein expression/secretion and enzymatic activity. Real time PCR assays were performed on whole blood cells, the expression levels of 6 interferon-induced genes was evaluated and the IS was calculated. DADA2AI was calculated based on criteria described by Bucciol et al.

Results: 14 patients from 11 families were included. All patients carried 2 pathogenic ADA2 variants and showed reduced serum ADA2 activity. Twelve patients presented with an inflammatory vasculitis phenotype while 2 had an haematological phenotype. One patient showed hypogammaglobilinemia. The enzymatic activity of ADA2 variants in an HEK2937 overexpression system correlated with residual enzymatic activity measured in patient serum samples. Longitudinal measurement of type I IS was performed in all patients in combination with assessment of DADA2 activity index. In our cohort, IS score was only slightly elevated in the majority of patients (median value of 4.055 versus normal IS<2.05) and did not correlate with DADA2AI or with routine laboratory parameters. In particular the IS did not normalize during TNF-I treatment. The DADA2DI remained stable or decreased in all patients with the inflammatory vasculitis phenotype treated with TNF-inhibitor, thus confirming the efficacy of this treatment in preventing new damage/sequelae

Conclusion: The DADA2AI and DADA2DI can be easily calculated from the patients charts and are valid and reproducible instruments to monitor patient's disease activity and response to treatment. The pathogenic mechanism in DADA2 is not entirely understood: type I IFN pathway activation is probably part of a much more complex mechanism and does not appear to be TNF-dependent. In our cohort, the 6gene type I IFN score did not prove to be a good biomarker for longitudinal follow-up of DADA2 disease activity and response to treatment

1 Bucciol et al, J. Clin Immunol. 2023; 2 Rice et al J. Clin Immunol. 2017

Fundings: IM, MW, are supported by grant G0B5120N from Research Foundation Flanders, and grant 948959 from the European Research Council under the European Union's Horizon 2020 research and innovation program.

Disclosure of Interest: None declared

Identifier: PO115

CLINICAL PHENOTYPE AND LABORATORY MARKERS IN PATIENTS AFFECTED BY A20 HAPLOINSUFFICIENCY (HA20): A CASE SERIES FROM TWO ITALIAN CENTERS

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Introduction: HA20 is a monogenic disease caused by heterozygous mutations in *TNFAIP3* which encodes A20, a negative regulator of inflammation.A20 reduced expression is associated with a wide range of clinical autoinflammatory and autoimmune phenotypes. Despite the increasing number of patients described no clear genotype-phenotype correlation has been found, and no laboratory markers of the disease have been defined thus far(1).Various neurobehavioral manifestations have been reported in murine models carrying *TNFAIP3* variants, but data on their prevalence in vivo are scarce(2).

Objectives: To describe a cohort of patients with HA20 from 2 centers evaluating the different clinical presentations and their variability with patients' age;to assess the prevalence of neuropsychiatric symptoms;to examine possible associations between the clinical phenotype and the inflammatory profile, including Interferon(IFN)γ-inducible chemokines (CXCL9/10) values and IFN signature (IS).

Methods: Clinical data of 17 Caucasian subjects from 6 families with heterozygous LOS mutation in *TNFAIP3* were collected (ACMG class 4-5). Symptoms included recurrent fever, oral and genital ulcers, skin lesions, musculoskeletal, gastrointestinal involvement, and neuropsychiatric manifestations; also the treatment received were collected. Circulating levels of CXCL9/10 and IS were measured at the onset and during disease course. IS>2 was considered positive.Categorical variables were expressed as medians and IQR, median ages of symptoms onset were compared through Kruskal-Wallis test and groups were compared using R function Wilcoxon test.

Results: 16 subjects carried mutations resulting in stop codon (*H577A, R138X, M476P, K759Q, Q379X*), one had a missense variants(*T647P*) resulting in NF-kB increased expression(3). Patients' clinical features were as follows: 88% oral aphtosis;59% recurrent fever;53% gastrointestinal inflammation; 53% autoimmunity;47% genital ulcers;41% neuropsychiatric symptoms;41% arthralgia;18% arthritis/tenosynovitis; 18% skin inflammation. Neuropsychiatric symptoms included mood disorders (3), anxiety (2), ADHD (2), pica (1) diagnosed according to Diagnostic and Statistical Manual of Mental Disorders (DSM-5). Patients with clinical onset <5 yrs presented more frequently neuropsychiatric involvement during lifetime (p=0.03).The median ages of the specific symptom onset were significantly different, with oral aphtosis and recurrent fever manifesting at younger age, while arthritis/tenosynovitis manifesting at later age (p<0.001, Kruskal Wallis test, table 1). Positive IS tended to be more prevalent in subjects with oral aphtosis (p=0.01). No other correlations were found between CXCL9/10 and IS values and the type of variant, clinical phenotype, disease activity or the ongoing therapy.

Table 1. Median ages (IQR) of the single symptom onset (yrs), Kruskal Wallis test for independent samples (p < 0.001).

	Median (Q1-Q3)
Overall (any symptom)	5 (3-6)

Oral aphtosis	5 (4.5-6)
Recurrent fever	5 (2.5-6)
Genital ulcers	5.5 (3.8-7.8)
GI involvement	9 (9-14)
Neuropsychiatric symptoms	11 (8-12.5)
Skin involvement	11.5 (10.8-12.3)
Arthritis/tenosynovitis	19 (14-22)

Conclusion: Clinical heterogeneity was evident among patients, even within the same variant. Neuropsychiatric symptoms have been observed in several subjects of the cohort and earlier disease onset has been associated to a higher prevalence of neuropsychiatric manifestations during lifetime. Also, specific symptoms appear to be more common within particular age ranges showing a recurring pattern of clinical presentations at specific stages of life. Finally, CXCL9-10 and IS cannot be used as reliable biomarkers of disease activity or response to treatment.

References

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Disclosure of Interest: None declared

Identifier: PO116

GENETICS, CLINICAL CHARACTERISTICS, AND MANAGEMENT OF FAMILIAL MEDITERRANEAN FEVER IN DIVERSE POPULATIONS: A COMPARATIVE STUDY OF BARI AND ISTANBUL

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Introduction: Familial Mediterranean Fever (FMF) is linked with the MEFV gene and is the most common among monogenic autoinflammatory diseases, with high prevalence in the Mediterranean basin. Genetic spectrum significantly impacts clinical presentation and varies between geographically isolated and cosmopolitan populations.
Objectives: To compare the clinical manifestation and genetic profile among 1286 FMF patients from two well-characterized FMF cohorts living in Italy (Apulia) and Turkiye.
Methods: One hundred sixty-five Italian patients (age 38.5±1.6 years, females 54.5%) and 1121 Turkish patients (age 40.4±0.3 years, females 62.5%) followed at referral centers (University of Bari "Aldo Moro" Department of Internal Medicine and Cerrahpasa Medical Faculty, Division of Rheumatology) were interviewed for demographic, clinical, and genetic features. Continuous data were expressed as mean ± standard error of the mean, and categorical data as numbers and percentages.
Results: The age at FMF diagnosis was comparable between cohorts (29.4±1.6 years in Italians and 25.0±0.4 years in Turkish patients, p=0.05), with a diagnostic delay of more than 5 years in 39.4% of Italians and 46.2% of Turkish patients (p=0.1). Italian patients had a higher prevalence of fever (91.5% vs. 83.7%; p=0.009), and a lower prevalence of abdominal pain (60.0% vs. 91.3%, p<0.001) and thoracic pain (20.6% vs. 35.4% p<0.001) compared to Turkish patients. The mean annual frequency of attacks without treatment was lower in Italian than in Turkish patients (12.4±0.8 vs. 19.9±0.6; p<0.001). The mean daily dose of colchicine was significantly higher in Turkish patients compared to the Italian cohort (0.45±0.04 vs. 1.25±0.01, p<0.001). The use of anti-IL-1 was more prevalent in the Turkish cohort (7.0%) compared to Italian patients (3.2%, p<0.001). E148Q/R761H mutations were identified in 41 patients (26.1%) of the Italian cohort, whereas no such mutations were observed in the Turkish cohort (p<0.001). In contrast, the homozygous M694V mutation was absent in the Italian cohort and significantly prevalent among Turkish patients (18.8%, p<0.001). Overall, homozygous mutations were less prevalent in the Italian cohort (7.6%), compared to 27.5% in Turkish patients (p<0.001). Conversely, heterozygous mutations were more common in Italian patients than in Turkish patients (43.9% vs. 28.0%, p<0.001). Details of genetic comparison are presented in Table 1.

Table 1. ***MEFV gene mutations***

Classification of mutation, N. (%)	Italy	Turkiye	**p-value**
Pathogenic	30 (19.1%)	938 (84.9%)	**<0.001**
Likely-pathogenic	50 (31.8%)	64 (5.8%)	**<0.001**
Variant of uncertain significance	88 (56.1%)	171 (15.5%)	**<0.001**

Variants, N. (%)			
A744S	10 (6.4%)	11 (1.0%)	**<0.001**
E148Q	56 (35.7%)	138 (12.5%)	**<0.001**
M680I	8 (5.1%)	234 (21.2%)	**<0.001**
M694V	15 (9.6%)	741 (67.1%)	**<0.001**
R202Q	56 (35.7%)	255 (23.1%)	**<0.001**

Conclusion: The more severe disease course observed in the Turkish patients' cohort could be influenced by epidemiological differences, whereas the higher prevalence of rare mutations in the Italian cohort underscores the impact of genetic homogeneity of a relatively isolated population. These findings highlight the importance of sociocultural and historical factors in shaping FMF genotypes and their influence on clinical presentation and disease progression.

Disclosure of Interest: None declared

Identifier: PO117

DIAGNOSTIC DELAY IN SYSTEMIC AUTOINFLAMMATORY DISEASE: PRELIMINARY RESULTS FROM THE EUROFEVER REGISTRY

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Introduction: Systemic Autoinflammatory Diseases (SAIDs) are an umbrella term that consists of monogenic and polygenic or multifactorial origin disorders. These are rare diseases with the estimated prevalence lowest as 1-3/ 1,000,000. Most of the SAIDs have an early disease onset, so that many patients present in childhood or adolescence. These complex patients often see many medical practitioners over time, resulting in fragmented care, emergency room visits and hospitalizations leading to diagnostic delays. Even though the early diagnosis is essential to prevent mortality and life-long complications, the rarity of the SAIDs and the variety of clinical spectrum limit the understanding of potential diagnosis for health-care professionals.

Objectives: we aimed to identify and evaluate possible factors related with diagnostic delay in selected SAIDs from the Eurofever database.

Methods: The most common monogenic SAIDs, including Familial Mediterranean Fever (FMF), cryopyrin-associated periodic syndromes (CAPS), Tumor Necrosis Factor Receptor-Associated Periodic Syndrome (TRAPS) and Mevalonate Kinase Deficiency (MKD), were selected for this study. Data on diagnostic delay is retrieved from the Eurofever database and defined as the time between symptom onset and diagnosis. Ages at disease onset and years of diagnostic delay were reported as median and interquartile range. Mann Whitney U and Kruskal Wallis tests were used to compare groups where appropriate.

Results: In total, 2249 patients (1519, FMF; 271, TRAPS; 254, CAPS; 205, MKD) from 32 countries were included in the study. 51.9% (n=1168) were male and 64.4% were Caucasian-European (n=1448). The median age at disease onset was 3.1[IQR 1-7.8] overall and, 3.6 [IQR 1.6-8] for FMF, 4.4 [IQR 1-13.4] for TRAPS, 1.2 [IQR 0-6.1] for CAPS and 0 [IQR 0-2.6] for MKD. The median age at diagnosis was 8 [IQR 4.1-16.5] overall and, 7 [IQR 4-13.2] for FMF, 16.1 [IQR 6.2-38.4] for TRAPS, 12.3 [IQR 4.3-30.5] for CAPS and 7.4 [IQR 3.7-15.2] for MKD. The median diagnostic delay in years was 2.9 [IQR 1-8.3] overall and, 2.3 [IQR 0-5.7] for FMF, 5.8 [IQR 1.4-21] for TRAPS, 5.8 [IQR 2-20] for CAPS and 5 [IQR 1.6-14.2] for MKD. Frequency of having at least one concomitant disease was 17.7% (n=399) and 14.9% (n=334) had at least one complication. Diagnostic delay was shorter in patients with FMF compared to others ($p<0.001$). There was no statistically significant difference in diagnostic delay between males and females (2.9 [IQR 1-8.2] and 3 [IQR 1-8.7] years, respectively, $p=0.82$). However, diagnostic delay was significantly higher in patients with at least one concomitant disease (4.2 [IQR 1.4-10.2] vs 2.7 [IQR 1-7.9] years, $p<0.001$) and patients with at least one complication (8.2 [IQR 2.4-24.2] vs 2.6 [IQR 1-6.5] years, $p<0.001$).

Conclusion: FMF patients have a shorter diagnostic delay compared to other SAIDs, which could be explained by the familiarity of the disease. Patients with concomitant disease and complications have longer diagnostic delay compared to others. One possible explanation could be that having concomitant diseases may confound physician's decision process. The next step of the project is to create a subset of patients fulfilling the Eurofever classification criteria and further identify and evaluate possible individual-, disease-, and country-level factors associated with diagnostic delay.

Disclosure of Interest: None declared

Identifier: PO118

ATTACK TRIGGERS IN CHILDHOOD FAMILIAL MEDITERRANEAN FEVER

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Introduction: Familial Mediterranean Fever (FMF) is the most common monogenic autoinflammatory disorder. Data regarding the triggers of this rare disease are scarce.

Objectives: The primary aim of our study was to analyze the demographic data, clinical findings, attack triggering, and relieving factors in pediatric patients with FMF with exon 10 *MEFV* mutations. We also aimed to determine whether there was a difference in the triggering and relieving factors between heterozygous, compound heterozygous, and homozygous patients. Our secondary objective was to compare *M694V* homozygous patients with the most severe phenotype with other 10th exon mutations.

Methods: Patients were diagnosed with FMF according to Eurofever/PRINTO clinical classification criteria. Patients with heterozygous, homozygous, and compound heterozygous mutations in the 10th exon of *the Mediterranean fever gene (MEFV)* were included in the study. Patients with less than six months of follow-up duration were excluded. Patients were interviewed about attack triggers face-to-face between February and May 2024, and other patient information was retrospectively obtained from their medical records.

Results: This study included 266 patients (Female: n=141, 53 %). The median age at diagnosis was 60 (6-198) months, and the median age at symptom onset was 48 (1-186) months. Heterozygous mutations were found in 46.6% (n=124) of the patients, homozygous in 30.8 % (n = 82), and compound heterozygous in 22.6 % (n = 60). More than two-thirds of our patients (n=184, 69.2%) had a family history of FMF and 80 patients (30.1%) had consanguineous marriages. A total of 39 patients (14.7%) resided in a city beyond our center, necessitating journeys ranging from 3 to 20 hours for medical consultations. The majority of patients (n=246, 92.5%) reported having fewer than 12 attacks per year. The most common presenting symptom was abdominal pain during the attacks (n=179; 67.3%). Attack triggers were identified in 189 patients (71.1%), and the most common was fatigue (n=141; 53%). The others were as follow: prolonged standing (37.6%), emotional stress (35.7%), cold exposure (32.3%), insomnia (27.8%), high-fat food consumption (12%), exercise (11.7%), long-term travel (10.2%), starvation (9%), menstruation (4.5%), sunlight exposure (4.1%), and physical trauma (1.9%) respectively. In total, 180 patients (67.7%) had attack relievers, and the most common one was the use of nonsteroidal anti-inflammatory drugs (n=152, 57.1%). The others were sleep (38.3%), fluid intake (29.7%), massage (23.7%), hot water compress (23.3%), warm showers (17.7%), fat-free diets (6.4%), and sweet food consumption (4.1%). Biologic agents were required in 13 (4.9 %) patients. Patients with compound heterozygous and homozygous mutations were more likely to benefit from attack-relieving factors (p=0.013). Attack triggers (p=0.023) were more common in patients receiving biological agents. Long-term travel was found to be a significantly more common trigger for attacks with arthritis/arthralgia (p=0.036) and erysipelas-like erythema (p=0.003). While NSAIDs was significantly more common (p=0.043), fat-free diet was significantly less common (p=0.047) attack relievers in children with *M694V* homozygote mutation.

Conclusion: This is the first study focused on attack triggers in childhood FMF. Although our study present unique findings, our data based on patient/parent statements. Therefore, our results need to be supported by clinical and laboratory evidence.

Acknowledgments: None

Disclosure of Interest: None declared

Identifier: PO119

IFIH1 GENE MUTATION AS A CAUSE OF SEVERE HYPERINFLAMMATION – CASE REPORT

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Introduction: Aicardi-Goutieres syndrome (AGS) belongs to the spectrum of rare primary immunodeficiencies, i.e. congenital immune disorders, which, depending on the type of genetic mutation, represent a heterogeneous group of diseases manifested by involvement of the central nervous system (CNS), immune system and skin. Aicardi-Goutieres syndrome-7 (AGS7) is an autosomal dominant autoinflammatory disease, characterized by severe neurological damage. The disease manifests itself in early childhood with delayed psychomotor development, axial hypotonia and spasticity. Typical is the MRI finding of calcifications present in the area of the basal ganglia, cerebral atrophy and white matter abnormalities.

Objectives: The authors present a case report of a 7-month-old infant, initially hospitalized for severe intracerebral haemorrhage during SARS-CoV-2 infection, followed by the development of a hyperinflammatory state of Multisystem inflammatory syndrome in children (MIS-C). Despite combined immunosuppressive therapy, the patient continues to have a febrile condition accompanied by worsening neurological findings in terms of quadruparesis progression, bulbar syndrome and dystonias. The dominant clinical and laboratory finding is hyperinflammation (expressed by the elevation of CRP, serum amyloid A, ferritin…), which after excluding infectious, metabolic and paraneoplastic causes, leads to the indication of genetic testing focused on autoinflammatory diseases with confirmation of the IFIH1 gene mutation: NM_022168.4 c.1806A>Tp.E602D. Mutation in this gene is typical for Aicardi-Goutieres syndrome type 7 (AGS7).

Methods: Case report

Results: Based on the international EULAR/ACR recommendations for the treatment of diseases from the type I interferonopathy spectrum, the patient was treated with a non-selective Janus kinase inhibitor (JAKi) – baricitinib (dose 4 mg/kg/ per day), with a significant effect especially on the neurological condition and thus improving the patient's quality of life.

Conclusion: Despite the severity of the disease, early confirmation of the diagnosis and targeted treatment leads to an improvement in neurological symptomatology and the management of often fatal hyperinflammation.

Disclosure of Interest: None declared

Identifier: PO120

THE ROLE OF DEMOGRAPHICS IN THE NATURE OF FAMILIAL MEDITERRANEAN FEVER AND ITS OUTCOMES: A COMPARATIVE INTERNATIONAL STUDY

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Introduction: Existing research on Familial Mediterranean fever (FMF) suggest that patients in North America are more treatment responsive and get less complicated, specifically with amyloidosis compared to patients in Middle Eastern countries, due to unclear reasons.

Objectives: The aim of this study was to describe the clinical and genetic characteristics of two cohorts, from Los Angeles in the US and Israel, and to evaluate for differences in disease presentation, disease severity, and treatment response.

Methods: Medical records of pediatric patients who were diagnosed with FMF and routinely being followed in the 2 tertiary rheumatology centers experienced in autoinflammatory diseases, were analyzed retrospectively. Measurement tools were recorded from at least three time points: time of diagnosis prior to any treatment, one year after diagnosis and at the last charted visit.

Results: The Israel and US cohorts consisted of 36 and 63 patients. The Israeli cohort consists of various ancestries, mostly Morocco (44%) and Iraq (33%); whereas more than 75% of the US cohort are from Armenian ancestry. The clinical characteristics in Israel vs. the US were similar, with fever being the most common (80% vs. 90%, p=0.16), followed by abdominal pain (83% vs. 79%, p=0.63), followed by joint pain (56% vs. 59%, p=0.76). Age of symptom onset was significantly younger in the Israeli cohort (6.2 months vs. 35 months, p<0.001), despite a similar percentage of patients homozygous to MEFV mutations (11% vs. 17%, p=0.7) and positive family history (53% vs. 49%, p=0.9). Time from symptom onset to diagnosis (2.3 ±6.9 vs. 27±53 months, p<0.001) and to colchicine initiation (2.3 ±2.3 vs. 28.9±28.2 months, p<0.001) were significantly shorter as well in Israel compared to the US.

The mean follow-up duration was 33.4 months (SD± 30.3) in Israel and 53.7 months (SD± 34.3) in the US. The attack frequency declined over time in both cohorts from diagnosis to the last charted follow-up, from an average of 12.3/year to 3.3/year for Israel and 16.2/year to ~1/year for the US. At the last visit recorded, none of the patients in either cohort demonstrated kidney injury. However, seven (11.1%) US patients and one (3.3%) Israeli patient presented with new, mild, proteinuria (p= 0.14). Of the proteinuric patients in the US cohort, three are homozygous M694V mutation, 3 are compound heterozygous MEFV mutations, and 1 is heterozygous to the M694V mutation. 6 started colchicine within 21.5 months of symptoms onset on average, similar to the rest of the cohort without renal involvement. The Israeli child with proteinuria is homozygous M694V mutation and was never treated with colchicine.

Conclusion: The US and Israel cohorts had similar clinical presentations despite the differences in their ethnic distribution. Attack frequency at the time of presentation was similar in both cohorts but the Israeli children had an earlier age of symptom onset. In Israel, the time from symptom onset to diagnosis and treatment initiation was shorter, possibly due to the high prevalence of FMF with increased awareness or/and access to pediatric rheumatology. Despite delays in diagnosis and treatment in the US cohort, the US children seemed to have favorable outcomes. Studies with a longer follow-up are needed to determine renal outcomes.

Disclosure of Interest: None declared

Identifier: PO122

NEUROLOGICAL MANIFESTATIONS AND VASCULOPATHY IN PLCG2–ASSOCIATED ANTIBODY DEFICIENCY AND IMMUNE DYSREGULATION (APLAID): REPORT OF TWO CASES

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Introduction: Autosomal dominant pathogenic variants in the *PLCG2* gene, and particularly gain-of-function (GOF) variants, are associated with autoinflammation and *PLCG2*–associated antibody deficiency and immune dysregulation (APLAID), characterized by immunological abnormalities and multi-systemic inflammation. Descriptions of associated neurological manifestations and vascular anomalies in the literature are limited.

Objectives: We describe two patients with APLAID and a variety of vasculopathies and, most strikingly, neuroinflammation and cerebral vascular tortuosity.

Methods: Chart reviews

Results: The first patient is a three-year-old girl with arterial and venous thrombosis, colitis, multiple respiratory tract infections, and diffuse subcutaneous granulomatous masses starting in infancy. She had low immunoglobulin (Ig) levels and low numbers of B and natural killer (NK) cells. Whole exome sequencing (WES) found a *de novo* variant in *PLCG2* (c.3420T>A; p.Asp1140Glu), suspected to confer GOF activity. Canakinumab and subcutaneous Ig (SCIg) were initiated with limited benefit. At 20 months, she was evaluated for focal seizures and magnetic resonance imaging (MRI) of the brain revealed right parietal leptomeningeal enhancement with patchy, mostly periventricular white matter changes, and decreased cortical perfusion of the left frontal lobe. MR angiography (MRA) showed arterial tortuosity of the anterior and posterior circulation with focal stenosis but without evidence of vasculitis or acute ischemia. Oxcarbazepine was added, and follow-up revealed resolution of seizures as well as improved leptomeningeal enhancement. Vascular imaging has been stable. She has now been diagnosed with extensive veno-lymphatic malformation, abnormal renal vasculature, absent Inferior Vena Cava (IVC), and bilateral pulmonary vein stenosis (PVS). She has been treated with obinutuzumab, imatinib mesylate, aspirin, enoxaparin, canakinumab, SCIG, oxcarbazepine and then levetiracetam, sirolimus, and azithromycin. She is undergoing hematopoietic stem cell transplantation (HSCT).

The second patient is a five-year-old boy with episodes of respiratory infections, failure to thrive, colitis, and recurrent peri-anal fistulas since infancy. He later developed skin lesions consistent with neutrophilic dermatosis/pyoderma gangrenosum. He also had low Ig levels and low numbers of B and NK cells. WES found a *de novo* variant in *PLCG2* (c.2122G>C, p.Ala708Pro), previously shown to confer GOF activity. He was being treated with canakinumab, SCIG, prednisolone, tacrolimus, and infliximab when, at four years, he had an episode of status epilepticus. Right parietal infarct was found on MRI with surrounding leptomeningeal enhancement and MRA showed proximal narrowing and distal dilation of the right middle cerebral artery (MCA), arterial tortuosity, and wide-necked carotid cave aneurysms. He was treated with levetiracetam and oral corticosteroids without further seizures or strokes, although leptomeningeal enhancement recurred during prednisolone wean requiring higher doses. Vascular imaging has remained stable. Subsequent echocardiography reported dilated aortic root and ascending aorta. He is planned for HSCT.

Conclusion: The exact etiology of the stroke and seizures in our patients is unclear, but neuroinflammation, vasculopathy leading to perfusion deficits, or thrombosis due to underlying thrombotic diathesis or abnormal vascular anatomy all may have been contributing factors. The co-occurrence of cerebral vascular tortuosity and other systemic vascular abnormalities supports underlying contributions of PLCG2 to vasculature beyond immune dysregulation. We recommend all patients diagnosed with APLAID undergo close monitoring for neurologic manifestations, with brain and vessel imaging included as a key component in their evaluations, even in the absence of overt neurologic signs.

Disclosure of Interest: K. Asna Ashari: None declared, R. MacRae: None declared, M. Ashoor: None declared, D. Hoytema: None declared, C. Platt: None declared, P. See Consultant for: NeuroBionics, Bionaut, KanekaHospital, Harvard Medical School, A. Kielian: None declared, A. Danehy: None declared, R. Kumar: None declared, M. Gorman: None declared, F. Dedeoglu Conflict with: Royalties for chapter review: UptoDate, Honorarium for a symposium talk: Sobi, M. Andzelm: None declared

Identifier: PO123

GENOTYPE-PHENOTYPE CORRELATIONS IN CRYOPYRIN-ASSOCIATED PERIODIC SYNDROME AMONG TURKISH PATIENTS IN GERMANY AND TURKEY: BEYOND BORDERS

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Introduction: The multifactorial nature of CAPS indicates that mutations in the *CAPS* gene alone are inadequate to account for the observed phenotypic variability and the differences in disease progression, underscoring the potential contributions of environmental and other factors.
Objectives: To compare the phenotypic and genotypic features of pediatric Turkish-origin CAPS patients residing in Turkey and Germany, and to assess the influence of regional differences.
Methods: A multicenter, longitudinal study was conducted from January to July 2024. Turkish-origin pediatric CAPS patients residing in Germany (German cohort) and Turkey (Turkish cohort) who met CAPS classification and/or diagnostic criteria were included. Data were collected on demographics, genotypes, clinical symptoms, and treatment regimens. Disease activity was measured using the Physician's Global Assessment (PGA), Patient/Parent's Global Assessment (PPGA), and the Autoinflammatory Disease Activity Index (AIDAI).
Results: The study included 51 patients, 23 in Turkey and 28 in Germany, with a median age of 13 years and a median disease onset at one year. Initial treatment included colchicine (72%), canakinumab (14%), and anakinra (14%).

Turkish vs. German Cohorts: Among the German cohort, 97% had VUS, all of which were the Q703K mutation, while 57% of the Turkish cohort had VUS (p=0.009), with the most common mutations being Q703K (26%) and V198M (17%). Pathogenic mutations were more frequent in the Turkish cohort (30% vs. 3.6%, p=0.009). Moderate CAPS (MWS) and severe CINCA/NOMID were more common in the Turkish cohort, while FCAS was unique to the German cohort (25%). Diagnostic delay (p=0.004), attack duration (p<0.001), and initial CRP levels (p<0.001) as well as PGA(p=0.001) and PPGA (p=0.046) were higher in the Turkish cohort. Clinical symptoms such as urticarial rash (p=0.007), fatigue (p=0.024), and fever (p=0.018) were more frequent in the Turkish cohort, while diarrhea was more common in the German cohort (p=0.011). Attack triggers differed, with infections being prominent in the German cohort (p<0.001) and cold/seasonality more frequent in the Turkish cohort (p=0.017). At the last visit, 57% of the German cohort were untreated, compared to none in the Turkish cohort (p<0.001). Canakinumab use was higher in the Turkish cohort (78%), while colchicine use was more common in the German cohort (28%). In the 65% of the Turkish and German cohorts, 65% and 46%, respectively, achieved complete remission with therapy (p<0.001). Complete remission without therapy was observed in 53% of the German cohort but was absent in the Turkish cohort.
Turkish vs. German Cohorts of the 39 Patients with VUS Mutations:
Among 39 patients with VUS, the Turkish cohort (n=12) had a significantly older age at diagnosis (7.5 years vs. 3 years, p=0.011) and a longer diagnostic delay (4 years vs. 1 year, p=0.002). All Turkish cohort patients had moderate MWS, while 25% of the German cohort had mild FCAS (p=0.016). The Turkish cohort had longer attack durations (5 vs. 3 days, p=0.006), higher PGA (8 vs. 6, p=0.016), and higher CRP (5.2 mg/dl vs. 2.9 mg/dl, p=0.002). None of the Turkish patients remained untreated, while 59% of the German cohort did (p<0.001). The Turkish cohort had higher canakinumab (75% vs. 8%) and anakinra (15% vs. 3%) use. At the last visit, 55% of the German cohort achieved remission without treatment, but none in the Turkish cohort. However, 75% of the Turkish cohort achieved remission with therapy, compared to 44% in the German cohort.

Conclusion: Regional differences seem to impact CAPS by influencing both the phenotypic and genotypic characteristics, potentially leading to variations in the disease course and treatment approaches.

Disclosure of Interest: None declared

Identifier: PO124

EVERYDAY LIFE OF PATIENTS WITH AUTOINFLAMMATORY PERIODIC FEVER SYNDROMES DURING LONG-TERM TREATMENT WITH CANAKINUMAB – 5-YEAR DATA FROM THE RELIANCE NON-INTERVENTIONAL STUDY

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Introduction: Autoinflammatory periodic fever syndromes (PFS) significantly impair quality of life (QoL) and everyday life. Treatment with the interleukin-1β inhibitor canakinumab (CAN) has been shown to be safe and effective in clinical trials and in practice.

Objectives: In the present study, the QoL and everyday life of patients with cryopyrin-associated periodic syndromes (CAPS), familial Mediterranean fever (FMF), hyper-IgD syndrome/mevalonate kinase deficiency

Methods: RELIANCE is a prospective, non-interventional observational study in Germany enrolling pediatric (age ≥2 years) and adult patients with a clinically confirmed diagnosis of PFS, who routinely receive CAN. Quality of life, effectiveness and safety parameters were recorded at baseline and assessed at 6-month intervals.

Results: Data from N=268 patients with autoinflammatory periodic fever syndromes enrolled in the RELIANCE non-interventional study between September 2017 and June 2023 were included in the present interim analysis. Median age of the total study cohort was 19.5 years (2−80 years [45.1% < 18 years]; N=137 female patients [51.5%]) and median duration of CAN treatment before study entry was 2 years (0−15 years).

At baseline, patients had a median number of days with absence from school/work during the last 6 months of 6.0 days (min.1.0; max. 184.0). At month 30 and month 60, the median number of days absent from school/work was 4.0 (min. 1.0; max. 60.0) and 10.5 (min. 1.0; max. 103.0) days, respectively (**Table 1**). The median number of 10.5 days of absence from school/work at month 60 should be viewed with caution, as only data from n=8 patients were available for month

60 visit. 47.9% (n=127) of baseline visits took place in or before the year 2019 and thus before the COVID-19 pandemic, which began in 2020. In comparison, with 85.8% (n=103) the majority of month 30 visits were carried out during the COVID-19 pandemic in the years 2020 to 2022, whereas 52.9% (n=9) of month 60 visits took place after the pandemic in 2023 (**Table 1**).

The number of physician visits due to study indication since the last visit remained consistent throughout the study. Patients had a median physician visit of 3.0 (min. 0.0; max. 15.0) at baseline, 1.0 (min. 0.0; max. 41.0) at month 30 and 3.0 (min. 1.0; max. 10.0) at month 60. At the median, there were no physician visits attributable to adverse drug reactions at baseline, month 30 and month 60 (**Table 1**).

Table 1: Overview of days absent from school/work and physician visits in the RELIANCE study across all study indications (N=268 patients).

	Baseline (n=265)*	Month 30 (n=120)*	Month 60 (n=17)*
Number of days absent from school/work during last 6 months, median (min.; max.)	6.0 (1.0; 184.0) n=49	4.0 (1.0; 60.0) n=38	10.5 (1.0; 103.0) n=8
Number of physician visits due to study indication during last 6 months/since last visit, median (min.; max.)	3.0 (0.0; 15.0) n=182	1.0 (0.0; 41.0) n=85	3.0 (1.0; 10.0) n=15
Distribution of visits at baseline, month 30 and month 60 for the years 2019-2023			
Year of visit	Baseline, n (%)	Month 30, n (%)	Month 60, n (%)
≤ 2019	127 (47.9)	0 (0.0)	0 (0.0)

2020	44 (16.6)	32 (26.7)	0 (0.0)
2021	30 (11.3)	40 (33.3)	0 (0.0)
2022	37 (14.0)	31 (25.8)	8 (47.1)
2023	27 (10.2)	17 (14.2)	9 (52.9)

*Of 268 patients enrolled between October 2017 and December 2023, n=265 with baseline, n=120 with month 30 and n=17 with month 60 visit yet documented.

Conclusion: Interim data of the RELIANCE study reveal sustained positive influence of CAN long-term treatment on patients' everyday lives as well as low necessity to utilize medical resources due to study indication. During the ongoing study, no adverse drug reactions (ADRs) occurred that required physician visits.

Disclosure of Interest: None declared

Identifier: PO125

CLINICAL FEATURES AND OUTCOMES OF A SMALL VEXAS SYNDROME PATIENTS' COHORT

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Introduction: VEXAS syndrome is an adult-onset systemic autoinflammatory condition caused by somatic mutations of the UBA1 gene. Patients display a combination of inflammatory and hematological manifestations. Diagnosis relies heavily on clinical suspicion and genetic confirmation, and treatment guidelines are lacking.
Objectives: This study describes the clinical features, treatment outcomes and comorbidities in an inception VEXAS syndrome cohort.
Methods: Medical data were retrospectively collected for 8 VEXAS syndrome patients. UBA1 variants were identified by Sanger sequencing and Variant Allele Frequency (VAF) by digital quantitative PCR. Statistical analyses were performed using SPSS 28.
Results: All patients were men. The mean age at symptom onset was 75 years (± 4.75). Diagnostic delay after first symptom averaged 43.38 months (± 27.95; maximum 76). Mean follow-up time was 19.38 months (± 9.58; range 5-30), with a 50% mortality rate, primarily due to infection (75%). UBA1 variants were: p.Met41Leu (4/8; 50% mortality), p.Met41Val (2/8; 100% mortality), and p.Met41Thr (2/8; no mortality). Mean VAF at diagnosis was 60.55% (± 13.26). Clinical features are summarized in Table 1.

Bone marrow studies were performed in all patients, mostly post-diagnosis by a mean of 2.5 months (±10.25). Myelodysplastic syndrome was present in 87.5% (n=7), including one case of refractory anemia with excess blasts, which progressed to acute myeloid leukemia 27 months post-diagnosis. Monoclonal gammopathy was observed in 50% (n=4).

All patients started anti-inflammatory treatment with glucocorticoids (GC). Tocilizumab (TCZ) was used in 75% (n=6). One patient received more than 2 different drugs (GC, TCZ, then ruxolinitib, and azacitidine).

Clinical remission (regardless of GC dosage, at any time during follow-up) was attained in 75% of patients (n=6), but persistent remission (≥2 consecutive visits) occurred in only 50% of patients (n=4), lasting on average 14.25 months (6-24 months). Complete response (4) – clinical remission, C-reactive protein ≤10 mg/L and a ≤10 mg/day of prednisone-equivalent therapy – was achieved in only 37,5% (n=3) (lasting from 3-12 months), all of them on TCZ.

Clinical features	**Frequency – no. (%)**
Skin involvement	8 (100 %)
Hematological manifestations	8 (100 %)

Constitutional symptoms	7 (87.5%)
Chondritis	6 (75.0%)
Fever	5 (62.5%)
Ocular involvement and Venous thromboembolism	4 (50.0%) each
Lung, articular and ENT involvement	3 (37.5%) each
Vasculitis, PMR-like and Gastrointestinal symptoms	2 (25.0%) each
Myositis, Orchitis and IgG4-related disease	1 (12.5%) each

Table 1. Clinical features of VEXAS syndrome patients (ENT - Ear-Nose-Throat)

Conclusion: VEXAS syndrome is a phenotypically diverse disease with pathophysiological mechanisms and optimal treatments still awaiting clarification. This study highlights the significant diagnostic delays and high mortality rates associated with the syndrome. This cohort consisted of elderly men with a high prevalence of myelodysplastic syndrome and monoclonal gammopathy. Considering more stringent criteria, complete response was achieved in only a minority of patients, with sustained remission even more infrequent. These findings underscore the need for early diagnosis and effective treatment strategies to improve outcomes for VEXAS syndrome patients.

Disclosure of Interest: None declared

Identifier: PO126

FAMILIAL MEDITERRANEAN FEVER AND PAPASH: IL-1 BLOCKERS RECOVER COMPLEX HIDRADENITIS

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Introduction: Familial Mediterranean Fever (FMF) is an interleukin (IL)-1β-driven monogenic autoinflammatory disorder caused by mutations on Mediterranean Fever (MEFV) gene.

Hidradenitis suppurativa (HS) has been recently described as a feature of several autoinflammatory syndromes.

The discovery of shared genes, including NOD2, NLRP3, PSTPIP1 and MEFV, has linked HS with autoinflammatory syndromes such as PASH and PAPASH (pyogenic arthritis,PG, acne and HS). MEFV encodes pyrin, a key component of the inflammasome that activates caspase-1 to process IL-1β. Pyrin interacts with the PSTPIP1 protein and the NLRP3 inflammasome, suggesting potential shared pathogenic autoinflammatory mechanisms in PAPASH. IL-1 inhibitors including anakinra, rilonacept and canakinumab have been shown effective in colchicine-resistant FMF. IL-1 overactivity is also implicated in HS. Two clinical trials demonstrating reductionsin HS disease severity, pain scores and Dermatology Life Quality Index on anakinra.

Objectives: We present two patients who were first diagnosed for HS and PAPASH unsuccessfully treated with steroids and biologics, who recovered PAPASH and HS, respectively, under IL-1 blockers after have been diagnosed for FMF.

Methods: Case reports

Results: Patient-1: a 31-year-old Armenian woman, was first seen in Dermatological Department in 2009 at the age of 16 and diagnosed with HS. The patient was diagnosed for PAPASH syndrome. Single-gene sequencing revealed a pathogenic missense variant (p.E277D) on PSTPIP1 gene. Between 2009 and 2020, the patient was treated with steroids and the anti-TNF-α, developing several infections with poor effectiveness on PAPASH manifestations. In September 2019, she arrived to our referring centre for autoinflammatory disorders and she was clinical diagnosed for FMF and started with colchicine 1mg/day. Single-gene testing of MEFV gene revealed two heterozygous compound pathogenic variants (p.M694V and p.V726A) confirming the clinical diagnosis. FMF attacks remitted under colchicine but new PAPASH lesions appeared in January 2021. She was first started with anakinra and then she was switched to canakinumab. After 3 years, this combined regimen of canakinumab and colchicine, led to a significant improvement of the cutaneous picture and no more flares of FMF occurred.

Patient-2: a 40-year-old Italian man, was first seen in Dermatological Department in 1999 at the age of 15 and diagnosed with HS. Between 1999 and 2024, he was treated with several conventional treatments for HS with no resolution and recurrent flares. In 2018, because of gastrointestinal symptoms, he was clinical diagnosed for FMF in another centre. He discontinued colchicine treatment because of diarrhoea. He arrived at our referring centre for autoinflammatory disorders in December 2023. He was started again with colchicine 1mg/day and FMF remitted. Single-gene testing of MEFV gene revealed two heterozygous compound pathogenic variants (p.M694V and p.M680I) confirming the clinical diagnosis. Because of worsening of HS lesions, in July 2024 he was first started with anakinra and then switched to canakinumab. He is under clinical remission.

Conclusion: Our report supports the growing evidence that HS and FMF are both autoinflammatory conditions that may share common immunogenetic pathways. Both patients achieved FMF remission under colchicine and were given IL-1

blockers for treatment of PAPASH/HS. When assessing a patient with HS, clinicians should ask about concurrent features suggestive of FMF, especially in patients less than 35 years of age and consider IL-1 inhibition if HS or PAPASH is active.
Disclosure of Interest: None declared

Identifier: PO127

EVOLVING PHENOTYPIC AND GENOTYPIC SPECTRUM OF HUMAN ISG15 AND USP18 DEFICIENCIES

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Introduction: IFN-mediated diseases are mendelian innate immunodysregulatory disorders comprise an expanding group of monogenic diseases that present early in life with fever, sterile organ inflammation, and a high type-I IFN-response gene signature. Loss of negative regulator in ISG15 and USP18 results in recently described condition with diversity of clinical charecterstics related to enhanced IFN-a/b immunity.
Objectives: To describe the phenotype, genotype and outcome of Saudi children with proved pathogenic mutation of ISG15/USP18 genes.
Methods: Multicenter descriptive study of pediatric patients with final genetically confirmed type I interferonopathies and ISG15/USP18 gene mutation. Medical records were reviewed for demographic, family history, clinical and genetic data.
Results: Total of sixteen patients from eight Saudi families; only eleven had proven gene mutation. Six patients (54.5%) presented within the first two years. Median age of disease onset was eighteen months (IQR: 12-36) and the median age of diagnosis was 9 years (IQR: 6.0-11.8). Consanguinity was evident in majority of the patients (88%). Constitutional features were found in all patients. The most frequent organ involvements were neurology (77%), interstitial lung diseases (66%), skin abscess (55%), and musculoskeletal (44%). All patients had elevated inflammatory markers. Two patients had severe macrophage activation syndrome. Autoantibodies were evident in six patients; two of them developed lupus like disease. Four patients had abnormal immunology work up and three had recurrent infections. Genetic sequencing identified ISG15 gene mutation in ten patients, of which all had novel genetic variants. Only one patient had USP18 gene mutation with previously reported variant. Majority of the patients were treated with corticosteroids (n=10), intravenous immunoglobulin (n=5), Janus kinase inhibitors (n=3), in addition to various other immunosuppressive agents. Only one patient died with MAS and multiorgan failure.
Conclusion: Loss of negative regulator in ISG15 and USP18 genes highlight a recently described interferon mediated disease. This the first and largest cohort from the Arab region to date. In this report we expand the phenotypic and genetic spectrum with novel identified variants of this seldom reported disease entity along with diversity of disease severity and outcome.
Disclosure of Interest: None declared

Identifier: PO128

IMPORTANCE OF POTENTIAL PROTHROMBOTIC STATE MARKERS IN BEHÇET'S DISEASE AND CORRELATION WITH VASCULAR ULTRASOUND

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Introduction: Behçet's Disease (BD) is a systemic vasculitis that can affect varying-sized vessels, including arteries and veins. Vascular events are one of the leading causes of death in BD. The Ultrasound (US) has limitations, including operator dependency and reduced efficacy in assessing deep venous structures like the iliac and caval veins. There is an unmet need for biomarkers to predict thrombosis, beyond imaging-based detection of vein wall thickness

Objectives: The study aims to evaluate the relationship between prothrombotic soluble serum levels of P-Selectin, Citrullinated Histone H3 (CitH3), Growth Differentiation Factor-15 (GDF-15), and the thickness measurements of the carotid artery, femoral, portal, and jugular veins in patients with BD.

Methods: Fifty-six BD patients who met the International Study Group criteria and 19 healthy control subjects were enrolled. We compared the groups' differences in B-mode ultrasound findings and biochemical prothrombotic markers. Logistic regression was used to analyze independent factors influencing thrombosis, and a receiver operating characteristic curve was plotted.

Results: A total of 34 non-vascular and 22 vascular BD patients (mean age 41.5±11.8 years, 38 [67.9%] male) were included in the study. No significant differences were observed between patients and healthy controls (HCs) regarding sex, age, and body mass index. BD patients had elevated serum levels of P-Selectin, CitH3, and GDF-15 compared to HCs ($p<0.05$). CitH3 and GDF-15 levels were significantly higher in BD patients with vascular involvement than those without vascular disease ($p<0.05$). (Table) The GDF-15 level in vascular BD patients significantly correlated with femoral vein thickness.

Conclusion: GDF-15 and CitH3, are potential biomarkers that show vascular involvement and thrombosis in BD.

Disclosure of Interest: None declared

Identifier: PO129

NEUTRALIZING ANTIBODIES AND ANTI-TUMOR NECROSIS FACTOR (TNF) MONOCLONAL ANTIBODY MEDICATIONS

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Introduction: Use of anti-TNF biologics has been a major advance in the treatment of patients with genetic autoinflammatory conditions. Anti-TNF monoclonal antibodies such as *infliximab, golimumab, certolizumab and adalimumab as well as the soluble receptor fusion protein, etanercept, have been used in genetic autoinflammatory diseases with significant positive impact. As much as we have come to know about these medicines,* less is known about the propensity of these agents to stimulate the production of antibodies against themselves and the clinical implications it has on patients if not used with disease modifying anti-rheumatic drugs (DMARDS) such as methotrexate (MTX) or azathioprine (AZA) to block the development of anti-drug antibodies.
Objectives: To investigate the risk of neutralizing antibody production against TNF-alpha blocking medications in patients with autoinflammatory diseases if not used in conjunction with DMARDs.
Methods: A case report of 6 autoinflammatory patients; 3 with deficiency of adenosine deaminase 2 (DADA2), 1 with familial Mediterranean fever (FMF) and 2 with undifferentiated autoinflammatory disease (UAD), none of whom were on a DMARD at the time of TNF-inhibitor initiation. All patients began to manifest symptoms of their disease on their current treatment with a TNF-inhibitor. All patients were evaluated and parameters of inflammatory disease activity were measured (C-reactive protein, erythrocyte sedimentation rate, ferritin and complete blood count). Drug-induced anti-TNF-alpha blocker antibodies were analyzed using ELISA.
Results: All 6 patients started to develop clinical symptoms which prompted the clinical team to test for anti-drug antibodies. They were all positive for anti-TNF antibodies. diagnosis of DADA2 was on adalimumab and developed a bilateral leg rash. They were switched to golimumab and MTX was added with good outcome and resolution of leg rash. Patient 2 with a diagnosis of DADA2 was on adalimumab and developed loss of consciousness and E. nodosum rash. They were switched to golimumab and MTX with resolution of symptoms. Patient 3 with a diagnosis of DADA2 was on adalimumab and developed skin lesions. They were switched to golimumab and MTX with resolution of symptoms. Patient 4 with a diagnosis of FMF was on infliximab and developed severe abdominal pain and blood in their stool. They were switched to adalimumab with MTX and symptoms resolved. Patient 5 with a diagnosis of FUO was on adalimumab and developed ulcerative colitis and PG lesions. Patient 6 with a diagnosis of FUO was on infliximab and AZA with ongoing disease activity. Recommendation was made to change to golimumab with AZA but they decided to remain on infliximab because they were getting some relief with the current dose of infliximab.
Conclusion: The presence of drug-induced neutralizing antibodies to TNF-α blockers has been associated with worse clinical response as evidenced by all 6 patients experiencing disease associated symptoms whilst neutralizing antibodies were present. The data support the use of DMARDs such as MTX or AZA to help prevent neutralizing antibodies in patients with autoinflammatory diseases.
Disclosure of Interest: None declared

Identifier: PO130

CARDIOVASCULAR COMORBIDITIES IN PATIENTS WITH FAMILIAL MEDITERRANEAN FEVER

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Introduction: Familial Mediterranean Fever (FMF) is a hereditary autoinflammatory disease that clinically manifests as fever, serositis, arthritis, and erysipelas-like erythema. With its anti-inflammatory effects, colchicine is considered the mainstay treatment for FMF.
Objectives: The understanding between Familial Mediterranean Fever (FMF) and cardiovascular diseases (CVDs) remains unclear. The objective of the study was to investigate the association between FMF and CVD as well as other comorbidities.
Methods: Based on a survey targeting individuals with FMF, the patients diagnosed with coronary artery disease, cerebrovascular disease, and hypertension were considered patients with CVD. A comparison was conducted between the general Turkish population (as reported in the TEKHARF study) and our study participants to assess the incidence of cardiovascular events in FMF patients.
Results: Out of 522 patients, 201 had CVD. The mean age was 53.00±6.42 in patients without CVD with a female predominance (59.9%) and 57.60±8.33 in patients with CVD with a female predominance (71.1%). Hypertension was present in 188 patients (36%), while coronary artery disease was observed in 51 patients (9.8%), and 10 patients (1.9%) had cerebrovascular disease. In patients with CVD, diabetes (30.3%) was the most common comorbidity. All (522) patients consumed colchicine. 35 patients with CVD (17.2%) and 25 patients without CVD (7.8%) had colchicine resistance.

All patients consumed colchicine for FMF. Among the patients with CVD, 35 (17.2%) exhibited resistance to colchicine, while 25 (7.8%) patients without CVD showed similar resistance. ($p<0.001$) 25 (12.4%) patients with CVD were using biologic agents, as were 18 (5.7%) patients without CVD. ($p=0.006$)

5% of patients had amyloidosis, and none of the patients had cardiac involvement.

Hypertension was observed in 36% (522/188) of cases compared to 46.1% (6401/2955) in the TEKHARF population ($p < 0.01$). Cerebrovascular disease occurred in 1.9% (522/10) of our group, and in 4% (7457/302) of the general population ($p = 0.016$). However, the prevalence of coronary artery disease in FMF patients was 9.8% (522/51) compared to 7.8% (7457/587) in the TEKHARF study, and this difference did not reach statistical significance.

Table 1. Cardiovascular Comorbidities and Medication Use in Study Participants

	Patients (n=201) with CVDs	**Patients (n=321) without CVDs**
History of smoking n(%)	84 (41.8%)	151 (46.8%)
Diabetes[a] n(%)	61 (30.3%)	33 (10.3%)

Arrhythmia n(%)	11 (5.5%)	8 (2.5%)
Colchicine response[b] n(%)	183 (91.0%)	308 (95.9%)
Colchicine resistance[c] n(%)	35 (17.2%)	25 (7.8%)
Biological therapy[d] n(%)	25 (12.4%)	18 (5.7%)
Total number of medications[d] (mean ± SD)	4.20±2.28	1.74±1.55
VAS score (mean ± SD)	2.73±3.08	2.59±3.04

[a]$p<0.001$, [b]$p=0.021$, [c]$p<0.001$ and [d]$p=0.006$

Conclusion: Colchicine resistance was associated with the incidence of cardiovascular diseases in our patient group. Higher CRP levels were observed in patients with cardiovascular diseases and those with hypertension. Hypertension, coronary artery disease, and cerebrovascular disease are not more prevalent in FMF patients compared to the general population. Colchicine and anti-interleukin-1 show promise in reducing the risk of cardiovascular diseases in patients with FMF.

Disclosure of Interest: None declared

Identifier: PO132

AN UNEXPECTEDLY HIGH PREVALENCE OF FAMILIAL MEDITERRANEAN FEVER IN SLOVAKIA – RESULT FROM NATIONAL AWARENESS CAMPAIGN

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Introduction: Familiar mediterranean fever (FMF) is the most prevalent and famous monogenic autoinflammatory disease world-wide. It is characterised by recurrent, self-limited fever attacks of short duration, polyserositis symptoms, and elevated acute phase reactants. Despite the fact that is well-known and well characterised, in many countries outside the risky regions its true prevalence is unknown, and general awareness is very low.

Objectives: Traditionally, FMF has the highest prevalence in the Eastern Mediterranean region. First description of FMF cases in central Europe are from the year 2014. The prevalence in Central European region was estimated to be 1:465 500 in the population of children. FMF patients which are homozygous carriers of p.Met694Val are considered at higher risk for the development of organ amyloidosis.

Methods: Over a decade, the National Centre for Periodic Fever Syndromes (University Hospital in Martin, Slovakia) has been raising the awareness about autoinflammatory disorders with special focus on FMF among selected medical specialist by providing focused lectures at national medical and scientific meetings and by running campaigns in media and on social networks. For this study, patients with confirmed or suspected FMF have been referred, or their data have been provided to the National Centre for Periodic Fever Syndromes (University Hospital in Martin and Bratislava, Slovakia) by general practitioners, immunologists, rheumatologists and gastroenterologists for evaluation, treatment, and genetic testing. We analysed and evaluated selected characteristics of the FMF cohort in Slovakia.

Results: The Slovak national FMF cohort currently consists of 123 living patients (59 males and 64 females; 30 children (< 18 years) and 93 adults). Mean age of first manifestation was 14.91 years ± 14.49 years (6 months – 51 years, median: 8 years) and mean age of diagnosis was 32.6 ± 18.96 years (20 months – 74 years, median: 34 years) with a diagnostic delay of 17.18 ± 15.53 years. First clinical manifestation at the age under 20 years was observed in 77 patients (62.6%). The prevalence of FMF in Slovak population is 1: 44 303 (1: 35 834 in children) which is significantly higher than expected. FMF type 2 (amyloidosis only phenotype) was observed in one patient with involvement of kidneys, large intestine, peripheral nervous system and genotype p.Lys695Arg/p.Arg202Gln.

Conclusion: The prevalence of FMF in Slovakia is significantly higher than previously expected. Raising the awareness on FMF and other monogenic autoinflammatory disorders among selected groups of specialists could lead to the increased detection of this diseases with significant disease-modifying effects regarding the correct treatment and better prognosis. The successful work and strategy of National Centre for Periodic Fever Syndromes in Slovakia could inspire also other surrounding countries with low detection rate of FMF.

Disclosure of Interest: M. Jesenak Grant /Research support from: Novartis, Speaker bureau of: Novartis, SOBI, AbbVie, E. Malicherova Jurkova: None declared, A. Bobcakova Speaker bureau of: Novartis, K. Hrubiskova: None declared, O. Petrovicova Speaker bureau of: Novartis, L. Kapustova: None declared, T. Dallos: None declared, A. Markocsy: None declared

Identifier: PO133

CUTANEOUS MANIFESTATIONS OF AUTOINFLAMMATORY DISEASES IN PATIENTS WITH GENETIC TESTING

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Introduction: The monogenic autoinflammatory diseases (AIDs) are difficult to diagnosis. The dermatologic lesions are frequently involved in AIDs patients (pts), could be a key for diagnosis and have various manifestations.
Objectives: To study cutaneous lesions in suspected monogenic AIDs.
Methods: From Feb 2021 to Jan 2024 115 pts with suspected monogenic AIDs were examined in V.A. Nasonova Research Institute of Rheumatology and underwent genetic analysis using massively parallel sequencing in research Centre for Medical Genetics. Inclusion criteria were: presence of systemic inflammation signs with fever and/or CRP increase; absence of response to previous therapy; presence of genetic testing. In most pts (90%) sequencing was performed through a 65-gene panel. The final analysis included 61 (53%) pts with skin involvement. Median age was 10 [0.7–47] yrs; M:F=1:1,4.
Results: In 61 pts cutaneous lesions include: maculopapular rashes or inflammatory plaques (26%, including 1 butterfly erythema), urticarial rashes (21%), pustular or pyogenic (10%), purpura (8%), erythema nodosum (5%), livedo (5%), alopecia (5%), photosensitivity (2%). Depending on the results of the genetic testing, 61 pts were divided into 2 groups: 26 pts (43%) with genetic mutations (group 1) and 35 (57%) negative cases (group 2). In group 1 there were identified 19 monogenic mutations (10 in gene MEFV, 2- NLRP3, RAG1, NOD2 and ADA2, 1- UNC13D) and 6 digenic/oligogenic mutations (MEFV/TNFRSF1A, MEFV/MVK/TNFAIP3, MEFV/NOD2/PSTPIP1, MEFV/NLRP12, IL36RN/STX11, SH2D1A/ TNFAIP3). The age at the onset (Me 5(0-34) and 5(0,25-35) yrs) and gender in the groups was not statistically significant difference. The types of rashes were various in both groups. In group 1 and 2 typically for AIDs urticarial rashes were observed in 4 and 9 cases, gangrenous pyoderma in 1 and 2 cases, respectively. Interesting, one case of photosensitivity was observed, who had likely pathogenic mutation in gene MEFV with untypical clinical picture: alopecia, butterfly erythema, aphthous stomatitis, lymphadenopathy and fever; laboratory markers of systemic lupus erythematosus (ANA, hypocomplentemia) were not detected. Two more cases of alopecia were observed also only in patients with likely pathogenic variants of MEFV, one of them with anti-DNA antibodies (aDNA). In group 1 and 2 the most frequent other symptoms were fever (92% and 86%), arthralgia (69% and 57%), arthritis (42% and 34%), gastrointestinal symptoms (35% and 31%), all not significant difference. Chest pain was observed only in group 1 (4 cases), eye damage in group 2 (5 cases). Laboratory inflammatory activity was present in 88% and 74% (p=0,197). Median CRP was 34 (0.1–183) and 30 (0.6–381) mg/L, p=0.919. Hyperproduction of autoantibodies (ANA, aDNA, aRo, ACL) was detected in 23% and 38% respectively (p=0.277).
Conclusion: In our group dermatological manifestations occurred in 53% cases, most often characterized by typical symptoms for AIDs: maculopapular, urticarial, pustular/pyogenic rashes; and no statistical differences of the incidence in groups with positive and negative genetic result. But presence of photosensitivity and alopecia (including in association with hyperproduction of antinuclear antibodies) did not exclude monogenic AIDs possibilities, including familial mediterranean fever.
Disclosure of Interest: None declared

Identifier: PO134

DADA2: THE FIRST REPORT OF A MULTICENTER EGYPTIAN EXPERIENCE

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Introduction: Adenosine Deaminase 2 deficiency (DADA2) is a rare autoinflammatory disorder first described in 2014. DADA2 arises from mutations in the ADA2 gene, leading to diminished ADA2 enzyme activity. Although DADA2 is considered rare, the global distribution of DADA2 is variable, and higher incidence rates in certain ethnic groups are expected. Collaborative efforts are crucial for elucidating the complex epidemiology of this disorder. Over the past few years, we have diagnosed several DADA2 patients in different University hospitals across Egypt.

Objectives: We aim to report the clinical and laboratory characteristics of a cohort of Egyptian children with DADA2

Methods: This cross-sectional study included patients from families with DADA2 diagnosed in several Pediatric University hospitals in Egypt. The data was collected from patients' files after approval of the ethics committee of the faculty of medicine, University of Alexandria; the patients' confidentiality was preserved. Any patient with symptoms suggestive of DADA2 was screened using ADA2 enzyme assay or molecular diagnosis. The patients were screened if they fell into one of these categories: first, patients with immunedysregulation/autoinflammatory manifestations. Second, patients with pure red cell aplasia (PRCA) or bone marrow failure (BMF) of unclear etiology, and the third category included patients with unexplained stroke or recurrent thrombosis, especially if associated with immunological or hematological manifestations. Clinical and laboratory data of the patients were analyzed.

Results: In total, 113 families were screened. In seven families, a molecular diagnosis was made first, either through an autoinflammatory panel or whole exome sequencing for immunedysregulation symptoms, and in one family for PRCA and stroke. The rest of the families were first screened using an ADA2 enzyme assay if they fell into one category of symptoms suggestive of DADA2. Some of these patients have been mistakenly diagnosed with familial Mediterranean fever or other periodic fever syndromes, thrombotic thrombocytopenic purpura, very early-onset inflammatory bowel disease, and Diamond-Blackfan syndrome. We recruited patients from six governorates from Upper Egypt and the Delta region. In total, we have diagnosed 15 families with 27 DADA2 patients and 40 carriers. The range of ADA2 enzyme levels in the affected individuals was from 0 to 0.96 IU/ml, while in the carriers, it ranged from 2.32 to 14.72 IU/ml with a median of 4.96 IU/ml; in four individuals, the ADA2 enzyme assay was in the normal range despite a confirmed heterozygous state. Four previously unreported ADA2 variants were identified. All but one homozygous patient (sister of a symptomatic child) had symptoms of DADA2, and some of the carrier individuals also have symptoms that may be attributed to DADA2. After confirmation of the diagnosis, several patients were started on anti-TNF therapy with a good response. Two sisters who presented with bone marrow failure underwent a successful hematopoietic stem cell transplant from their fully matched mother.

Conclusion: Although DADA2 is a rare disease, it is important to report the epidemiology of the disease in different regions of the world. Our population is underrepresented, which explains why we found several new ADA2 variants. The opportunity for international collaboration for ADA2 enzyme assay and molecular testing helped to confirm the diagnosis in these patients. Implementing targeted therapy improved the patients' condition. Spreading awareness among pediatricians is essential to increase the rate of diagnosis of DADA2 and prevent complications.

Disclosure of Interest: None declared

Identifier: PO135

PERIODONTITIS IN DADA2 PATIENTS WITH SEVERE NEUTROPENIA

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Introduction: Deficiency of adenosine deaminase 2 (DADA2) is an autosomal recessive disease caused by pathogenic mutations in *ADA2.* Severe and refractory neutropenia is a hematologic feature in the phenotypic spectrum of DADA2. Periodontal disease is often recognized as a manifestation of severe neutropenia, but not previously highlighted in neutropenic DADA2 patients.
Objectives: To describe five cases of periodontal disease in DADA2 patients affected by severe neutropenia.
Methods: Case report of five DADA2 patients identified with known periodontal disease and severe neutropenia in the NIH DADA2 cohort. Medical records from 12/18/2005 to 12/01/2024 were reviewed.
Results: Patient 1 (R169Q/deletion in exon 7) is a 57-year-old edentulous female with a 28-year history of neutropenia (ANC = 0), fevers, cervical lymphadenopathy, and splenomegaly with splenectomy. No known history of strokes. Periodontal disease manifested with chronic tooth decay, gingival inflammation, severe mandibular regression, dental extractions, and poor osseointegration of dental implants. Dental imaging demonstrated severe bone loss. The patient was treated with cyclosporine, glucocorticoids, and a TNF-inhibitor induction dose of infliximab, followed by adalimumab, with positive treatment response and neutrophil count normalization (ANC = 2.07). No recurrence of periodontitis after blood count stabilization has been reported.
Patient 2 (H112Q/R34W) is a 44-year-old female with a history of transient neutropenia (ANC = 0.8), Raynaud's, fevers, arthralgia, genital ulcers, livedo reticularis, splenomegaly, and recurrent non-healing skin ulcers in both lower extremities. No history of strokes. Periodontal disease manifested by extensive painful oral ulcerations and mucositis which correlated with episodes of severe neutropenia. She was treated with adalimumab for DADA2 with resolution of neutropenia and no recurrence of oral ulcers and fevers.
Patient 3 (R169Q homozygous) is a 43-year-old female with a history of neutropenia (ANC = 0), Raynaud's, two episodes of central retinal artery occlusions (resulting in right eye blindness), fevers, headaches, arthralgia, livedo reticularis, lymphadenopathy, esophageal necrosis, and common variable immunodeficiency. Periodontal disease was manifested by oral ulcers and painful gingivitis. She was treated with etanercept for DADA2, response was not observed due to medication discontinuation after patient's decision to withdraw all medical care. Patient expired 07/2024.
Patient 4 (H112Q/R169Q) is a 26-year-old male with a history of neutropenia (ANC = 0.3), fevers, skin rashes, and splenomegaly. Periodontal disease was manifested by periodontal abscess and oral ulcers. No history of strokes. Patient received a hematopoietic stem cell transplant with no known recurrence of neutropenia or periodontal issues.
Patient 5 (R169Q/G47W) is a 23-year-old male with a history of neutropenia (ANC = 0), lymphadenopathy, arthralgia, myalgia, polyarteritis nodosa, fevers, and hepatomegaly. Periodontal disease was manifested by oral ulcers. No history of strokes. Patient was initially treated with filgrastim with short term improvement of neutropenia and oral ulcers. Patient received a hematopoietic stem cell transplant with eradication of DADA2 and no oral ulcer recurrence.
Conclusion: These case reports highlight periodontitis in the severe neutropenia of DADA2. We hypothesize that DADA2 neutropenia induces IL-23 and IL-17 release by resident macrophages in the gingiva, similar to leukocyte adhesion deficiency (which may be treatable with Ustekinumab). Since the neutropenia of DADA2 is at least partially due to destruction of precursors in the bone marrow, local cytokine production is unabated, leading to hyperinflammation. To further understand the mechanisms leading to periodontitis in neutropenic DADA2, we plan to conduct careful assessments of DADA2 patients' oral history/dental exams, and when appropriate, gum biopsies.
Disclosure of Interest: None declared

Identifier: PO136

DETERMINATION OF THE RELATIONSHIP BETWEEN SERUM PROTEIN 14-3-3 ETA LEVELS AND CLINICAL FEATURES OF THE DISEASE IN PATIENTS WITH FAMILIAL MEDITERRANEAN FEVER

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Introduction: Protein 14-3-3 belongs to the family of intracellular proteins. Protein 14-3-3 eta is a regulator of pyrin activity [1]. While 14-3-3 binding to pyrin inhibits inflammation, 14-3-3 binding decreases in the presence of mutant pyrin and inflammasome activation occurs [2].

In patients with rheumatoid arthritis, protein 14-3-3 levels have been found to be elevated in both synovial fluid and circulation and have been shown to have early prognostic significance [3].

Objectives: The aim of the study was to evaluate serum protein 14-3-3 eta levels in patients with and without FMF and to investigate the association of protein 14-3-3 eta with clinical disease activity, and acute phase values and other laboratory correlates.

Methods: The study included 104 FMF patients and 50 healthy controls. Patients diagnosed with FMF were also analyzed in subgroups as those experiencing an attack and those not experiencing an attack, as well as those with and without amyloidosis.

Parameter	FMF (n:104)	Control (n:50)	P-value
Age, Med (min-max)	35 (18-69)	29 (19-65)	0.324
Gender, F/M	55/49	34/16	0.075
BMI (kg/m²)	23.16 (15.43-36.73)	22.6 (18.29-31.11)	0.068
CRP (mg/L)	6.18 (1-212)	2.5 (1-7.8)	<0.001
Erythrocyte Sedimentation (mm/h)	17 (1-114)	11 (3-36)	<0.001
Protein 14-3-3 eta (ng/mL)	1.32 (0.25-10.7)	2.34 (0.03-7.89)	<0.001

Serum protein 14-3-3 eta levels from peripheral blood samples were analysed by ELISA method using ELK Biotechnology kit (China).

Results: The clinical characteristics of the FMF patients are shown in Table 1. . Protein 14-3-3 eta levels were significantly lower in FMF patients compared to controls ($p<0.001$). However, there was no correlation between the molecular level

and the clinical features of the disease ($p>0.05$). There was no significant difference in protein 14-3-3 eta levels between attack and non-attack patients, with or without amyloidosis ($p>0.05$).
Conclusion: Protein 14-3-3 levels seem to be decreased in sera of FMF patients with no significant correlation with clinical and laboratory parameters.
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Disclosure of Interest: None declared

Identifier: PO138

ST2 AS AN INFLAMMATORY AND CARDIOVASCULAR MARKER IN FMF-ASSOCIATED AMYLOIDOSIS

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Introduction: Familial Mediterranean Fever (FMF) is the most common inherited periodic fever syndrome, with AA amyloidosis as its primary complication. FMF attacks trigger acute inflammation, while amyloidosis involves continuous inflammation, potentially increasing cardiovascular risk. ST2, part of the IL-1 receptor family, is linked to inflammation and autoimmune diseases and is now a marker for cardiovascular screening.
Objectives: To assess the potential cardiovascular risk in individuals with FMF and amyloidosis and evaluate the utility of ST2 as a biomarker for identifying cardiovascular risk in this population.
Methods: Blood samples were collected from four groups including FMF patients with the attack, same FMF patients during the attack-free period, FMF patients with amyloidosis, and healthy volunteers. Duplicate determination of ST2 levels was performed via the enzyme-linked immunosorbent assay (ELISA).
Results: Among FMF patients with amyloidosis (n=28), the average age was 41.5 ± 10.3, with 57.1% (n=16) females. In FMF patients with attacks (n=20), the mean age was 33.5 ± 11.0, with 40% (n=8) females. FMF patients without attacks (n=12) had a mean age of 37.3 ± 12.0, with 50% (n=6) females. Healthy volunteers (n=24) had an average age of 34.4 ± 8.44, with 66.7% (n=16) females. One-way ANOVA showed a significant difference in mean ages among groups ($p = 0.034$). M694V homozygosity was observed in 67.9% of the amyloidosis group, 40% of the attack group, and 46.2% of the attack-free group, while none of the healthy controls had this mutation. CRP levels differed significantly between the amyloidosis and attack group ($p = 0.014$) and the attack and attack-free group ($p = 0.019$). A significant difference in CRP levels was also found between the attack group and controls ($p < 0.001$), but not between the attack-free group and controls ($p = 0.989$). ST2 levels were significantly higher in FMF patients with amyloidosis and attacks compared to healthy controls (6.91 ± 3.24 vs 3.18 ± 2.01, $p = 0.004$; 10.8 ± 6.22 vs 3.18 ± 2.01, $p < 0.001$, respectively). Among FMF patients without amyloidosis, ST2 levels were significantly elevated during attacks compared to the attack-free period (10.8 ± 6.22 vs 4.9 ± 2.16, $p < 0.001$). ST2 levels were higher in FMF patients with attacks than in those with amyloidosis (10.8 ± 6.22 vs 6.91 ± 3.24, $p = 0.004$). While ST2 levels were elevated in FMF patients with amyloidosis compared to the attack-free period, the difference was not statistically significant. Triglyceride levels differed significantly between the amyloidosis and control group ($p = 0.006$). Significant correlations were found between ST2 and LDL ($p = 0.025$), triglycerides ($p < 0.001$), total cholesterol ($p = 0.034$), and creatinine ($p = 0.024$), but not HDL ($p = 0.313$) or CRP ($p = 0.835$). Mann-Whitney U analysis revealed significant differences in ST2 levels between FMF patients with and without amyloidosis ($p = 0.049$) and between those with and without coronary artery disease ($p = 0.022$). No significant differences were observed in ST2 levels between patients with and without hypertension or diabetes mellitus.
Conclusion: This study identifies ST2 as a reliable marker of systemic inflammation in FMF, reflecting acute inflammation during attacks and chronic inflammation in amyloidosis. Its correlation with lipid parameters links ST2 to metabolic dysfunction, while its elevation in FMF patients with coronary artery disease highlights its potential for monitoring disease activity and cardiovascular risk.
Disclosure of Interest: None declared

Identifier: PO140

REAL-LIFE DATA ON TAPERING OF ANTI-IL-1 THERAPY IN PATIENTS WITH MEVALONATE KINASE DEFICIENCY (MKD)

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Introduction: Mevalonate kinase deficiency (MKD), one of these diseases, is caused by autosomal recessive loss-of-function mutations in the mevalonate kinase (MVK) gene, resulting in a deficiency of the mevalonate kinase enzyme. Patients with MKD typically present within the first year of life with recurrent episodes of fever, gastrointestinal symptoms cervical lymphadenopathy, aphthous stomatitis, and/or rashes

IL-1-targeted therapeutic strategies to reduce disease activity and normalize systemic inflammation. Both anakinra and canakinumab have been demonstrated to control and prevent exacerbations in these patients.

Objectives: However, there is no consensus in the literature regarding the optimal dosing regimen or tapering strategies for anti-IL-1 therapies in pediatric MKD patients. In this study, we present a 7-year treatment experience of our patient with MKD.

Methods: This retrospective case series included eight patients with MKD who were followed between April 2018 and December 2024. Two patients were excluded from the analysis due to amyloidosis and renal failure.

Results: The study included six patients with mevalonate kinase deficiency (MKD), comprising five females and one male. Among the patients, four were homozygous for the V377I mutation, one was homozygous for the V8M mutation, and one was compound heterozygous for the I268T/V377I mutations. The median follow-up duration was 71 months, ranging from 32 to 95 months. The median age at symptom onset was 1 month, ranging from 1 to 4 months. The median age at diagnosis was 75 months, with a range of 56 to 118 months. The median symptom duration per episode was 3 days, ranging from 3 to 7 days. The frequency of attacks was a median of 1 episode per month, ranging from 1 to 2 episodes. Aphthous stomatitis was observed in two patients. Abdominal pain and diarrhea were present in five patients each, while rash occurred in 4% of episodes. Lymphadenitis was observed in four patients.

Four patients were initially treated with anakinra. Five patients transitioned from anakinra to canakinumab. The duration of anakinra therapy varied between 2 and 17 months.

Results of Canakinumab Therapy: Among the five patients treated with canakinumab, dose adjustments were made based on treatment response. By the end of the 6th month, dose interval extension was achieved in only one patient. Three patients continued the same dose, while one patient required a dose increase due to inadequate control of attacks. At the 12th month of therapy, dose interval extension was maintained in one patient, while two patients continued the same dose. One patient remained on a higher dose due to persistent disease activity. By the 18th month, dose interval extension was achieved in three patients. However, one patient continued a higher dose regimen. In one additional patient, dose interval extension was achieved only at the 24th month of follow-up.

Conclusion: In our experience, MKD patients exhibit a different treatment response trajectory compared to Familial Mediterranean Fever (FMF) patients, particularly in terms of dose reduction strategies. Unlike FMF, where dose reduction is often achievable within a shorter timeframe, MKD requires prolonged and individualized treatment strategies. Based on our limited number of cases, treatment tapering in MKD appears to be more challenging, requiring a longer duration and more personalized approaches. The variability in response among MKD patients underscores the complexity of tailoring IL-1 inhibitor therapies in this population. Further studies with larger patient cohorts are needed to optimize treatment regimens for MKD. Close monitoring and early identification of treatment-resistant patients are

crucial for optimizing therapeutic outcomes. Additionally, further longitudinal studies are needed to evaluate long-term outcomes and the sustainability of IL-1 inhibitor therapies in MKD.

Acknowledgments: *

Disclosure of Interest: None declared

Identifier: PO141

INFLAMMATORY LINEAR VERRUCOUS EPIDERMAL NEVUS (ILVEN) - A NEW SKIN MANIFESTATION IN A CHILD WITH BLAU SYNDROME

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Introduction: A gain-of-function mutation in the *NOD2* gene causes Blau syndrome (BS), characterized by dermatitis, polyarthritis, and uveitis, exhibiting variable expressivity and incomplete penetrance. ILVEN, a rare entity, presents as localized or systematized lesions along the lines of Blaschko, typically manifesting in infancy or early childhood. It has been linked to genetic variants in the *GJA1, ABCA12, CARD14, PMVK, NSDHL, HRAS*, and *KRT10* genes. ILVEN associated with *NOD2* gene variants has not been previously reported.
Objectives: We describe a three-generation Indian family with BS, in which the proband presented with ILVEN besides inflammatory arthritis marking the first reported association of ILVEN with BS.
Methods: We diagnosed a three-generation family with a paternal grandmother, father, and daughter (proband) carrying a pathogenic *NOD2* gene mutation identified through next-generation sequencing (NGS) gene panel analysis, and familial segregation confirmed by Sanger sequencing.
Results: The proband is a 9-year-3-month-old female, born of a non-consanguineous marriage. She first presented at 2 years and 5 months of age with swelling over the dorsum of the hands and feet. The swelling began at 1 year and 6 months of age and was accompanied by fever, morning stiffness, and bilateral knee swelling. This was followed by ankle swelling, which began at 2 years of age. She was suspected to have juvenile idiopathic arthritis and was referred for refractory disease. Her weight and height were at the 25th percentile. She exhibited linear, sharply demarcated, nonpruritic, hyperpigmented unilateral near continuous nevi involving the right side of the body, extending from the upper limb, chest, abdomen, inguinal region, and right lower limb, which had first appeared at 8 months of age. Her mother reported that the nevi had grown progressively and become more palpable. Additional findings included a café au lait spot on the abdomen, clinodactyly, dystrophic nails, swelling of the bilateral wrists with synovial cysts, swollen ankles, and puffy fingers and toes.
The paternal grandmother had a history of prolonged deforming ankle, wrist, and small joint arthritis and was on alternative medicine. The father had a history of chronic uveitis with multiple flares, leading to painless blindness and secondary glaucomatous optic nerve changes, with arthritis involving the ankle, wrist, and small joints of the hands and feet, with fixed flexion deformities and hallux valgus. History elicited frequent callus formation, dystrophic brittle nails, and palmoplantar hyperkeratosis in both the paternal grandmother and father. The father also had a café au lait spot on his back.
Laboratory investigations of the proband revealed hemoglobin levels of 51–132 g/L, white cell counts of 8.5–10.1 x 10^9/L, platelet counts of 270–550 x 10^9/L, and an erythrocyte sedimentation rate of 15–60 mm/hr. Rheumatoid factor and antinuclear antibodies by IIF were negative. Her skin biopsy confirmed the diagnosis of ILVEN. With the positive vertical family history, an NGS gene panel for systemic autoinflammatory diseases was performed. A pathogenic heterozygous mutation, c.1000C>T; p.R334W, in the *NOD2* gene, was identified. Sanger sequencing confirmed the same pathogenic *NOD2* variant in the paternal grandmother and father. The proband's initial ophthalmic evaluation was normal. At 5 years and 4 months of age, she was diagnosed with bilateral panuveitis. Treatment included oral steroids, methotrexate, anti-TNF drugs, and topical therapies. Tofacitinib was added for persistent eye inflammation. She is now maintained on oral methotrexate and Tofacitinib, achieving good systemic and ophthalmic disease control, though the ILVEN remains unchanged.
Conclusion: This is the first report describing ILVEN associated with a *NOD2* mutation
Disclosure of Interest: None declared

Identifier: PO142

A TIGHT ROPE (D) WALK IN A CHILD WITH ACUTE ABDOMEN

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Introduction: We report the journey of a child with Mevalonate Kinase Deficiency (MVKD), describing briefly her clinical course prior to diagnosis and subsequently sequelae of delayed initiation of definitive therapy.
Objectives: To expand clinical profile of MVKD and highlight the challenges faced during management in resource constraint settings.
Methods: Review of case records.
Results: Case report: A 9-year-old girl child, 2nd born to a 3rd degree consanguineously married couple, first presented to our unit in the year 2019, at the age of 04 years. Her symptoms started at 9 months of age with recurrent episodes of asymmetrical large joint arthritis. Her initial evaluation revealed persistently raised ESR, CRP and positive Rheumatoid factor. Consequently, she was diagnosed as juvenile idiopathic arthritis and treatment with intra-articular steroids and methotrexate was commenced. However, the disease was poorly responsive to the treatment and by 4 years of age, she started developing abdominal pain with bleeding per rectum, which lead to referral to our institute.
On further evaluation at our centre, she was found to have arthritis, active colitis, dyserythropoetic anemia with hepatosplenomegaly and markedly elevated inflammatory parameters. This constellation along with early age of onset of symptoms prompted us to consider the diagnosis of an autoinflammatory disorder. Clinical exome sequencing revealed a homozygous pathogenic mutation in *MVK* in Exon 6 (c.546G>T, p.Leu182Phe). She was initiated on corticosteroids, methotrexate and thalidomide due to nonavailability of treatment of choice, anti IL1 therapy (Anakinra). She continued to have poorly controlled disease activity with recurrent cytopenias, hyperferritinemia and raised triglycerides suggestive of Macrophage Activation Syndrome (MAS) requiring repeated admissions.
In the year 2023, Anakinra was procured on a 'named patient basis" aided through Government of India's initiative under the National Policy for Rare Diseases 2021. Marked improvement in arthritis, hepatosplenomegaly, abdominal symptoms, arthritis and growth was noted. However, a year later, while being on therapy, the child developed features of acute intestinal obstruction. Plain Xray abdomen was suggestive of the same and accordingly a CT abdomen was done which revealed jejunoileal intussusception. The child was treated with pulse methylprednisolone and increase in the dose of anakinra, with which the obstruction was relieved transiently. However, in a few days, she again showed features of subacute intestinal obstruction for which an exploratory laparotomy had to be done. Upon exploration, she was found to have multiple peritoneal adhesions which were managed with adhesiolysis. Post operatively, she made a complete recovery and has had no recurrences since then. Presently, she is doing well on Anakinra.
Discussion: This case highlights the need for early diagnosis and initiation of appropriate treatment in MVKD. Many developing countries face challenge of nonavailability of Anakinra resulting in poorer prognosis. Clinical dilemmas often encountered, is in treatment of ischaemic pain, serositis which can often be tackled with anti-inflammatory therapy. However, despite timely institution of anti-inflammatory therapy in these patients, low index for surgical explorations should be kept as adhesions can be frequently encountered.
Conclusion: MVKD has varied presentations including dyserythropoietic anemia, MAS and intussusception. It further underlines the importance of early identification and initiation of appropriate immunosuppression in preventing devastating complications and ensuring long-term well-being.
Acknowledgments: Allergy and Immunology Unit, Advanced Pediatrics Centre, Post Graduate Institute of Medical Education and Research, Chandigarh, India.
Disclosure of Interest: None declared

Identifier: PO143

VEXAS SYNDROME AND INFECTIONS: ANALYSIS OF A MULTICENTRIC COHORT AND BRIEF LITERATURE REVIEW

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Introduction: VEXAS syndrome (Vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) is a monogenic "hemato-autoinflammatory" disease provoked by mutations in the UBA-1 gene, with a broad spectrum of clinical manifestations due to systemic inflammation and the frequent coexistence of myelodysplasia and other hematological conditions. Infections are one of the most serious complications.

Objectives: This study described the infectious manifestations of a group of patients affected by VEXAS as well as the associated outcomes. Then, a brief literature review was conducted to analyze the incidence of infections reported in VEXAS subjects.

Methods: Fourteen patients (mean age 74 years±7.2) referred to two Rheumatology Units (Padua University Hospital and Verona University Hospital), were included. The NGS analysis revealed the following mutations on UBA-1: p.Met41Thr (7 patients), p.Met41Leu (2), p.Met41Val (3), c.118-1G>C (1) and c.118-2A>G (1). Therapeutic management of the patients at the time of infection included glucocorticoids (13 patients, mean dose 15 mg/day), JAK inhibitors (4 patients), methotrexate (1 patient) and canakinumab (1 patient). An online literature search was conducted in Medline (via PubMed), and Embase (via Ovid). The search included articles from inception until September 2024. After an abstract screening, a total of 4 papers were rated as suitable, including single case reports and a multicenter registry study.

Results: Eleven out of fourteen patients (78%) of our cohort had at least one episode of serious infection during the disease course regardless the therapy undertaken. Five of them (50%) developed SARS-CoV2 infection (2 mild form, 2 moderate and 1 severe form); three patients (30%) presented with pneumonia, (two due to *L. pneumophila* with fatal outcome, one due to *Herbaspirillum huttiense* with resolution); 1 patient (10%) presented with bacterial endocarditis; one patient (10%) had recurrent oral candidiasis and tracheobronchitis (isolated S.*haemolyticus* from bronchoalveolar lavage), and one (10%) had peri-prosthetic hip osteomyelitis caused by *L. monocytogenes* and *P. mirabilis*. Data obtained from the literature showed that the main areas of infections were localized at the bronchopulmonary tract, followed by skin, urinary tract and bloodstream infections. Viral re-activations were observed as well.

Conclusion: Patients with VEXAS syndrome have a higher risk of developing severe infections. According to the recent literature, the main risk factors for severe infections are advanced age at VEXAS onset, therapy with JAK inhibitors and the prolonged use of glucocorticoids. Given the disease's complexity and the possibility of a rapid evolution, it is necessary to provide prophylaxis coverage in patients most at risk.

Disclosure of Interest: None declared

Identifier: PO144

VALIDATION OF THE COLCHICINE RESISTANCE PREDICTION CRITERIA FROM THE TURPAID COHORT TO THE JIR COHORT: A MULTICENTER DESCRIPTIVE ANALYSIS

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Introduction: Colchicine is the standard treatment for familial Mediterranean fever (FMF), yet around 10% of patients will be considered colchicine-resistant, requiring then the use of IL-1 inhibitors to control the disease and prevent the development of inflammatory AA amyloidosis. In 2023, predictive criteria for colchicine resistance were proposed based on the Turkish TURPAID pediatric cohort.

Objectives: This study aimed to evaluate the application of the TURPAID criteria to the JIR cohort, including adult patients.

Methods: FMF patients from the international JIR registry who met EUROFEVER criteria were analyzed. Colchicine resistance was defined as the need for bDMARDs. The use of the TURPAID score was evaluated in these patients. A score ≥ 2 predicts colchicine resistance.

Results: Of 116 colchicine-resistant patients, 70.7% had a pediatric diagnosis. Pediatric-diagnosed patients had an earlier onset of symptoms (mean 3.8 vs. 7.5 years; ***p<0.001***) and shorter attacks (2.66 vs. 3.25 days; ***p=0.018***) than adult-diagnosed patients. Only 6 % of the patients receiving IL-1 inhibitors and though considered colchicine resistance did not fulfill the TURPAID criteria. Mean TURPAID scores were higher in pediatric patients (2.8 vs. 2.5; ***p=0.02***), as was the number of patients with a score ≥ 2 (96.3% vs 88.2%, *p=0.192*). Genetic findings showed 100% with exon 10 MEFV mutations.

Conclusion: Although defining colchicine resistance based on bDMARD use alone has limitations, the TURPAID criteria were shown to be applicable to patients from the JIR cohort, including adults. Pediatric patients tended to have higher TURPAID scores, probably reflecting age-related differences in FMF presentation, with fever being less common in adults. According to our study, the genetic criterion "Exon 10 *MEFV* mutations" with a weighting of 1.5 points may be controversial. Indeed, according to the recent EUROFEVER/PRINTO classification criteria for FMF, homozygosity or compound heterozygosity for exon 10 MEFV mutations is mandatory for genetic diagnostic, and the absence of these mutations should lead to reclassification of the patients as undifferentiated systemic autoinflammatory syndrome, a condition in which colchicine is generally less effective than in FMF. The importance of this criterion, which plays a role in determining the diagnosis of FMF, probably prevents a more detailed analysis of the predictive criteria for colchicine resistance in patients with a genetic diagnostic.

Disclosure of Interest: None declared

Identifier: PO145

EXPANDING THE GENETIC AND CLINICAL SPECTRUM OF NFKB1 VARIANTS IN CHINESE PATIENTS WITH PRIMARY IMMUNODEFICIENCY

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Introduction: The nuclear factor κB (NF-κB) is critical in regulating inflammatory and immune responses, including cell activation, proliferation, survival, and effector functions. Dysfunction of the NF-κB pathway has been linked to various primary immunodeficiency disorders. Recently, NF-κB1–related diseases have been increasingly recognized as an inborn error of immunity (IEI) with immune dysregulation. These disorders encompassed not only common variable immunodeficiency (CVID12 [MIM: 616576]) but also manifestations of autoinflammation, autoimmunity, and malignancies.

Objectives: To investigate and analyze the clinical and genetic characteristics of NF-κB1–related diseases in the Chinese population, where reports remain sparse compared to the numerous cases documented in European populations.

Methods: Clinical manifestations, genetic variants, and treatments were analyzed in four Chinese Han patients with novel *NFKB1* variants. Data were collected through comprehensive medical reports and laboratory results. The pathogenicity of the variants was predicted using *in-silico* tools. Clinical data from three additional reported Chinese patients with *NFKB1* variants were included for comparison, bringing the total to seven. Findings were compared with those of a larger cohort in the literature to identify differences.

Results: Our cohort included three men and one woman. Four patients all exhibited recurrent fever and hypogammaglobulinemia. Three patients experienced recurrent sinopulmonary infections, accompanied by decreased B cells and NK cells, while two patients developed pneumonia, bronchiectasis, and hepatitis. One developed arthritis and rash. No malignancies were observed. Four novel *NFKB1* (NM_003998) variants were identified: c.559C>T (p.R187W), c.730+5G>A, c.1509del (p.Glu504Argfs*19), and c.1753-17_1754delGCCCTTTCACTTTCCAGAC. All variants were predicted to be disease-causing and likely to alter protein structure based on computational tools such as Mutation Taster, SIFT, and CADD. Decreased frequencies of infections and improvements in symptoms could be achieved by immunoglobulin replacement therapy and glucocorticoids. Compared to a cohort reported in the literature, Chinese patients were predominantly male, had a later median age of disease onset (27 vs. 12 years), and were diagnosed at an older age (41 vs. 23 years). Chinese patients exhibited higher rates of viral infections, sepsis, bronchiectasis, cirrhosis, and hepatitis, alongside more severe immune dysfunction——greater reductions in NK cells and B cells. Conversely, autoimmune diseases and bronchitis were less frequent in Chinese patients.

Conclusion: This study represents the first and largest case series of Chinese patients with NF-κB1-related diseases, including the identification of four novel variants. These findings highlight distinct clinical and immunological features in the Chinese population and underscore the critical role of IVIG. Further research is needed to elucidate genotype-phenotype correlations, population-specific features, pathogenicity of variants, and targeted therapies.

Acknowledgments: We would like to acknowledge the patients for their consent to participate in the study.

Disclosure of Interest: None declared

Identifier: PO146

A CASE OF CANDLE SYNDROME PRESENTING AS SERONEGATIVE POLYARTHRITIS

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Introduction: Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE) syndrome, is autoinflammatory disease caused by homozygous/compound heterozygous mutations in proteasome-associated genes. It presents early in life with recurrent fevers, violaceous skin lesions, eyelid swelling, hepatomegaly, lipodystrophy, growth delay, anaemia and elevated inflammatory markers. Histologically, skin lesions display infiltration of immature, myeloid, mononuclear cells, resembling leukaemia cutis.

Objectives: We describe a case of CANDLE caused by compound heterozygous mutations in the proteosome-associated gene *PSMB4*, presenting with chronic seronegative polyarthritis. Skin lesions in early infancy were misdiagnosed and treated as leukaemia cutis.

Methods: Genetic analysis was carried out by a systemic autoinflammatory diseases gene sequencing panel, which identified gene variants in the *PSMB4 (Proteasome 20S Subunit Beta 4)* gene. Interferon gene expression was measured by interferon-stimulated gene signature (ISG) assay.

Results: An 11-year-old girl, born to non-consanguineous parents, presented with difficulty walking due to gradual-onset pain, stiffness and swelling of her knees, ankles and feet with deformity. Hand and wrists were also affected with joint swelling, contractures, muscle wasting and lipodystrophy. The hands appeared aged and function was impaired. She was systemically well with no fevers or rashes and normal growth. There was no family history of autoimmune or autoinflammatory disease. Previously, aged 6 weeks, she developed anaemia, neutropenia and intermittent red-brown skin lesions on her extremities. Skin biopsy revealed a complex neutrophilic granulomatous infiltrate. She was diagnosed with cutaneous acute myeloid leukaemia (AML), or 'leukaemia cutis', and received two cycles of cytotoxic chemotherapy with no response. Skin lesions settled on their own and she remained well under follow-up.

Investigations showed chronic mild neutropaenia (1.1-1.9 x10*9/L), elevated inflammatory markers (CRP 40 mg/L and ESR 30 mm/hr, serum amyloid A at 40 mg/L) and elevated immunoglobulins. Other tests were normal apart from a positive anti-PM Scl-75. Hand and foot X-rays showed crowding of the proximal carpal bones but no erosion. MRI scans showed peroneal tenosynovitis and metatarsophalangeal joint synovitis with bone and soft tissue oedema. Initial treatment consisted of NSAIDs, prednisolone and methotrexate for presumed seronegative polyarticular arthritis. Joint swelling persisted so treatment was escalated to anti-TNF agent ertanercept.

Response was initially good but aged 15 years, she developed recurrent fevers and erythematous swellings on her eyelids, face and tongue. Bloods were similar to her initial presentation, infective screens were negative, lesional biopsy showed inflammatory infiltrate and interferon signalling was grossly abnormal. Autoinflammatory gene testing revealed *de novo* compound heterozygous mutations *PSMB4*: a novel pathogenic frame shift p.(Gln192Hisfs*14) caused by a deletion of c.576delG in exon 4 and a -9G>A variant of unknown significance. The -9G>A variant was associated with CANDLE in a single case report (PMID 26524591; doi: 10.1172/JCI81260). Treatment with JAK inhibitor tofacitinib was commenced but break-through symptoms occured so she was switched to baricitinib. Despite significant clinical improvement, inflammatory markers remain mildly elevated and there are occasional joint symptoms.

Conclusion: We describe a novel case of atypical CANDLE presenting as polyarticular seronegative arthritis due to compound heterozygous mutations in *PSMB4*. We surmise that initial misdiagnosis with leukaemia cutis and subsequent chemotherapy may have supressed early cutaneous and systemic inflammatory features.

Acknowledgments: Professor Helen Lachman, National Amylodosis Centre, Division of Medicine, National Amyloidosis Centre, University College London, London, UK.

Disclosure of Interest: None declared

Identifier: PO147

FAMILIAL MEDITERRANEAN FEVER: DISEASE SEVERITY AND AMYLOIDOSIS IN AN EGYPTIAN COHORT

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Introduction: Familial Mediterranean fever (FMF) is the prototype of periodic fever syndromes. It is commonly seen in populations of the Mediterranean area and where high rates of consanguineous marriage prevail. It is characterized by recurrent short episodes of fever and serositis associated with the elevation of acute phase reactants. Amyloid A amyloidosis is a serious complication of severe and/or uncontrolled disease. Colchicine is the mainstay of treatment to stop the clinical attacks and prevent complications. Anti-interleukin 1 (anti-IL1) therapy is the second line in resistant cases.

Objectives: This study aims to describe a cohort of Egyptian FMF children with severe disease and/or amyloidosis and the effect of anti-IL1 therapy in these patients.

Methods: This cross-sectional descriptive study included FMF children who attended Alexandria University Children's Hospital from January 2021 to October 2024. After approval of Alexandria University Faculty of Medicine's Ethics Committee, consent was obtained from all parents or legal guardians. Patients were diagnosed following the Tel Hashomer diagnostic criteria. Molecular testing was done using PCR, covering 12 pathogenic mutations. The duration and dose of colchicine and/or anti-IL1 therapy, number of clinical attacks, acute phase reactants, and urinary proteins were assessed regularly for each patient. Disease severity was evaluated using the International Severity Score for FMF (ISSF score), and the response to treatment was evaluated using the FMF 50 score.

Results: A total of 170 patients were enrolled in the study. According to the ISSF score, most studied cases had mild to intermediate severity (34.1% and 57.1 %, respectively), while fifteen patients (8.8%) had severe disease. The most common variants in the patients with severe disease were (V726A, M694V, I692del). As regards the FMF 50 score, 89.4 % of cases responded well to the maximum tolerated doses of colchicine, while 18 (10.6%) cases did not improve sufficiently. Of these 18 cases, 12 received IL-1 receptor antagonist (Anakinra is the only available form of anti-IL 1) at a dose of (1mg/kg/day) while the drug was not available for 6 cases. A good response to Anakinra was measured by a 50% improvement in 5 domains of FMF 50 score, which occurred in 10/12 cases. Five cases developed amyloidosis confirmed by renal biopsy, one male and four females. The mean disease duration in these patients was 6.6 years of active severe disease despite colchicine in 4 patients, while one patient was not compliant with therapy. Their MEFV mutations were (E148Q/V726A/I629del, M694V/V726A, M680I/M694V, heterozygous and homozygous M694V). All five patients started anakinra with a dose of 1 mg/kg/day; proteinuria markedly decreased (mean urinary proteins in 24-hour urine was 1.72 gm protein /24hrs urine before anakinra and 0.456 gm protein /24 hrs urine after anakinra) in 4 of them, In these four patients, proteinuria worsens during infections or on stoppage of anakinra. One patient still has persistent nephrotic range proteinuria despite anakinra (1mg/kg/dose), and the dose could not be increased due to drug unavailability. None of the patients with severe disease or amyloidosis stopped anakinra with a mean duration of therapy of 2.75 years (Min-Max: 1.5-7.75).

Conclusion: Although most of the patients have mild or intermediate disease severity and are mostly well-controlled on colchicine, it is important to highlight the challenges of patients with severe or complicated diseases and the role of anti-IL1 therapy especially in regions where it is not readily available. This cohort of patients showed improvement in previously unresponsive cases as well as patients with amyloidosis after administration of anakinra.

Disclosure of Interest: None declared

Identifier: PO149

A CASE WITH DIAGNOSIS OF MACROPHAGE ACTIVATION SYNDROME AND FAMILIAL MEDITERRANEAN FEVER

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Introduction: Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening clinical condition. Dysfunction of cytotoxic T-lymphocytes and natural killer (NK) cells, activation of macrophages and T-lymphocytes causes excessive production of proinflammatory cytokines and hemophagocytosis. Secondary HLH associated with rheumatological diseases, especially with systemic juvenile arthritis and with systemic lupus erythematosus, is known as Macrophage activation syndrome (MAS). However, MAS is not expected in patients with familial Mediterranean fever (FMF). Hereditary fibrinogen disorders cover a wide spectrum of fibrinogen deficiencies including type 1 (afibrinogenemia and hypofibrinogenemia) and type 2 (dysfibrinogenemia and hypodysfibrinogenemia); the clinical phenotype is heterogeneous, from mild to major bleeding and thrombotic events.
Objectives: Here we present the development of MAS in a patient with FMF concomitantly diagnosed with hereditary hypofibrinogenemia.
Methods: We present here a case report.
Results: Case: An 11-year-old girl presented with swelling in her left knee. She had no additional complaints, and was admitted to the hospital with a preliminary diagnosis of septic arthritis, and antibiotic therapy was started after performing a synovial fluid sampling. She complained of fever and rush on the third day of her hospitalization. Fever continued during the second week of hospitalization she developed pancytopenia. She had recurrent mono-arthritis and splenomegaly on her medical history. On physical examination, she had cervical lymphadenopathy, hepatosplenomegaly, arthritis in the left knee. On laboratory examination she had lymphopenia, anemia, thrombocytopenia, high C-reactive protein, hyponatremia, high liver function tests, hyperferritinemia and hypofibrinogenemia. She was diagnosed with MAS. Bone marrow smear showed hemophagocytosis. Her echocardiogram was normal. Viral and bacterial tests were nonspecific. The patient treated with IVIG, pulse methylprednisolone (30 mg/kg/d, 3 days) and then 2mg/kg/d prednisolone continued. The fever and laboratory values improved with the treatment, however, hypofibrinogenemia persisted. An autoinflammatory gene panel was performed because of the recurrence of arthritis, splenomegaly, pancytopenia, high acute phase reactants, and development of MAS. The patient was diagnosed with FMF due to M694V homozygous mutation in the MEFV gene on genetic analysis, and was started on colchicine treatment. Methotrexate was added to the treatment due to development of chronic arthritis. Hypofibrinogenemia persisted on follow-up and A315G homozygous mutation in the FGG (Fibrinogen Gamma Chain) gene were detected in whole exome sequence analysis WES was performed on the patient.
Conclusion: MAS is rarely developed in FMF patients and has been reported only in case reports. Although it is a rare finding in patients with FMF, MAS should be kept in mind in cases of prolonged fever. The FGG gene mutation associated with hereditary fibrinogen disorders was detected in our case. It is unknown whether this mutation causing hypofibrinogenemia contributed to the development of MAS in our patient. Hereditary fibrinogen disorders may be present if hypofibrinogenemia persists in patients with MAS despite improvement in other laboratory findings.
Disclosure of Interest: None declared

Identifier: PO150

A PARTICULAR PHENOTYPE IN TWO PATIENTS WITH SIDEROBLASTIC ANEMIA, B-CELL IMMUNODEFICIENCY, PERIODIC FEVERS AND DEVELOPMENTAL DELAY

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Introduction: Infection with recurrent fever is very suggestive for primary immunodeficiency, but immunodeficiency associated with autoinflammation is very rare recognized.

Biallelic mutations in TRNT1 gene cause SIFD syndrome-Sideroblastic anemia, B-cell Immunodeficiency, periodic Fevers and Developmental delay. This is a very rare disease with 46 patients described in the literature.

Objectives: The aim of this study is to present two patients with SIFD from a clinical, biological, immunological, therapeutic and evolutionary point of view . Both of them have a Down syndrome phenotype, association that wasn't reported.

Methods: Patient 1 (P1)-female come from non-consanguineous parents. Since 3 months of age, after the vaccination, she presented at each 2-3 weeks fever, vomiting and diarrhea for 5-10 days. Clinical exam revealed a Down sd. like face, psychomotor delay, microcephaly. Laboratory tests showed a microcytic hypochromic anemia with normal ferritin confirmed as sideroblastic anemia by bone marrow aspiration, variable leucocyte(2200 – 8000/µL), neutrophil(630-4500/µL) and lymphocyte count(1180-3500/µL), negative coprocultures and coproantigenes, hypogammaglobulinemia (1,7%), a C reactive protein >100 mg/L. Down sd., celiac disease, hypothyroidism, cystic fibrosis, Schwachmann-Diamond sd, IBD were excluded. Immunological explorations showed low IgA, IgG and IgM, poor response to vaccination, B lymphopenia and low switched memory B cells. P2 come from non-consanguineous parents with insignificant disease family history. The onset of the disease in P2 was at 3 weeks after birth with fever every 2-3 weeks, lasting 5-10 days accompanied by diarrhea and vomiting. P2 has a similar phenotype with P1 and laboratory tests were similar with P1. P2 developed also mezenteric thrombosis with gut necrosis and antithrombin III deficiency was also identified.

Results: We performed WES in P1, revealing a heterozygous double missense pathogenic mutation c.608+1G > T/c.1246A > G in the TRNT1 gene. In P2 the diagnosis was much faster, being suggested by the Downian phenotype associated with periodic fever and proven by gene panel sequencing-heterozygous double mutation c.428_431del /c.1246A > G. Both patients were treated with corticosteroids and intravenous immunoglobulin. P1 died due to COVID infection. P2 was also treated with anti-IL1 with no response but with a decrease in fever periods under colchicine treatment.

Conclusion: SIFD is a rare disease characterized by the association of autoinflammation with hypogammaglobulinemia. It should be suspected in any case of recurrent fever associated with hypogammaglobulinemia and Downian phenotype. Early diagnosis will allow the early establishment of treatment and even the optimal time for bone marrow transplantation.

Disclosure of Interest: None declared

Identifier: PO151

INFLAMMATORY BOWEL DISEASE IN NEONATAL-ONSET MULTISYSTEM INFLAMMATORY DISEASE: A GENETIC RISK ASSESSMENT

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Introduction: Neonatal-Onset Multisystem Inflammatory Disease (NOMID) is a severe form of cryopyrin-associated periodic syndrome caused by gain-of-function mutations in *NLRP3*. It presents with systemic inflammation, neutrophilic urticaria, aseptic meningitis, and sensorineural hearing loss. Although inflammasome activity is linked to inflammatory processes and SNPs in *NLRP3* have been reported in inflammatory bowel disease (IBD)[1], IBD is rarely reported in NOMID patients. In that context the presentation of 2 NOMID patients who developed IBD on optimized IL-1 blocking treatment prompted the assessment of additional genetic risk factors, including polygenic risk scores (PRS) and HLA types, for IBD in NOMID.

Objectives: This study aimed to evaluate contributing genetic risk factors for IBD in NOMID patients by assessing PRS and HLA typing, comparing these factors between patients with and without IBD.

Methods: A total of 41 NOMID patients enrolled in the NCT02974595 natural history protocol were included in a long-term outcome evaluation. All had confirmed *NLRP3* mutations and were treated with IL-1 blockers (anakinra, canakinumab, or both) for 11–22 years (median: 19 years). Whole genome sequencing (WGS) was conducted on two NOMID patients who presented with Crohn's disease (CD) at the ages of 9 and 15yrs, after 7 and 12 years on IL-1 blocking treatment respectively, and two age-matched NOMID patients without IBD. A PRS, calculated using a model from Monti[2] et al. (PGS003981)[3], was compared to IBD patients (n=28) and non-IBD controls (n=2,673). HLA typing for IBD-associated alleles[4-5] was also analyzed.

Results: Among 41 NOMID patients (median age: 25 years; range: 13–61; 58% female), two developed biopsy-proven CD.

Case 1: A 16-year-old female with a somatic *NLRP3* mutation (p.Gly309Cys) developed CD at age 9, achieving remission with ustekinumab and anakinra.

Case 2: A 20-year-old male with a germline NLRP3 mutation (p.Gly571Arg) developed CD at age 15, achieving remission with infliximab and IL-1 blockers.

WGS did not identify rare variants associated with IBD[6]. SNP analysis revealed homozygosity of a disease-associated LRRK2 SNP rs3761863 in both CD cases, a variant also present in 12 of 25 NOMID patients without CD in homozygosity. PRS values for NOMID patients with CD fell within the range observed in the IBD cohorts. Patients without IBD had lower PRS values, below the median PRS for IBD controls. HLA typing showed no significant skewing of IBD-associated alleles in NOMID patients.

Conclusion: IBD was also reported in 4 of 101 pts from a Japanese CAPS cohort[7]. Including our patients the IBD risk in NOMID may be as high as ~6 in 100 in CAPS/NOMID which is higher than in the general population with a prevalence of 1.3%. A slightly higher PRS and HLA typing do not fully explain IBD susceptibility in NOMID, however the emerging data on CAPS suggests that the CAPS causing NLRP3 variants may contribute to an increased IBD risk. Further research is needed to explore these mechanisms.

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Acknowledgments: This work was supported by the Intramural Research Program at NIAID, NIH.

Disclosure of Interest: None declared

Identifier: PO152

DIAGNOSTIC CHALLENGE: TACKLING VEXAS SYNDROME IN LOW RESOURCE COUNTRIES

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Introduction: The diagnosis of VEXAS requires the presence of a mutation in *UBA1.* Since the discovery of this disease, numerous publications have appeared, mainly from developed countries. To the best of our knowledge, very few or no cases of VEXAS syndrome have been published from emerging countries, This situation raises many questions, including whether the lack of publication is due to a lack of knowledge about VEXAS syndrome or limited access to molecular diagnosis.

Objectives: The aim of our work was to analyse the situation of VEXAS syndrome in resource-poor countries and to answer these questions.

Methods: A cross-sectional study was conducted between 15 May 2024 and 15 June 2024. An electronic form was constructed using Eval and Go® and distributed via email to physicians practicing in emerging countries. The number of patients with suspected VEXAS syndrome and the number of patients with a confirmed diagnosis of VEXAS syndrome were enquired about.

Results: A total of 211 responses were collected. The median age of the physicians was 34 years (interquartile range 29–43). The physicians were based in the following countries: The majority of respondents (67, 31.8%) were from Tunisia, while 44 (20%) were from Morocco, 42 (19.9%) from Romania, 39 (18.5%) from Senegal, 12 (5.7%) from Algeria, 1 (0.5%) from Lebanon, and 5 (2.4%) from other countries.

The second part of the survey comprised a series of questions, which are outlined below:

Are you familiar with the condition known as VEXAS syndrome?

One hundred and twenty-three respondents (60%) indicated that they were aware of VEXAS syndrome, while 81 (40%) stated that they were not.

How many patients in whom VEXAS was suspected?

A total of 172 practitioners responded to this question. The median number of patients in whom VEXAS was suspected was zero (0-10). The median number of patients diagnosed with VEXAS was zero, with a range of 0–1.

Is a molecular diagnosis test for VEXAS available in your country?

Ninety-two respondents (51%) indicated that they were unsure, 42 (24%) responded in the affirmative, and 41 (23%) responded in the negative.

Please specify which genetic diagnostic technique is available in your country.

One hundred and eighteen respondents (77%) indicated that they were unsure. The remaining responses were as follows: Sanger UBA1 (n=21, 14%), new generation sequencing (n=3, 2%), and whole genome sequencing (n=5, 2%).

Did you have a patient with confirmed VEXAS syndrome The patients with VEXAS syndrome originate from Romania (n=5), Morocco (n=2), Tunisia (n=2) and Algeria (n=2), with one additional case from an unidentified country.

Conclusion: The results of our study indicated that 60% of the respondents had heard of VEXAS syndrome and had at least one suspicion of this diagnosis. The responses indicate that 12 cases of patients with VEXAS have been diagnosed, primarily in Romania. According to our survey, the main challenges in VEXAS syndrome are the unavailability of genetic testing and the high cost of testing abroad and a lack of knowledge about the disease among physician.
Disclosure of Interest: None declared

Identifier: PO153

ADULT PATIENTS WITH FAMILIAL MEDITERRANEAN FEVER - A SINGLE CENTER CASE SERIES

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Introduction: Familial Mediterranean Fever (FMF) is a classic autoinflammatory disease (AID) presenting with recurrent attacks of peritonitis, fever and arthritis. It is caused by pathogenic variants in the *MEFV* gene which encodes the pyrin protein. Like many genetic disorders, FMF is often diagnosed in childhood and is well described in the pediatric population. It is increasingly recognized however, that FMF patients may present for the first time in adulthood. The clinical characteristics and challenges faced when accessing treatment may be different in adult patients with FMF.
Objectives: Describe the clinical and genetic characteristics of adult patients with FMF and identify potential challenges in the diagnosis and treatment in this population.
Methods: Patients over age 18 years meeting the Tel HaShomer diagnostic criteria for FMF were recruited from an Autoinflammatory Clinic in Toronto. Clinical records and data were reviewed and analyzed. Gene panel testing was performed at the Division of Genome Diagnostics, Hospital for Sick Children. All patients provided written consent to be included in a case series.
Results: A total of 24 patients were included (58% male). The including Middle Eastern (45%), Caucasian (18%), Southeast Asian and African (both 14%). The median age at: i) enrollment was 44 years, ii) symptom onset was 12.5 years, and iii) diagnosis was 35.5 years. Seven patients had first symptom onset after age 18. The median diagnostic delay was 6.5 years. A family history of FMF was present in 63% of patients.

Two-thirds of patients reported specific triggers for flares for which the most common was stress (41%). The most common symptoms were abdominal pain (96%), followed by fever (91%) and arthritis (72%). CRP was elevated during flares in 89% of patients. Notable comorbidities included spondyloarthropathy in two patients.

Genetic testing was available in 23 patients - 14 were homozygous/compound heterozygous and eight were heterozygous for variants in *MEFV*. One patient did not carry any *MEFV* variants. The most common variants were V726A (8/23), M694V/M680I/E148Q (each in 5/23), and M694I (2/23). All were variants of uncertain significance, or likely/pathogenic as classified by the American College of Medical Geneticists. One patient carried three variants in *MEFV* (homozygous E148Q, and p369S), while two patients carried additional *NOD2* variants (R791W, R702W).

Eighty-six percent of patients responded to colchicine, but 55% reported side effects. As such, IL-1 inhibitors (anakinra or canakinumab) were applied for eight patients to the provincial Exceptional Access Program. Funding for this medication was denied in seven. Compassionate medication-release was provided to five patients, for which four exhibited marked benefit.

Conclusion: FMF remains an under-recognized entity as demonstrated by the significant diagnostic delay (maximum 42 years) in our cohort. Moreover, it can present for the first time in adulthood (33% of our cohort). Although colchicine is the first line treatment in FMF, over half of our cohort experienced intolerance. IL-1 blockade has been shown to be

highly effective, but limited access to public funding remains a significant barrier. It will be important to continue to raise awareness for FMF and advocate for improved access to genetic testing as well as effective, evidence-based therapy.
Acknowledgments: We thank all the patients and their families for involving us in their care and allowing their stories to be anonymously shared. We thank our collaborators for sharing their cases and contributing to our cohort.
Disclosure of Interest: None declared

Identifier: PO154

PATH TO DIAGNOSIS IN FAMILIAL MEDITERRANEAN FEVER (FMF)

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Introduction: Familial Mediterranean Fever (FMF) is a genetic disorder characterized by recurrent febrile episodes and inflammation, most commonly presenting with peritonitis, pleuritis, and arthritis. The study investigates the varied pathways to FMF, exploring the duration from symptom onset and diagnostic processes among a cohort of participants.
Objectives: To address the path to diagnosis of FMF, diagnostic delay and need for standardized protocols.
Methods: This study involved surveying patients at an autoinflammatory clinic to explore the diagnostic pathways leading to the identification of FMF.
Results: A sample of 300 patients with a mean age of 38.2 years (12.2 years, range 16-72), consisting of 209 males and 92 females was examined. Before their FMF diagnosis, patients consulted various specialties: 38.9% with internal medicine, 18.9% with pediatrics, and 15.3% with emergency medicine. Additionally, 26.7% consulted other departments. Regarding referrals, 47.5% were referred to another specialty, while 52.5% were not. Among the participants, 25.9% were initially referred to rheumatology. 46.5% did not receive any initial referral. In the initial consultation with the rheumatologist, 59.8% received an FMF diagnosis and started colchicine treatment with a follow-up appointment scheduled. (Table 1.) 38.9% waited between 1 to 5 years from the onset of initial symptoms to their diagnosis by the rheumatologist for FMF. Following the diagnosis of FMF, 31.9% of patients continued their follow-up with the doctor who initially diagnosed them, while 68.1% did not continue with the diagnosis doctor. After receiving a diagnosis of FMF, treatment for FMF typically started within one day for 68.6% of patients, 14.0% began treatment within 1-2 weeks, 6.6% within 1 month, 3.7% within 1-3 months, and 7.0% started treatment after 3 months or more. After starting their first FMF preventive medication, 68.4% experienced four or more attacks requiring additional medication. Additionally, 8.3% had two episodes, 4.7% had three episodes, and another 4.7% had one episode. 14.0% did not experience any attacks after starting treatment. 89.7% secured appointments with their rheumatologist in less than a week, while 7.0% experienced waits exceeding a month. 17.9% of participants reported trying alternative approaches, while 82.1% did not pursue alternative treatments. 49.5% expressed confidence regarding future improvement in their condition, 31.9% were not optimistic, and 18.6% were uncertain.

Table 1. Processes Following FMF Diagnosis and Treatment Initiation

Process Description	n (%)
Diagnosed with FMF, started colchicine treatment, no follow-up appointment given	10 (3.3)
Diagnosed with FMF, started colchicine treatment, follow-up appointment provided	180 (59.8)
Tests conducted, treatment initiated, follow-up appointment scheduled	91 (30.2)

Tests conducted, advised for treatment-free monitoring, follow-up appointment scheduled	13 (4.3)
Treatment initiated, no follow-up appointment provided	7 (2.3)

Conclusion: These findings highlight varied initial consultations for FMF, showing significant diagnosis delays and frequent changes in healthcare providers post-diagnosis, emphasizing the need for standardized protocols to improve care continuity.

Disclosure of Interest: None declared

Identifier: PO155

TNF-RECEPTOR ASSOCIATED PERIODIC SYNDROME: AN ANALYSIS OF SLOVAKIAN COHORT OF TRAPS PATIENTS

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Introduction: TNF-Receptor Associated Periodic Fever Syndrome (TRAPS) is a rare autosomal dominant systemic autoinflammatory disease. It is caused by mutations in *TNFRSF1A* gene. TRAPS is a disease with very variable clinical presentation.

Objectives: We have aimed to characterise the clinical and genetic features of TNF-Receptor Associated Periodic Fever Syndrome (TRAPS) patients diagnosed and treated in Slovakia. Our intent was also to evaluate therapeutic response to canakinumab.

Methods: We have concluded a retrospective analysis of seven TRAPS patients diagnosed between 2019 and 2022 across three national centres for periodic fever syndromes in Slovakia.

Results: The cohort consists of 6 adult patients and one child patient. The gender ratio was 7:0, all of the patients were female. The median age of clinical disease onset was 6 years (0.67 [8 months] – 30 years). One patient had adult-onset form of the disease. The average diagnostic delay was 25.43 years (0–54). Six of the seven patients had a positive family history of TRAPS. The most frequent symptoms were **recurrent episodes of fever** (6/7), a **skin rash** (mostly in form of a migratory painful erythematous rash) (6/7), **arthralgia** (6/7), **myalgia**, (5/7), **abdominal pain** (4/7), **chest pain** (4/7) and **general fatigue** (4/7). Organ **amyloidosis**, the most severe consequence of TRAPS, was present in one patient. All of the patients were treated with interleukin-1 beta (IL-1ß) inhibitors. Four variants in TNFRSF1A gene were detected, including **R121Q** (also referred to as R92Q), **N145S** (also referred to as N116S), **C30Y**, and **C52F**. Variant N145S is very scarcely described in literature.

Conclusion: This is the first and largest cohort of TRAPS patients reported in the Slovak republic. According to the prevalence of the disease, it is most likely that we have identified and detected all of the patients in the country. We have identified the clinical diversity of the disease and favourable therapeutic response to IL-1ß inhibition. Although TRAPS is a rare disease, it is important to improve awareness of it.

Acknowledgments: This publication has been produced with the support of the Integrated Infrastructure Operational Program for the project: Systemic Public Research Infrastructure –
Biobank for Cancer and Rare Diseases, ITMS: 313011AFG5, co-financed by the European Regional Development Fund.
This work was supported by the Comenius University
Grant No. UK/3133/2024.

Disclosure of Interest: None declared

Identifier: PO157

FAMILIAL MEDITERRANEAN FEVER AMONG ADULT PATIENTS: A MULTICENTRIC STUDY IN TUNISIA

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Introduction: Familial Mediterranean Fever (FMF) is the most common auto inflammatory disease.

Tunisia is a high-prevalence country for FMF. To date, we have no prevalence for FMF in Tunisia, and few studies have been published on the subject.

Objectives: The aim of our study was to determine the clinical, biological and genetic profile of adult patients followed for FMF.

Methods: We conducted a multicenter cross-sectional study over the month of December 2024 including adult patients with genetically confirmed FMF.

Results: We included 55 patients with a genetically confirmed diagnosis of FMF. The sex ratio was 1.57. Mean age at inclusion was 39.78 years +/- 11.51.

Mean age of onset of FMF-related symptoms was 17.08+/- 11.91. Mean age of FMF diagnosis was 26.6 years +/- 14.84. Median year of FMF diagnosis was 2013[1987-2024]. A delay of more than 10 years between onset of symptoms and FMF diagnosis was reported in 25 patients (45%). Febrile abdominal pain was noted in all patients.Arthralgia or arthritis was reported in 30 patents (54%) Pseudoerysipelas of the ankles was noted in 3 patients. The mean white blood cell count during crisis was 11464 +/- 5650 Elements/ mm3. Mean CRP during cris was 102+/- 77 mg/l.

Regarding genetic mutations in the *MEFV* gene : 28 (50%) patients had homozygous or double heterozygous mutation. Seventeen (30%) patients had an heterozygous mutation in *MEFV.* two patients had a mutation I692del/E148Q and two patients had E148Q/- mutation.

The diseases associated with FMF were distributed as follows

Ankylosing spondylitis (n=4), IgA vasculitis (n=1), FMF coxitis (n=1), Psoriatic rheumatism (n=1). AA amyloidosis was noted in 3 patients. Therapeutically, 48 patients were on colchicine and 3 patients were on TNF blockers for associated spondylarthritis. The disease was well controlled in 41(80%) patients, and poorly controlled in 8 (16%). One patient was in chronic renal failure without hemodialysis.

Conclusion: Despite Tunisian physicians' awareness of FMF, 45% of patients in our cohort were in diagnostic wandering. Eight patients (16%) in our cohort had poorly controlled disease, given the unavailability of anti-Il1 drugs in our country, which represents a therapeutic challenge.

Acknowledgments: Société Tunisienne de médecine interne
All the collaborators from TUN-FMF working group

Disclosure of Interest: None declared

Identifier: PO158

NEMO-NDAS: DIVERSE CLINICAL PRESENTATIONS AND PENETRANCE IN THREE PEDIATRIC PATIENTS

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Introduction: The NF-KB essential modulator deleted exon 5 auto-inflammatory syndrome (NEMO-NDAS) is a recently described X-linked recessive autoinflammatory disease caused by the deletion of exon 5 of the IKBKG gene. Patients typically present with autoinflammatory manifestations such as early-onset panniculitis, fever, and lipoatrophy. This disease is characterized by hyperactivation of NF-kB, leading to increased production of type 1 interferons.
Objectives: We report 3 patients with NEMO-NDAS syndrome who exhibit variable manifestations, including recurrent infections and autoinflammatory symptoms.
Methods: This report is based on a retrospective chart review that includes clinical manifestations, laboratory investigations, extended genetic segregation analysis, treatment, and outcomes of three patients with NEMO-NDAS managed at two tertiary hospitals in Riyadh, Saudi Arabia.
Results: Three patients (2 males and one female) from three unrelated families were identified, all with heterozygous variants of *the IKBKG* gene (NM_001099856.2: c.723-19_723-2del). Their current ages are 15, 24, and 30 months, with disease onset occurring within the first three months of life. Common presentations included early-onset fever, and subcutaneous nodules resembling lobular panniculitis. Two patients have conical teeth, while two others presented with short stature, lymphadenopathy, and hepatosplenomegaly. Marked anemia requiring blood transfusions was observed in two patients. All the patients displayed significantly elevated C-reactive protein (CRP)levels, with one showing a mild elevation of sedimentation rate (ESR). Liver enzymes were elevated in two patients, and all patients had low albumin levels. Two patients had low immunoglobulin G and A levels; among them, one had B-cell lymphopenia. MRI of the brain revealed ventriculomegaly in one patient. The clinical course of one patient was complicated by recurrent opportunistic infections, including adenovirus viremia associated with ARDS, pneumatocele, respiratory failure with Pneumocystis jiroveci pneumonia, oral candidiasis, and multiple positive blood cultures for Enterococcus faecalis, Lactococcus Lactis, and E coli, ultimately leading to death. Extended family segregation analysis of patient 1 identified the same genetic mutation in his asymptomatic mother, a 14-year-old brother, and four asymptomatic adult uncles. The family segregation of patient 2 revealed the same mutation in his mother and two asymptomatic sisters, while parents of patient 3 showed no detectable mutations. In terms of management, one patient achieved disease control with adalimumab and IVIG, while another showed significant improvement on Baricitinib, adalimumab, and prednisone, albeit with mild residual disease activity.
Conclusion: This report suggests a potential autosomal dominant-like inheritance pattern with variable penetrance of NEMO-NDAS. The disease manifestations, clinical course, and response to therapy varied significantly ranging from autoinflammatory manifestations to an immunodeficiency phenotype.

Disclosure of Interest: None declared

Identifier: PO159

A CASE OF MUCKLE-WELLS SYNDROME WITH HYPERTROPHIC PACHYMENINGITIS IN WHICH A NOVEL NLRP3 GENE VARIANT WAS IDENTIFIED

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Introduction: We present the case of a 50-year-old man with hearing loss. He has had cold urticaria since childhood. He suffered bilateral hearing loss at the age of 23 and began using bilateral hearing aids at the age of 35. He had repeated migraines since he was young. At the age of 49, his headache worsened, and he was referred to the neurosurgery department of our hospital. He was transferred to our department for the purpose of examining the primary disease. He had hearing loss from the age of 23, a family history of hearing loss (mother, uncle, brother), cold-stimulated urticaria, daily headache suspected of chronic aseptic meningitis, and joint symptoms, so he suspected an autoinflammatory disease, especially Muckle-Wells syndrome (MWS).
Objectives: The purpose of this study was to clarify the clinical features of this case, and because the possibility of MWS was high, to identify the *NLRP3* gene variant and determine whether the variant was a disease gene variant.
Methods: 1) We clarified the clinical features and complications of this case. 2) The presence or absence of *NLRP3* variants was examined using the Sanger method. 3) To confirm whether the obtained variant was a disease gene variant, a THP1 cell death assay was performed. After stimulating THP1 cells with PMA to differentiate, a plasmid incorporating GFP with a *NLRP3* variant was introduced by electroporation, and the proportion of dead cells was measured by flow cytometry at each time point.
Results: 1) His head MRI showed hypertrophic pachymeningitis (HP). Cryopyrin-associated periodic fever syndromes, including MWS, can present with aseptic meningitis, but there have been no reports of HP as in this case, making this a rare case. 2) A genetic test was performed and a novel heterozygous gene variant M635T (c.1910T>C, p. Met635Thr) was found in the *NLRP3* gene, and he was diagnosed with MWS. 3) An increase in dead cells was observed at each time point in the M635T-introduced cells, suggesting that the M635T variant may be a disease gene variant.
Conclusion: To our knowledge, this is the first case of MWS with a new disease gene variant complicated with HP.
Acknowledgments: The authors would like to thank Ms. Kyoko Yamaguchi and Ms. Masako Hayakawa for their help with experiments.
Disclosure of Interest: None declared

Identifier: PO160

VEXAS SYNDROME IN TUNISIA: A RARE DIAGNOSIS, A FIRST REPORT

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Introduction: The VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) syndrome is a recently described autoinflammatory condition caused by somatic mutations in the *UBA1* gene. It is characterized by systemic inflammation, hematological abnormalities, and multisystemic involvement posing diagnostic challenges.

Since its initial description, VEXAS has been reported in several countries.

Objectives: This report describes the **first case** of VEXAS syndrome diagnosed in Tunisia, emphasizing the importance of recognizing this rare condition in North Africa.

Methods: Observation:

A 70-year-old male patient was admitted for the evaluation of recurrent fever in the context of general health deterioration, associated with episodes of arthritis.

His medical history included recurrent anterior uveitis since 2022, sensory-motor polyneuropathy predominantly affecting the lower limbs, and two episodes of myopericarditis.

Clinical examination revealed profound asthenia, synovitis affecting large joints, and generalized maculopapular lesions sparing the face.

Biological investigations showed a marked inflammatory syndrome with bicytopenia consisting of leuko-lymphopenia and severe normochromic normocytic anemia. Serum protein electrophoresis (SPEP) demonstrated a polyclonal gamma-globulin peak.

Radiologically, thoraco-abdominal-pelvic CT (TAP) revealed bilateral pulmonary parenchymal consolidations and hepatosplenomegaly, with no additional evidence of malignancy.

Comprehensive infectious and inflammatory workups were unremarkable, and the immunological panel was negative. PET imaging showed no abnormalities, particularly no deep infectious focus, malignancy, or vasculitis. Bone marrow analysis demonstrated signs of dyserythropoiesis.

In the absence of infectious, inflammatory, or neoplastic causes and considering the patient's medical history, an autoinflammatory etiology was suspected, with a strong suspicion of VEXAS syndrome. Genetic testing confirmed the presence of somatic mutations in the *UBA1* gene with the presence of the pathogenic variant c.122T> C in the *UBA1* gene at the heterozygous state, detected in both peripheral blood and bone marrow, leading to the diagnosis. The patient was started on corticosteroid therapy while awaiting access to with anti-interleukin-6 therapy, with a favorable clinical and biological response observed.

Results: Discussion

This case highlights the diagnostic complexity of VEXAS syndrome due to its overlapping clinical features with other inflammatory and hematological disorders. The presence of recurrent systemic inflammation, hematological abnormalities, and multiorgan involvement should raise suspicion for VEXAS syndrome, particularly in elderly males. Genetic confirmation of UBA1 mutations is essential for definitive diagnosis.

Conclusion: This report represents the first documented case of VEXAS syndrome in Tunisia. Early recognition and diagnosis are critical for appropriate management and prognosis. Further studies are needed to explore the prevalence and clinical spectrum of VEXAS syndrome in North Africa.

Disclosure of Interest: None declared

Identifier: PO161

ANAKINRA IS A FAST AND EFFECTIVE TREATMENT OPTION IN SUBSIDING FMF EPISODES AND THEREBY, IN DECREASING HOSPITALIZATION RATES : FUTURE PROSPECTS FOR READILY AVAILABLE, HOME-USE ANAKINRA INJECTORS

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Introduction: Familial Mediterranean fever (FMF) is the most common inherited autoinflammatory disease worldwide. Although the episodes of FMF are usually self-limiting, there is a significant need for therapies to terminate/shorten or subside these episodes, thereby to decrease hospitalization rates and to improve the health quality of FMF patients with frequent attacks.
Objectives: To compare the efficacy of two widely-used treatment modalities during an FMF episode.
Methods: The study only enrolled FMF patients admitted to emergency room (ER). In order to form a genotype-homogeneous group, patients with homozygous or compound heterozygous mutations for only 4 variants (M694V, M680I, M694I, V726A variants, all of which are pathogenic according to INFEVERS database) were included in the study. In the routine clinical setting, for patients admitted to the ER with an FMF attack, one of the following two different treatment modalities is selected as a first-line therapy according to the decision of the consultant pediatric rheumatologist: subcutaneous anakinra (Group 1) and intravenous 0.9% saline ± any NSAID (Group 2). Acute phase markers, clinical characteristics of attack, and pain visual analog scale (VAS) scores were recorded at baseline and also prospectively recorded after the administration of these treatment options. Following discharge of the patients, pain VAS scores were monitored by phone call at every two hours, and CRP levels were measured at the 24th hour of therapy.
Results: Of 56 patients, 28 (50%) were female. The median age of the patients at disease onset, at diagnosis, and at last visit were 3 (1.5-6), 4 (2.5-7), and 14.8 (9.8-18.5) years, respectively. The yearly median number of attack was 3.5 (2-10). More than half (53.5%) the patients reported an irregular use of colchicine. The most frequent clinical manifestations during the attack were abdominal pain (85.7%), chest pain (57.1%) and fever (53.5%) . The median duration of the attack was 24 (6-48) hours after administration of the treatment.

Of 56 patients, nine (n=9) were excluded since they received combination of therapies including anakinra plus intravenous 0.9% saline or anakinra plus any NSAID. Group 1 included 22 FMF patients and Group 2 included 25 patients. Compared to Group 2, patients whose FMF episode have been treated with only anakinra had statistically lower pain VAS scores at 6^{th},12^{th} and 24^{th} hours of drug administration ($p<0.05$). Moreover, the reduction in CRP levels at 24^{th} of drug application was more pronounced in anakinra group (Mean baseline CRP: 140.7 (±79.9), Mean CRP at 24^{th} hour: 108.0 (±45.9)) than those in Group 2 (Mean baseline CRP: 88.2 (±68.9), Mean CRP at 24^{th} hour: 87.3 (±63.8)).

Conclusion: Anakinra treatment provided a rapid improvement in pain VAS scores and a marked decline in CRP levels comparing to other widely used inpatient /outpatient FMF episode therapy. This result could pave the way for readily available, home-use anakinra injectors for a particular group of FMF patients with frequent attacks. In conclusion, faster alleviation of FMF episodes by a single-dose anakinra injection could decrease the hospitalization rates of FMF patients, which in turn also could result in a decrease in financial medical burden of FMF patients particularly in countries prevalent for FMF.
Disclosure of Interest: None declared

Identifier: PO162

CLINICAL SPECTRUM AND GENETIC PROFILE OF MEVALONATE KINASE DEFICIENCY: OUR EXPERIENCE FROM NORTH-WEST INDIA

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Introduction: Mevalonate kinase (MVK) deficiency is a rare autoinflammatory disorder characterized by recurrent fever, rash, musculoskeletal symptoms, & gastrointestinal manifestations. The condition often mimics other inflammatory diseases, leading to delayed diagnosis & complications. The lack of anti-IL-1 therapy in resource-limited countries further complicates management.

Objectives:

Methods: We reviewed case records of 7 patients from 5 families with genetically confirmed MVK deficiency under treatment at our center. Clinical features, laboratory findings, genetic results, & treatment responses were analyzed to highlight the disorder's phenotypic variability.

Results: Patients exhibited various clinical features, including recurrent fever, rash, arthritis, hepatosplenomegaly, & lymphadenopathy. Initial diagnoses included Behçet's disease, inflammatory bowel disease, & systemic juvenile arthritis. Prominent gastrointestinal symptoms were noted in 5/7 children. Elevated inflammatory markers and IgA levels were observed in all patients, while elevated urinary mevalonic acid levels were detected in 4/7 patients during acute attacks. Genetic testing revealed compound heterozygous mutations in Exons 9, 10, & 11, and homozygous mutations in Exons 6 & 11. The Dutch variant (p.Val377Ile) was identified in 3 patients from 2 families. Due to the unavailability of anakinra, corticosteroids and colchicine were initially used for most patients. Anakinra, procured on a named patient basis, resulted in clinical improvement for some, though financial constraints limited optimal treatment

Table: Clinical features, lab results, genetic findings, and treatments of MVK patients at our center

Patients	Symptoms	Investigations	Genetics	Outcome
Pt 1	Neonatal cholestasis Refractory anemia Recurrent fever Hepatosplenomegaly & tender lymphadenopathy	ESR- 80mm/hr CRP- 56mg/dl Ig A- 144 mg/dl (N 28-112 mg/dl) Urine mevalonic acid-Positive	Compound heterozygous Exon 9 c.803T>C p.Ile268Thr Exon10c.976G>Ap.Gly 326 Arg	Canakinumab
Pt 2 (sibling of Pt 1)	Same as Pt 1	Urine mevalonic acid-Positive	Compound heterozygous Exon 9 c.803T>C p.Ile268Thr Exon 10 c.976G>A p.Gly326 Arg	Canakinumab

Pt 3	Arthritis and maculapapular rash, abdominal pain, hepatosplenomegaly, motor delay, tender lymphadenopathy, colitis; Dyserythropoetic anaemia	ESR- 109mm/hr CRP- 100mg/dl Ig A- 303mg/dl (N 28-112 mg/dl) Urine mevalonic acid- Positive		Corticosteroids, colchicine Anakinra
Pt 4 (North Indian)	Periodic fever, associated with oral and genital ulcers, tender lymphadenopathy, abdominal pain	ESR- 42mm/hr CRP- 207mg/dl Ig A- 140 mg/dl (N 28-112 mg/dl) Urine mevalonic acid- negative	Homozygous MVK Exon 11, c.1129G>A p.Val377Ile (Dutch variant)	Thalidomide, colchine corticosteroids, Anakinra
Pt 5	Fever for 5 days, 8-10 episodes per year, hepatosplenomegaly Bilateral non-tender cervical lymphadenopathy, frontal bossing	ESR- 80mm/hr CRP- 118mg/dl Ig A- 886 mg/dl (N 46-144 mg/dl)Urine mevalonic acid- positive	HomozygousMVK Exon 11, c.928G>A p.Val310Met	corticosteroids,colchicine No recurrence of fever
Pt 6 (South India)	Recurrent fever Oral ulcers Hepatosplenomegaly and tender lymphadenopathy Failure to thrive	ESR- 80mm/hr CRP- 56mg/dl Ig A- 144 mg/dl (N 28-112 mg/dl) Urine mevalonic acid- negative	Compound heterozygous mutation *MVK* Exon 11 c.1129G>A (p.Val377Ile);	Colchicine To be initiated onanakinra

			Intron 8 c.768+1G>A(p.Gly326 Arg)	
Pt 7 (sibling of Pt 6)	Similar complaints	Urine mevalonic acid-negative	Compound heterozygous mutation *MVK* Exon 11 c.1129G>A (p.Val377Ile); Intron 8 c.768+1G>A(p.Gly326 Arg)	Colchicine To be initiated onanakinra

Conclusion: MVK deficiency presents diverse clinical symptoms that often overlap with other autoinflammatory & rheumatologic disorders. High clinical suspicion is crucial in pediatric patients with recurrent fever, rash, arthritis, & systemic inflammation, especially when symptoms don't align with conventional diagnostic criteria for other inflammatory conditions.

Disclosure of Interest: None declared

Identifier: PO164

PROLONGED URTICARIA AND FEVER IN A LIBYAN TODDLER BOY

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Introduction: Cryopyrin-associated periodic fever syndrome (CAPS) is a disease group entity that is becoming more widely recognised, exhibiting a variety of symptoms.CAPS consists of three clinical entities: familial cold-induced autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS), and chronic inflammatory neurologic cutaneous and articular syndrome (CINCA), all of which share significant clinical symptoms. These individuals frequently appear with early-onset fever and rash, as well as a variety of systemic signs and symptoms, making it an excellent mimic for other systemic autoimmune disorders.

Objectives: Highlighting the challenges, such as a lack of genetic analysis and an absence of biological treatment for these cases , as well as the importance of genetic tests, can help in prompt diagnosis and early initiation of biological agents, potentially reducing the patient's long-term complications.

Methods: Case report

Results: A 15-month-old boy who presented with history of chronic urticaria-like rash, fever,conjunctival injection and high inflammatory markers, and was initially diagnosed with "Kawasaki disease." Twenty days '' after admission.The laboratory results showed significant leucocytosis, neutrophilia, and raised inflammatory markers (elevated levels of acute phase reactants 280mg/dl, ESR 135ml/hr), without indications of circulating autoantibodies or underlying infections .He received i.v. immunoglobulin (2 g/kg) first, followed by a second dose of IVIG and methpredinsolone (30mg/kg) for 3 days, with only a brief relief of fever, conjunctival injection, and rash , he met his developmental milestones adequately, but his head was noted to have a distinctive shape. An MRI brain indicated crynosynotosis (he tolerated standard vaccines without problem).There is no family history of urticaria or immunodeficiency ,autoimmune disease or recurrent fever. Both his parents are in good health. Multiple treatment options, including NSAIDs, corticosteroids, methotrexate, and colchicine, resulted in poor or partial responses.Following a series of rigorous diagnostic investigations included (bone marrow aspiration & biopsy), the patient eventually came up with a case of CAPS.Further investigations are required including skin biopsy, and genetic analysis may be beneficial to clarify the diagnosis.

Conclusion: We herein describe the case of a patient with a clinical features compatible with CAPS, whether it is CINCA or MWS.our findings highlight the significance of genetic testing and biological therapy in dealing with this complex illness in children.which may improve long-term outcomes for patients with CAPS.

Disclosure of Interest: None declared

Identifier: PO165

CLINICAL AND GENETIC PROFILE OF ROMANIAN PATIENTS DIAGNOSED WITH MEFV-ASSOCIATED AUTOINFLAMMATORY DISEASE: PRELIMINARY RESULTS OF THE RO_FMF STUDY

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Introduction: Despite the scarce information regarding Familial Mediterranean fever patients from low prevalence countries, the increasing accessibility of genetic testing, in conjunction with phenotype-genotype correlation, will allow for a better characterization of the MEFV spectrum of autoinflammatory diseases.
Objectives: Clinical and genetic characterization of a group of Romanian patients included in the RO_FMF study (Romanian Familial Mediterranean Fever Study), diagnosed with autoinflammatory disease associated with MEFV gene mutations (predominantly with a phenotype of Familial Mediterranean fever).
Methods: We retrospectively included 17 patients with confirmed MEFV gene mutations that presented compatible symptoms for autoinflammatory diseases associated with this spectrum.
Results: The cohort of 17 patients is predominantly comprised of males (53%), half of which presented a symptom onset during adulthood. The clinical picture was mainly characterized by fever (88%), abdominal pain (65%) and arthralgia/arthritis (47%). Regarding their genetic spectrum: only one patient presented a homozygous pathogenic mutation (c.2080A>G [p.Met694 Val]), two patients presented a homozygous status for the benign variant c.605G>A (p.Arg202Gln), with mild clinical manifestations and responsiveness to colchicine, eight patients presented a double heterozygous status and five patients presented heterozygous pathogenic mutations (compatible clinical presentation, but with mild phenotypes, responsive to colchicine). We note a single patient presenting a heterozygous variant of unknown significance at the level of exon 2.
Conclusion: In our cohort we observed a low frequency of homozygous status for pathogenic mutations, but an increased frequency of the double heterozygous status. Also, a significant proportion of heterozygous patients was noted, associated with milder forms of the disease, responding well to colchicine treatment. Such studies need to be expanded upon in order to have more data regarding the profile of patients from low prevalence countries, such as Romania, with autoinflammatory diseases linked to MEFV gene mutations.
Disclosure of Interest: None declared

Identifier: PO166

CLINICAL PRESENTATION AND GENETICS OF SUSPECTED MONOGENIC AUTOINFLAMMATORY DISEASES IN A SINGLE CENTRE AUSTRALIAN PAEDIATRIC RHEUMATOLOGY COHORT

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Introduction: Genomic testing may be indicated for a subset of paediatric rheumatology patients suspected to have a monogenic autoinflammatory disease. The clinical presentation of these conditions and the utility and yield of genetic testing in this group in Australia is unknown.
Objectives: To describe the clinical presentation and genomic testing of a single centre cohort of Australian paediatric rheumatology patients with suspected monogenic autoinflammatory disease.
Methods: All patients referred from rheumatology to genetics, all autoinflammatory clinic patients and any patients who underwent genetic tests requested by rheumatology at a single centre in Melbourne Australia between 2009 and 2024 were identified.

Data collected included patient demographics, clinical features, genetic testing method and results. The Eurofever/PRINTO classification criteria for autoinflammatory recurrent fevers were retrospectively applied in cases of recurrent fever.

Results: 141 patients were identified. 36 patients were excluded due to non-inflammatory indications.

Indications for genetic testing in 105 patients were; 22 (21%) suspected FMF (group 1), 28 (27%) suspected PFAPA (group 2), 11 (11%) undefined recurrent fever (group 3), 16 (15%) suspected monogenic syndrome other than FMF (group 4) and 25 (24%) with a primary manifestation other than fever (group 5).

Group 1

14 (64%) met clinical classification criteria for FMF. The median FMF score was 6/9. No patients met classification criteria for PFAPA. The most common clinical features were fever (100%), no urticaria (90%), abdominal pain (86%) and eastern Mediterranean ethnicity (86%).

All patients had genetic testing. 14 (64%) had single gene Sanger sequencing, 5 (23%) multiple gene panel and 3 (14%) had Sanger sequencing combined with whole exome sequencing.

17 (77%) had an actionable genetic result. If classification criteria were met this increased to 79%.

3 (18%) had a single MEFV variant, 14 (82%) had two MEFV variants. The most common MEFV variants of the 31 identified were c.2080A>G (p. Met694Val) (16 (52%)) and c.2177T>C (p. Val726Ala) (6 (19%)).

Group 2

12 (43%) met clinical classification criteria for PFAPA. The median PFAPA score was 6/8. 1 (4%) met clinical classification criteria for FMF. The most common clinical features were fever 28 (100%), no chest pain 28 (100%), no arthritis 28 (100%) and periodicity 26 (93%).

14 (50%) had genetic testing. 1 (7%) had an actionable genetic result (heterozygous MEFV) which remained stable at 8% for those meeting PFAPA classification criteria. VUS was reported in 4 (23%).

Group 3

For undefined recurrent fever, 2 (18%) met classification criteria for PFAPA with a median PFAPA score of 6/9. 4 (36%) met classification criteria for FMF with a median FMF score of 5/9. 10 (91%) had genetic testing and 2 (20%) had an actionable genetic result (compound heterozygote AIRE, heterozygous MEFV). VUS was reported in 4 (40%).

Group 4

16 patients had a suspected monogenic syndrome other than FMF: CAPS 9(56%), TRAPS 4 (25%), DADA2 1(6%), SAVI 1(6%), MKD 1(6%). All had genetic testing. 12 (75%) had an actionable genetic result. VUS was reported in 3 (19%).

Group 5

Primary clinical manifestations other than fever for 22 patients included rash, uveitis, carditis, bone marrow syndromes, vasculitis, arthritis, ulceration and family history of immune dysregulation. 22 (88%) had genetic testing. 12 (55%) had an actionable genetic result. VUS was reported in 5 (23%).

Conclusion: Yield of genetic testing was highest in cases of suspected FMF and suspected monogenic fever syndromes and lowest in patients with suspected PFAPA. The results of this audit may inform the future use of genetic testing in paediatric rheumatology in Australia.
Acknowledgments: Melbourne Genomics Health Alliance -Implementation Fellowship
Disclosure of Interest: None declared

Identifier: PO167

PRESENTATION OF PATIENTS WITH NOD2 GENE VARIANTS - A CASE SERIES

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Introduction: NOD2 is an intracellular receptor involved in the innate defense against pathogens, which induces an inflammatory response through various pathways, including NF-κB, caspase 1, IL-1, and type 1 interferon. Most commonly, variants of the genes encoding NOD2 are associated with Crohn's disease, Blau syndrome, early-onset sarcoidosis, and Yao syndrome.

Objectives: To describe the clinical phenotypes of patients with NOD2 gene variants and symptoms of autoinflammatory diseases, as well as the treatments they received.

Methods: Adult patients with NOD2 gene variants were selected from the databases of the authors' institutions, members of the Romanian Autoinflammatory Disease Group (GRAI).

Results: Ten cases were diagnosed (6 females and 4 males), with a mean age of onset of 27.2 years (3-50) and a mean age at molecular diagnosis of 41 years (25-60). Presentations included vasculitis (leukocytoclastic, Behcet's or Behcet-like disease, Cogan syndrome, aortitis) (5/10), Blau syndrome (3/10), Yao syndrome (2/10), relapsing polychondritis, recurrent panniculitis, chronic recurrent multifocal osteitis, undifferentiated spondyloarthritis, juvenile idiopathic arthritis, psoriatic arthritis, sarcoidosis, recurrent serositis, autoimmune hepatitis, or recurrent lower limb edema. Fever was inconsistently present (6/10 patients, brief episodes at various intervals). Inflammatory bowel disease was excluded in all cases, while 3 patients presented with irritable bowel syndrome. Most patients had heterozygous variants of uncertain significance (VUS) of the NOD2 gene; only one patient, with Blau syndrome and recurrent granulomatous uveitis and arthritis, carried a pathogenic NOD2 mutation. The most common variant was c.2104C>T (p.Arg704Trp), found in 4 unrelated patients-2 presenting with vasculitis and 2 with Yao syndrome. Treatments, in addition to glucocorticoids and non-steroidal anti-inflammatory drugs, included colchicine, azathioprine, methotrexate, sulfasalazine, or leflunomide. The majority of patients responded favorably to glucocorticoids and azathioprine (5/10), while the 2 patients diagnosed with Yao syndrome responded to sulfasalazine.

Conclusion: Patients with NOD2 gene variants and suspected autoinflammatory disease may present with a wide range of clinical manifestations. Autoinflammatory diseases should be highly suspected in cases with unusual manifestations and genetic testing could be taken into consideration. Even variants of uncertain significance could be relevant in specific clinical contexts and can guide the clinician towards a clearer diagnosis. Further genotype-phenotype correlation studies are necessary as well as gene descriptions according to geographical location since there could be differences in variants depending on the population.

Disclosure of Interest: None declared

Identifier: PO168

INFLAMMATORY BIOMARKER ANALYSIS CONFIRMS REDUCED DISEASE SEVERITY IN HETEROZYGOUS PATIENTS WITH FAMILIAL MEDITERRANEAN FEVER

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Introduction: Familial Mediterranean fever (FMF) is a genetic disease leading to recurrent episodes of inflammation. Two pathogenic variants are required for classical disease, but the disease can occur in heterozygous patients. Patients are treated continuously with colchicine to prevent amyloid A (AA) amyloidosis, including heterozygous patients who display a moderate form of FMF and rarely develop AA amyloidosis. The need for lifelong colchicine treatment in heterozygous FMF is therefore controversial.
Objectives: We aimed to characterise genotype-specific levels of inflammatory biomarkers, and to focus on heterozygous patients who discontinued colchicine.
Methods: All patients with FMF from the European databases AIDnet and JIRcohort who received colchicine during follow-up were included. Demographics, C reactive protein (CRP), serum amyloid A (SAA), S100A8/A9 and S100A12 levels, leucocyte and neutrophil counts were extracted. Visits were classified as active, subclinical or inactive according to symptoms, CRP and SAA levels.
Results: Data from 747 patients were extracted (233 homozygous, 201 compound heterozygous, 224 heterozygous patients, 49 heterozygous with one class III variant and 40 compound heterozygous with two class III variants). During active visits, all biomarker levels were higher compared with inactive visits ($p<0.001$). Heterozygous patients showed lower levels of CRP, SAA, S100A8/A9 and S100A12 during inactive and subclinical visits than patients with two class IV-V variants. Colchicine was discontinued in 52 heterozygous patients and reintroduced in 23 of them (44%).
Conclusion: S100A8/A9 and S100A12 proteins are biomarkers that can be used to assess disease activity. Heterozygous patients have lower levels of inflammatory biomarkers and some of them can sustainably discontinue colchicine treatment.
Disclosure of Interest: None declared

Identifier: PO169

PERIPHERAL ANEURYSMS IN A PATIENT WITH DEFICIENCY OF ADENOSINE DEAMINASE 2 (DADA2)

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Introduction: Deficiency of Adenosine Deaminase 2 (DADA2) is the first identified monogenic vasculitis syndrome at the molecular level. It results from biallelic hypomorphic mutations in the ADA2 gene, which encodes the adenosine deaminase 2 (ADA2) enzyme. The condition is characterized by a spectrum of vascular abnormalities, ranging from livedo reticularis to polyarteritis nodosa (PAN), as well as severe ischemic or hemorrhagic strokes that can be life-threatening. The associated vasculitis and inflammatory processes affect multiple organ systems, accounting for gastrointestinal, hepatic, and renal manifestations (1).

Objectives: To the best of our knowledge peripheral aneurisyms has not been reported in DADA2 before. Herein, we present a patient with giant peripheral arterial aneurisyms.

Methods: a 24-year-old woman presented in 2007 with two episodes of massive lower gastrointestinal bleeding of unknown origin at the age of thirteen. Following stabilization, the patient was referred to gastroenterology, rheumatology, and cardiovascular surgery departments for further evaluation. She exhibited positive Raynaud's phenomenon, elevated ESR and CRP levels, and polyarthritis of hands. Digital ischemic ulcers were noted on the hands and feet. Initial investigations, including ANA and ENA profile, were negative. The patient was started on 4 mg/day methylprednisolone, hydroxychloroquine and nifedipine.

Between 2007 and 2017, the patient exhibited recurrent ischemic and ulcerative skin lesions, requiring treatment with azathioprine, hydroxychloroquine, leflunomide, and methylprednisolone without a significant benefit. Due to ischaemic symptoms an angiographic examination was performed in 2017 revaling multiple ~1 cm aneurysms at intrarenal and intrasplenic regions. A pseudoaneurysm approximately 4 cm in size, caused by aneurysm rupture and extravasation, was detected in the right axillary region, along with millimeter-sized aneurysms in small vessels in solid organs. Further evaluations ruled out ANCA-associated vasculitis and Behçet's disease.

Results: Genetic analysis was performed with a presumtive diagnosis of ADA2 deficiency yielded c.139G>C homozygos variant. Persistent active vasculitis and non-responsive digital ischemia led to the initiation of etanercept. The patient remained stable until 2021 but subsequently experienced persistent nausea, headache, and dizziness. Brain MRI findings showed microhemorrhages and features consistent with chronic small vessel occlusion and cerebrovascular accident, prompting a switch to certolizumab.

Conclusion: ADA2 deficiency is a rare systemic vasculopathy that manifests with recurrent ischemic complications, however, to the best of our knowledge and aneurisym formation has not been reported before. Early genetic testing and early treatment with anti-TNF agents are crucial for stabilizing disease progression.

Acknowledgments: References

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Figure 1 : A) An aneurysm or pseudoaneurysm approximately 8x6.5x7 cm in size, extending posteriorly to the pectoral muscle planes in the right axillary region, is thought to originate from the descending scapular artery. **B)** Same plane at BT image after treatment

Disclosure of Interest: None declared

Identifier: PO170

SUSPECTED NLRC4 IN LIBYAN PATIENTS WITH PERSISTENT SKIN RASH

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Introduction: Inflammasomopathies count for the largest subgroup of autoinflammatory (AI) diseases. NLRC4-inflammasome is a consequence of gain-of-function mutation in the NLRC4 gene. NLRC4 is a protein which plays a role in the innate immunity. The disease has a wide spectrum of symptoms and severity.

Objectives: Highlighting the importance of considering NLRC4-inflammasome in all patients with systemic manifestations and persistent skin rash. As well as the difficulties faced to reach a diagnosis, such as, unspecific symptoms, prolonged disease duration and lack of facilities and financial support for gene testing and biological medication.

Methods: Two case reports.

Results: first case: a four -years-old Libyan boy, presented with high grade fever,arthralgia, arthritis, generalized LAP/ no organomegaly, rash (urticarial rash, not itching nor painful, distributed on face and trunk mainly appears in relation to fever) and eye symptoms (conjunctivitis and puffiness). He has a cousin with S.O. JIA. Blood tests: RFT, LFT, Lipid profile, immunoglobulin assay, ANA, ENA, RF, Bone marrow biopsy and aspirate, serology screen for (brucella, TB, CMV, Typhoid, EBV ASO) all negative/normal. During the flares he had leucocytosis, mildly elevated ESR, LDH, CRP and raised urine Pr:Cr ratio all normalized. MRI and U/S for LAP Result showed reactive lymphadenitis. ECO and ECG normal. Approached as S.O.JIA. He received NSAIDs, MTX SC inj 15mg/m 2 once/ week, and steroids. Symptoms improved but the skin rash and fever persistedn relapse and remission course. Anakinra 2mg/kg SC/ once started. Unfortunately, due to lack of the medication it was stopped after 10 mnts, MTX resumed with low dose steroids.After three years, he developed abdominal pain and vomiting, oral ulcers with fever and skin rash. TNFRSF1A gene for TRAPS came neg, further gene FMF and MVK testing requested.

Second case: a eight -years- old Libyan girl, presented in a relapse for a previous diagnosis of S.O.JIA on MTX inj 15mg/m 2 SC once/week, folic acid and steroids. She had an itchy persistent skin rash distributed over extremities and trunk that was contributed initially to urticaria and severe eczema. There was arthritis involving of large and small joints of upper and lower limbs in association of fever. Blood tests: LFT, RFT,Lipid profile, were normal. She had Leucocytosis, thrombocytosis, anaemia (blood film excluded blood disorder) with very high s.ferretin, ESR, CRP and LDH. ANA neg, HLA B27 neg, IgE high, RAST test so evidence of allergy. She developed intolerance to MTX, so anakinra 2mg/kg SC once/ day with low dose steroid. Over the following four years her rash worsened and other dermatological conditions were considered, scabies, psoriasis, SLE after developing of malar rash and TRAPS. Her general symptoms improved despite the persistence of the rash. On her last visit she developed thrombocytopenia, leukopenia (side effects of anakinra). Treatment changed to colchicine tab 1mg once/day due to unavailability of anakinra. Waiting for gene testing and response to colchicine.

Conclusion: Due to the nature of AI diseases the delay in diagnosis can be maximized due to lack of proper investigation and medication. Introduction of early gene testing and the availability of biological medication are cornerstones in the management of such cases hoping for better outcomes.

Disclosure of Interest: None declared

Identifier: PO171

UNRAVELING INFLAMMASOMOPATHIES: INSIGHTS FROM A SINGLE -CENTER EXPERIENCE IN ARGENTINE

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Introduction:

Monogenic systemic autoinflammatory diseases (SAIDs) are disorders characterized by dysregulation of the innate immune system, leading to an exaggerated inflammatory response. Inflammasomopathies represent a subgroup of both monogenic and polygenic autoinflammatory diseases caused by inappropriate activation of the inflammasome, resulting in aberrant production of pivotal cytokines such as IL-1 and IL-18. Although various reported inflammasomopathies are often mechanistically related, the resulting pathologies can differ significantly depending on the specific inflammasomes involved. The diagnosis may be guided by clinical phenotypes, overlapping features between different entities highlight the importance of genetic testing. There are different genes whose defects affect the inflammasome

Objectives: Our objective was to describe the clinical, biochemical and genetic characteristics of a cohort of patients with inflammasomopathies under follow-up at a tertiary pediatric hospital.
Methods: A dedicated database of monogenic autoinflammatory syndromes from the rheumatology department of a tertiary care center was used for analizing the clinical, demographic, laboratory, and genetic features of patients diagnosed with inflammasomopathies. Genetic testing included panel-based exome sequencing. Over the past 10 years, 36 patients with suspected inflammasomopathies were evaluated, of whom 12 (33 %) received a definitive diagnosis. A diagnosis was considered definitive when genotype and phenotype were mutually validated. Descriptive statistics were performed.
Results: Twelve (7 female) patients met the criteria for inclusion, all of whom exhibited features consistent with inflammasomopathies. The mean age at symptom onset was 18 , range1-96 months , and the mean age at diagnosis was 99, range 29-223 months. The most frequent clinical manifestations, in descending order, were fever 25%, ocular abnormalities12,5%, rash 9 %, arthritis and aphthous ulcers 9 %, splenomegaly, lymphadenopathy, abdominal pain, diarrhea and growth retardation 6%, chest pain 3%. The clinical phenotypes of cases 1, 2, 3, and 4 differed significantly despite sharing identical genetic mutations. Biochemical markers showed inflammation at onset: median erythrocyte sedimentation rate (ESR) 64 mmh (9-140), C-reactive protein (CRP) 21UI (0.6-51.25), MRP8/14 6800 ng/ml (5180-9980), hemoglobin 11.2 gr/dl (6.7-13.4), white bllod cell count 10105mm^3 (6320-18900), platelets 373000 mm^3(221000-449000). No autoantibodies were found. Genetic analysis findings are summarized in Table 1.

Table1 Cases	Chromosome position	Reference allele	Variant allele	Inflammasome/ Gene	Position	Zygosity	Variant Classification *	Treatment
1,2,3,4	chr1-247588067	C	T	NLRP3	Exon3	Het	pathogenic	Canakinumab Adalimumab

								Mpredniso ne Thalidomid e
5	chr16-3293407	T	C	MEFV	Exon10	Het	pathogenic	Mpredniso ne Colchicine
6	Chr12-6443274	C	T	TNFRSF1A	Exón 2	Het	Likely pathogenic	canakinum ab
7	Chr12-6333477	C	T	TNFRSF1A	Exon 4	Het	VUS	canakinum ab
8	Chr16-3299765	G	A	MEFV	Exon3	Het	VUS	colchicine
9	Chr16-3293405	C	G	MEFV	Exon10	Het	pahogenic	Anakinra
10	Chr16-3293407	T	C	MEFV	Exon10	Hom	pathogenic	adalimuma b
11	Chr12-110034353	C	T	MVK	Exon 11	Het	Likely pahogenic	Canakinum ab
12	Chr12-6442643	C	T	TNFRSF1A	Exon4	Het	VUS	LFU**

*ACMG: American College of Medical Genetics and Genomics

** LFU : lost of follow up

Conclusion: In our cohort of monogenic inflammasomopathies diseases, there is a significant overlap of clinical manifestations, which can make diagnosis challenging. Identifying the involved inflammasome not only aids in diagnosis but also helps guide targeted treatment. Delays in diagnosis often reflect a lack of clinical suspicion, highlighting the need for greater awareness and understanding of these conditions

Disclosure of Interest: None declared

Identifier: PO172

MULTISYSTEM INFLAMMATORY SYNDROME IN CHILDREN IS ASSOCIATED WITH TGF-B-INDUCED EPSTEIN-BARR VIRUS REACTIVATION

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Introduction: Multisystem inflammatory syndrome in children (MIS-C) is a severe post-infectious autoinflammatory complication of SARS-CoV-2 infection in children, marked by systemic hyperinflammation and specific expansion of T-cells bearing the T-cell receptor variable chain (TCRV)β21.3. Despite advances in understanding COVID-19 immunopathology, the mechanisms driving MIS-C remain poorly understood.
Objectives: This study investigates the immunological and molecular basis of MIS-C, focusing on the role of TGF-β in modulating T-cell reactivity and its association with EBV reactivation and hyperinflammation.
Methods: We conducted an integrated analysis of immune cells, cytokine profiles, and T-cell receptor (TCR) repertoires in a total of 145 patients diagnosed with MIS-C and 221 paediatric controls. Flow cytometry, single cell RNA sequencing, and serological assays were used to evaluate TGF-β signaling, T-cell reactivity and cytotoxicity, and EBV reactivation. Functional assays examined the reversibility of immune dysfunction through TGF-β blockade. Comparative analyses were performed with age-matched controls, including children with severe COVID-19.
Results: MIS-C patients exhibited significantly elevated serum TGF-β levels, comparable to those observed in severe COVID-19 cases. In MIS-C median serum TGF-β levels were 398 pg/ml, in severely affected COVID-19 adult patients' median serum TGF-β levels were 415 pg/ml ($p \geq 0.9999$) and in paediatric controls 6 weeks p.i. without MIS-C median serum TGF-β levels were 63 pg/ml ($p=0.0365$). TGF-β signaling was enriched across T cells, B cells, and monocytes in MIS-C, correlating with reduced antigen-presentation capabilities of monocytes. This was associated with impaired reactivity of virus-specific memory T cells (median 9.9-fold less specific T-cell activation ($p=0.0391$) for $CD8^+$ T cells) and an expansion of $TCRV\beta21.3^+$ T cells. In a hyperinflammation control using children with acute viral inflammation these phenomena could not be observed. The expansion of $TCRV\beta21.3^+$ T cells was especially prominent, when analyzing *in vivo* activated T cells of MIS-C patients (+30.9 percentage points higher frequencies of $TCRV\beta21.3^+$ T cells in in vivo activated T cells compared to all T cells from the same MIS-C patients; $p<0.0001$). $TCRV\beta21.3^+$ T cells are enriched among T cells specific to an EBV-nuclear antigen-2 (EBNA2)-derived epitope. Notably, serum TGF-β levels triggered EBV reactivation, which exacerbated hyperinflammation. Blockade of TGF-β restored T-cell cytotoxicity and mitigated EBV reactivation. Clinically, EBV seroprevalence were strongly elevated in MIS-C patients compared to age-matched controls (MIS-C: 80.7% vs. controls: 56.0%; $p<0.0001$) and EBV viremia was frequently observed. We could detect EBV transcripts in MIS-C patients (1 UMI per 286 cells), while none were found in healthy controls or patients with mild COVID-19 ($p<0.0001$). Furthermore, we analyzed the killing capacity of EBV-infected B cells by T cells and found that $TCRV\beta21.3^+$ $CD8^+$ T cells showed on median 16.5 percentage-points increased killing capacity ($p=0.0156$).
Conclusion: Our findings identify TGF-β as a pivotal driver of MIS-C pathogenesis, linking SARS-CoV-2 infection to impaired T-cell immunity, EBV reactivation, and systemic inflammation. Therapeutic strategies targeting TGF-β may represent a promising avenue for mitigating hyperinflammation and EBV-related complications in MIS-C.
Disclosure of Interest: None declared

Identifier: PO173

LONG-TERM VIRAL PRESENCE IN MONOCYTES CORRELATES WITH DYSREGULATION OF INNATE IMMUNITY IN PATIENTS WITH MIS-C

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Introduction: Multisystem Inflammatory Syndrome in Children (MIS-C) is a severe post-infectious complication associated with SARS-CoV-2. Although the crucial pathogenic role of the monocyte compartment is known, information regarding the mechanisms and maintenance of the inflammatory trigger is lacking. Genetic variants in the OAS/RNase L pathway, involved in viral double-stranded RNA (dsRNA) sensing and the modulation of inflammatory responses, have been identified in patients with MIS-C.
Objectives: We conducted a comprehensive analysis including the study of NLRP3 inflammasome activation, blood biomarkers and autoantibodies, as well as transcriptomic and proteomic profiling.
Methods: Peripheral blood mononuclear cells (PBMCs), plasma, and RNA samples from MIS-C patients were analyzed. PBMCs were stimulated with lipopolysaccharide (LPS) and adenosine triphosphate (ATP), and inflammatory responses were quantified using enzyme-linked immunosorbent assay (ELISA), flow cytometry, and Imaging Flow Cytometry (IFC). Apoptosis was assessed via Annexin V staining. Type I interferon (IFN) signatures were measured using quantitative PCR. Pro-inflammatory cytokines were evaluated using an automated ELISA system (ELLA). RNA sequencing (RNA-seq) data were analyzed through bioinformatics pipelines, including gene set enrichment analysis (GSEA), while proteomics data were processed using weighted gene coexpression network analysis (WGCNA).
Results: We found a monocyte exhaustion phenotype, demonstrated by reduced inflammasome activation in response to stimuli and an associated lack of IL-1β secretion (Figure 1A-B). Intriguingly, dsRNA was detected in monocytes from MIS-C patients even during follow-up, suggesting a long-lasting viral presence that could drive sustained immune activation. Blood biomarker profiling, bulk RNA-seq, and proteomic analyses revealed a signature characterized by the activation of genes involved in antiviral response, systemic inflammation, oxidative stress, and coagulation pathways. Additionally, we observed anti-IL1RA autoantibodies in 40-50% of patients, consistent with previous reports.
Conclusion: Our findings underscore the multifaceted nature of immune dysregulation in MIS-C, encompassing monocyte exhaustion, persistence of intramonocytic dsRNA, autoantibody formation, and a distinct transcriptomic and proteomic signature. This study provides insights into the underlying mechanisms driving sustained inflammation in post-COVID syndromes.
Disclosure of Interest: None declared

Identifier: PO174

UNDERSTANDING HOST-MICROBIOME RELATIONSHIPS IN THE PATHOPHYSIOLOGY OF BEHÇET SYNDROME: ANALYSIS OF SALIVARY CYTOKINES, SERUM CYTOKINES, AND TRYPTOPHAN METABOLITES CONCENTRATIONS IN PATIENTS FROM THE BEHCETBIOT STUDY.

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Introduction: Behçet syndrome (BS) is a chronic, multisystemic disease whose manifestations include mainly oral and genital ulcerations, uveitis, central nervous system disorders, enterocolitis and vascular involvement. Although its etiology remains unexplained, the microbiota could play a triggering role in BS. The gut microbiota influences metabolic processes in immune cells by producing active metabolites. In BS patients, *Bacteroides* and *Clostridia* abundance is decreased. Interestingly, these bacteria produce biologically active tryptophan metabolites. The decrease in tryptophan-metabolizing bacteria abundance could contribute indirectly to the significant release of IL-1β. BS patients with oral ulcers have higher levels of salivary Il-1ß, TNF-α and Il-6 than healthy controls (HCs).

Objectives: The aims of this study were 1) to compare tryptophan metabolites blood concentrations between cases and HCs and 2) to compare serum and salivary cytokines concentrations (IL-1β, IL-17A, IL-18, IFNγ, TNF-α, IL-6 and IL-22) between cases and HCs and according to clinical phenotypes.

Methods: BEHCETBIOT is a French multicenter case-control study that included patients meeting the international classification criteria for Behçet's disease revised in 2013 [4]. HCs were recruited from the patients' environment. Blood and saliva samples were taken from the entire study population. Tryptophan, hydroxytryptophan, kynurenine and hydroxykynurenine were measured by Liquid Chromatography Mass Spectrometry. IL-1β, IL-17A, IL-18, IFN-γ, TNF-α, IL-6 and IL-22 serum and salivary levels were measured using the Ella® microfluidic Single Plex cartridges (ProteinSimple™, Bio-Techne). Cytokines and tryptophane measurements were compared between patients and matched HCs. GraphPad Prism version 7.04 was used for analysis.

Results: Thirty-three paired patients (18 women – 54,5 %)/HCs were enrolled. Thirty three percent (11/33) had a mucocutaneous and articular phenotype, 42 % (14/33) a neurological and ocular phenotype and 24 % (8/33) a vascular phenotype. No patient was in flare up at the time of inclusion. Twenty seven percent (9/33) of patients were on anti-TNF-α agents and 9 % (3/33) on anti-IL-6 receptor agents at the time of inclusion. Eighty-one percents of patients were on long term colchicine. No difference in tryptophane metabolites concentrations was found between cases and matched HCs. Regarding salivary cytokines, IL-18 levels were significantly higher in controls ($p< 0.05$). There was no difference between cases and HCs for IL-1β, TNF-α, IL-6 and IL17-A. IL-22 and IFN-γ were not interpretable, as they were below the detection threshold. IL-6 saliva was tendency increased in vascular phenotype between cases and their matched HCs. Regarding serum cytokines, IFN-γ levels were higher in cases than in controls ($p = 0.03$). Il-1β was not interpretable.

Conclusion: Our clinical trial is one of the first to investigate the relevance of salivary cytokines and tryptophan metabolites in BS including patients matched with HCs living in the same environment. These preliminary results did not reveal difference in tryptophan metabolites concentrations between cases and HCs in BS. High salivary levels are in accordance with previous data. Analysis of serum and salivary cytokines reveals few differences between cases and their matched controls. These results must be analyzed considering the treatments received and according to the phenotypes. Indeed, one third of patients were treated with biologics the day of inclusion. They may reflect counter-regulatory mechanisms, or the effects of the treatments received. Oral and fecal microbiota PCR sequencing of the DNA coding for 16 S RNA will provide clues on these questions.

Acknowledgments: National society of internal medicine.

Disclosure of Interest: None declared

Identifier: PO175

DISSECTING THE HLH IMMUNE SYNAPSE (IS): CRITICAL ROLES FOR IS TERMINATION, CYTOKINE INTENSITY, AND TARGET CELL DEATH

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Introduction: Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening hyperinflammatory syndrome arising in many contexts. Its underlying mechanisms are often unclear, but defective granule-mediated cytotoxicity (familial HLH) and excess IL-18 (Macrophage Activation Syndrome, MAS) provide important and complementary clues. Mounting evidence suggests the various genetic, infectious, malignancy-associated, and rheumatic causes of HLH all converge on cytotoxic T lymphocyte (CTL) hyperactivation and overproduction of IFNγ. Current clinical guidance emphasizes the need to address multiple HLH contributors, but is challenging without a more functional mechanistic framework.
Objectives: We sought to develop an in vitro platform to better study and understand the many different and interacting contributors to HLH/MAS.
Methods: We developed an *in vitro* system to simultaneously quantify how multiple parameters of the murine CTL immune synapse (CTL-IS) responded to various HLH-related stimuli or specific cell death pathway inhibitors. We defined IS duration in CTL/target cell dyads as the time between CTL Ca^{++} flux and target cell PI uptake by live-cell microscopy. We also measured cytokine levels longitudinally in co-culture supernatants. We assessed the effects of cell death inhibition on HLH in vivo in *Il18tg* and *Prf1*$^{-/-}$ mice infected with LCMV(Armstrong).
Results: Perforin haploinsufficiency prolonged IS duration and increased IFNγ production, demonstrating the system's sensitivity. Target cell death resistance (immortalization or caspase inhibition) similarly prolonged CTL-IS duration and cytokine production, substantiating "Impaired IS Termination" as a category of HLH contributors. By contrast, strong CTL activation, via TCR or IL-18 signaling, increased IFNγ secretion but accelerated target cell death. This pattern, which we call "CTL Cytokine Production Intensity", has been observed in CART IS and may represent a distinct category of HLH contributors. Surprisingly, IL-18 exposure drove some CTL-IS to terminate, even in the absence of perforin, via a morphologically inflammatory form of cell death inhibitable by blocking necroptosis. *In vivo*, RIPK1 inhibition ameliorated virus-triggered HLH in Il18tg but not Prfl$^{-/-}$ mice.
Conclusion: By quantifying CTL-IS duration, cytokine production, and mode of cell death, we modeled multiple HLH contributors and their interactions, and identified three HLH mechanistic categories: impaired IS termination, intense CTL cytokine production, and inflammatory target cell death. Integrating the inputs and outcomes of a hyperinflammatory CTL-IS may provide a useful framework for understanding, predicting, or treating HLH in its many forms.
Disclosure of Interest: A. Frank-Kamenetskii: None declared, H. Klinghoffer: None declared, J. Varghese: None declared, V. Dang: None declared, J. Morrissette: None declared, J. Burkhardt: None declared, S. Canna Grant /Research support from: In-kind support, Simcha Therapeutics, Consultant for: Bristol-Myers Squibb, Sobi, AB2Bio, Novartis, Speaker bureau of: Bristol-Myers Squibb, Sobi, PracticePoint CME

Identifier: PO176

NATURAL KILLER CELL EXHAUSTION AND DYSFUNCTION AS A HALLMARK OF THE INFLAMMATION IN STILL'S DISEASE

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Introduction: Still's disease (SD) exemplifies a rare systemic inflammatory disorder of unknown etiology, belonging to the growing family of autoinflammatory syndromes (AID), a heterogenous group of rare immune dysregulation disorders. The exact role of natural killer (NK) cells in the pathogenesis of SD remains unclear due to inconsistent findings regarding their numbers, maturation and function.

Objectives: In this study, we set out to conduct a comprehensive analysis of the phenotype and function of NK cells across different AIDs.

Methods: Through a collaboration of 34 European clinical centers (ImmunAID) we were able to recruit a large cohort of 121 patients with various AIDs [SD (53), chronic recurrent multifocal osteomyelitis (23), Familial Mediterranean fever (23) and inflammation of unknown origin (22)] as well as 32 healthy controls (HC). We used high-parameter flow cytometry to perform an in-depth immunoprofiling of the NK cell pool of these patients.

Results: While the NK cell repertoire of most included AIDs was comparable to that of HC, we found that the proportion of NK cells in total peripheral blood mononuclear cells from SD patients was dramatically decreased. NK cells in SD patients exhibited a unique overactivated and exhausted phenotype with upregulated expression of HLA-DR, CD69, TIGIT, CTLA-4 and PD-1, and showed impaired IFN-γ production upon stimulation with IL-12 or IL-18. *In vitro* stimulation of healthy donor NK cells with SD-associated cytokines, including IL-12, IL-15 and IL-18, could replicate the phenotype of SD NK cells. During disease remission, NK cell numbers returned to normal, and the exhausted phenotype was corrected, yet the impaired IFN-γ production persisted.

Conclusion: Altogether, our data define NK cell deficiency and exhaustion as a distinguishing feature of SD. Specific inflammatory cytokines play complementary roles in the NK cell exhaustion and defective IFN-γ production in SD.

Acknowledgments: This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 779295. ADV and JB hold PhD Fellowships of the Research Foundation-Flanders (FWO-Vlaanderen, ADV: 11K0722N/11K0724N and JB: 11A0523N/11A0525N). We also wish to acknowledge the contribution of all donors included in this study.

Disclosure of Interest: A. De Visscher: None declared, J. Beliën: None declared, B. Malengier-Devlies: None declared, E. Bernaerts: None declared, T. Mitera: None declared, N. Berghmans: None declared, P. Regnier: None declared, D. Saadoun: None declared, C. Girard-Guyonvarc'h: None declared, C. Gabay: None declared, M. Gouwy: None declared, P. Proost: None declared, C. Wouters Grant /Research support from: Novartis, Roche, GlaxoSmithKline and Pfizer, Consultant for: Novartis, Sobi and UCB, P. Matthys: None declared

Identifier: PO177

MULTI-OMIC STUDY IN PATIENTS WITH SITRAME SYNDROME IDENTIFIES DIFFERENCES IN SYSTEMIC IMMUNE RESPONSES

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Introduction: SITRAME (*Systemic Inflammatory Trunk Recurrent Acute Macular Eruption*) syndrome is a newly described autoinflammatory disorder affecting adult patients with no family history. Patients present with recurrent flares of stereotypical truncal rash and biologic inflammation, often associated with fever, asthenia and arthralgia. The majority of patients have flares following either mRNA Covid-19 vaccination or a history of suspected viral infection. All investigations for autoimmune, viral or allergic origins of the disease had negative results. In addition, genetic testing in several patients, using whole exome sequencing, did not identify known pathogenic variants in monogenic autoinflammatory disorders.

Objectives: In this study, we aimed to identify the inflammatory pathway(s) involved in the disease.

Methods: 14 patients were recruited to perform a multi-level characterization of the disease using blood samples, including cellular phenotyping by mass cytometry, transcriptomic analysis by RNA-sequencing, assessment of plasma cytokine levels and post-stimulation production of cytokine by multiplexed ELISA. For each data set, results were compared between healthy donors, and patients in either the basal or active flare state.

Results: Patients all had SITRAME defined clinical criteria. The sex ratio of patients was 1:1 and the median age of onset was 29 years, ranging from 18 to 45 years. 92.8% of patients (13/14) presented with flares following a history of viral infection or mRNA vaccination, compared with 73.3% (22/30) of all known SITRAME patients. The median CRP level during a flare was 22mg/L, ranging from 8 to 100mg/L. Patients in the basal and flare states had expansion of subsets of myeloid cells, corresponding to NKG2A+KIR- CD56dim NK cells, and intermediate monocytes in patients in the flare state. In the basal state, patients had a common transcriptomic signature consisting of activation of the innate immune inflammatory response. In the flare state, they had activated pathways involved in antiviral defense and interferon production. Patients in the flare state also had significantly higher plasma levels of CXCL10 (*p=0.0384*) and IFNα (*p=0.0438*) compared to healthy donors. After whole blood stimulation of TLR3/MDA5 by Poly(I:C) and TLR7/8 by R848, basal state patients had decreased IFNα production compared to healthy donors (*p=0.0477* and *p=0.001*, respectively). No differences were observed for the other inflammatory markers tested.

Conclusion: SITRAME syndrome is an adult onset disease characterized by an innate immune inflammatory background and dysregulation of the type I interferon pathway during flares. The reduced levels of IFNα production after RNA-sensing TLR stimulation could be explained by either cellular exhaustion or preferential migration of interferon-producing cells from the blood to skin. Ongoing analyses will test these different hypotheses.

Disclosure of Interest: None declared

Identifier: PO178

EVALUATION OF TYPE I INTERFERON SIGNATURE AS A BIOMARKER FOR DISEASE ACTIVITY IN JUVENILE DERMATOMYOSITIS

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Introduction: Juvenile dermatomyositis (JDM) is a rare autoimmune disease characterized by skin rash and progressive muscle weakness. Upregulation of type I interferon (IFN-I) signaling plays a relevant role in the pathogenesis of JDM. A 28-IFN response gene score (IRG-S) has been validated for measuring IFN-I signature.
Objectives: To quantify the 28-IRG-S in patients with JDM and associate it with disease activity.
Methods: IFN-I signature was measured in whole blood using the 28-IRG-S by NanoString and considered positive above 1.73. Clinical and biological data were collected from medical charts.
Results: A total of 27 patients with JDM and 21 healthy controls (HC) were enrolled. In 16 patients, the IFN-I signature was evaluated repeatedly in the period 2021-2024. A total of 46 patients' samples were collected and classified into the following groups: i) "naïve" or samples obtained at diagnosis, clinically active and without any treatment (n: 5), ii) "active" but not naïve (n: 26) and iii) "inactive" (n: 15) including 4 that achieve complete remission under treatment. An elevated 28-IRG-S was found in all "naïve" samples [median: 6.14; range: 3.93-22.17] and in nearly 70% (18/26) of "active" samples [median: 10.34; range: 2.49-35.68]. A normal 28-IRG-S was obtained in all "inactive" samples. In addition, patients were classified according to the presence of myositis-specific autoantibodies (MSA) including anti-MDA5 (48.2%), MSA-negative (22.2%), anti-NXP2 (11.1%), anti-Mi2 (7.4%), anti-TIF1 (7.4%) and anti-PM-Scl (3.7%). Among "active" group and considering MSA groups, an elevated 28-IRG-S was observed in 75% of anti-MDA5 positive (12/16) and MSA-negative (3/4) patients compared with 50% of anti-Mi2, anti-NXP2 and anti-TIF1 positive patients (3/6).
Conclusion: Overall, this study demonstrates that the IFN-I signature is useful as a biomarker for disease activity in JDM and is a reliable assessment that can be easily applied in routine clinical practice.
Acknowledgments: All patients and families.
Disclosure of Interest: None declared

Identifier: PO179

PLASMA PROTEOMIC PROFILES SEPARATE SURF PATIENTS FROM FMF AND PFAPA: PRELIMINARY DATA FROM THE PERSAIDS PROJECT.

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Introduction: Syndrome of Undifferentiated Recurrent Fever (SURF) is an emerging group of patients displaying recurrent inflammatory episodes. Although very similar to Familial Mediterranean Fever (FMF) clinical presentation, they do not share their genotype, being negative for mutation in the MEFV gene or in other genes related to autoinflammatory diseases. Furthermore, SURF enter in differential diagnosis with the most common multifactorial recurrent fever, namely PFAPA syndrome.

Objectives: Our aim is to evaluate the differences in the expression of plasma proteins in patients with SURF compared with healthy subjects, FMF and PFAPA patients to clusterize and better understand the mechanisms underlying these disorders.

Methods: Plasma samples from 15 SURF, 20 FMF, and 9 PFAPA patients, along with 22 age-matched healthy donors, were analyzed using high-resolution mass spectrometry-based proteomics. The analyses were performed in Data-Independent Acquisition (DIA) mode using an Orbitrap Exploris 480 mass spectrometer coupled with the Evosep One chromatography system.

Results: In total, we identified 485 proteins. T-tests were conducted to identify differentially expressed proteins among the different groups. For the significantly modulated proteins, a functional enrichment analysis was performed using Gene Ontology annotations to uncover the biological processes that vary across the conditions. This analysis aimed to identify proteins associated with the disease and to reveal potential novel biomarkers. Our findings indicate that protein expression profiles are differentially enriched depending on the specific conditions analyzed, providing insights into disease mechanisms and potential diagnostic targets.

Conclusion: In this study, we explored how a high-resolution plasma proteomics approach can enhance our understanding of SURF as a distinct clinical entity. Specifically, SURF proteomics shows similarities with FMF but exhibits significant differences compared to PFAPA. The comprehensive characterization of a broad spectrum of proteins, coupled with functional enrichment analysis, provides valuable insights into the biological processes underlying these distinct pathologies. This approach offers the potential to identify novel biomarkers and improve our understanding of genetically undefined disorders.

Disclosure of Interest: None declared

Identifier: PO180

PERSONALIZED MEDICINE FOR SYSTEMIC AUTOINFLAMMATORY DISEASES: THE EUROPEAN MULTICENTER "PERSAIDS" PROJECT

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Introduction: Systemic autoinflammatory diseases (SAIDs) are a rapidly growing number of rare conditions with monogenic or polygenic/multifactorial etiology, which cause deregulation of mechanisms controlling innate immune responses. While specific monogenic SAIDs may benefit from personalized medicine approaches, “undefined” SAIDs (uSAIDs) are still lacking molecular testing and specific treatments.

Objectives: To improve the classification, diagnosis and prognosis of uSAIDs and to support the discovery of personalized therapies through the development of multi-omics signatures. To develop tools for SAID diagnosis and management in clinical practice.

Methods: We have undertaken a project aimed at analyzing available data and producing new data from a total of 200 SAIDs and uSAIDs, by integrating structured clinical data, multi-omics approaches (genomics, transcriptomics, proteomics, metabolomics, lipidomics, epigenomics, immunomics and inflammatory panel) and Artificial Intelligence technologies. Both supervised and unsupervised learning algorithms have been used to build models.

Results: Clinical and omics data have been collected and harmonized through a uniform semantic schema implemented in dedicated instance of the MOLGENIS database. Biological samples (DNA, RNA and sera) from patients recruited from three clinical centers were used by five centers to generate data from genomics, transcriptomics, proteomics, metabolomics, lipidomics, epigenomics, immunomics and OLINK inflammation panel. Preliminary results using hierarchical clustering followed by differential expression analysis and supervised Machine Learning approaches on individual omics showed relevant stratification between different SAIDs and uSAIDs and highlighted the presence of differentially expressed disease-associated markers that can provide insight into which biological processes or pathways differ between patient groups.

Conclusion: Omics-based clustering of yet unclassified SAIDs, already feasible using single omics datasets, will further increase in definition in the multi-omics analysis phase where integrated datasets can reveal novel associations between biological markers and disease phenotypes of relevance in clinical decision-making.

Disclosure of Interest: None declared

Identifier: PO181

UNVEILING THE UNIQUE IMMUNOPATHOGENESIS OF CHRONIC RECURRENT MULTIFOCAL OSTEOMYELITIS THROUGH SINGLE-CELL RNA SEQUENCING

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Introduction: Chronic Recurrent Multifocal Osteomyelitis (CRMO) is a rare inflammatory disease, representing the most severe manifestation of chronic nonbacterial osteomyelitis. Unlike traditional osteomyelitis, CRMO is intimately linked with autoimmune diseases like inflammatory bowel disease (IBD) and psoriasis. Although the precise immunopathogenesis of CRMO has yet to be fully elucidated, the interleukin (IL)-1 axis, specifically the NLRP3 inflammasome pathway, has been identified as a pivotal element.

Objectives: In this study, we aimed to explore the underlying immunopathogenesis of CRMO by employing single-cell RNA sequencing (scRNA-seq).
Methods: Peripheral blood mononuclear cells (PBMCs) were collected from six CRMO patients and compared with those from four healthy controls (HCs). For sequencing, we utilized the Chromium Next GEM Single Cell 5'v2 kit for library preparation.
Results: Differential gene expression analysis in innate immune cells, including monocytes and dendritic cells (DCs), revealed an upregulation of genes associated with inflammation in CRMO patients. Specifically, CD14+ monocytes from CRMO patients exhibited heightened IL-1B expression, with an increased frequency of these cells compared to healthy controls. In conventional dendritic cells (cDCs) from CRMO patients, there was an elevated expression of CXCR4, likely in response to increased CXCL12 from bone marrow.

Moreover, T cells in CRMO patients showed an upregulation of inflammatory markers such as S100A11, indicating a systemic activation of T cells potentially driven by interactions with innate immune cells.

Conclusion: In summary, our findings suggest significant immunophenotypic alterations in the circulating immune cells of CRMO patients when compared to healthy controls, shedding light on the complex immunological landscape of CRMO.
Disclosure of Interest: None declared

Identifier: PO182

BRIDGING THE GAP: DISPARITIES IN GENETIC TESTING AND TRAINING FOR AUTOINFLAMMATORY DISEASES BETWEEN EMERGING AND DEVELOPED COUNTRIES: A SURVEY ON 258 DOCTORS FROM 10 FRENCH SPEAKING COUNTRIES

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Introduction: Autoinflammatory diseases (AIDs) are a group of rare disorders of innate immunity. Some of them are monogenic like Familial Mediterranean Fever (FMF).. Since the discovery of the *MEFV* gene mutation associated with FMF in the 1990s, advances in genetics have significantly enhanced our understanding of AIDs and actually more than 50 monogenic AID have been discovered. However, disparities in access to genetic testing and expertise persist between emerging and developed countries, impacting diagnosis and management.

Objectives: The aim of our study was to determine the disparities between developed and emerging countries in genetic knowledge and access to new-generation sequencing technologies.

Methods: We conducted a survey of 17 short questions among healthcare practitioners (medical doctors) to explore disparities in genetic testing practices and training in French speaking countries in December 2024 by electronic voting. Numeric variables were expressed as mean (±SD) and discrete outcomes as absolute and relative frequencies (%). Respondents were categorized into two groups: emerging countries and developed countries. Statistical analysis included Student's t-test, Welch's t-test, Mann-Whitney U test, chi-squared test, or Fisher's exact test, as appropriate. The significance level was set at 5%, and analyses were performed using EasyMedStat (version 3.38).

Results: A total of 258 responses were analyzed, with 187 (72.5%) from emerging countries and 71 (27.5%) from developed countries. Practitioners from emerging countries were from Morocco (24%), Senegal (20%), Tunisia (12%), Romania (10%), Algeria (10%) and Lebanon (4%) while those from developed countries were mainly from France (12%), Belgium (4%), Switzerland (2%) and Canada (2%).Most respondents practiced internal medicine (56%), followed by rheumatology (12%), nephrology (10%), clinical immunology (8%). The majority (84%) worked in academic hospitals.

Genetic testing access varied significantly: 82% of practitioners in developed countries had access compared to only 50% in emerging countries ($p<0.001$). In emerging countries, available genetic tests primarily targeted the *MEFV* gene (58%), with limited access to advanced techniques like next-generation sequencing (NGS). Among practitioners in developed countries, 45 reported access to NGS, compared to only 12 in emerging countries ($p<0.001$).

Training in genetics also differed markedly. Few doctors had received genetic training, while 60% of doctors from developed countries did not receive any training in genetics, 84% of doctors from emerging countries didn't have so ($p<0.001$).

Moreover, 91% of respondents from emerging countries and 55% from developed countries expressed a need for training in genetics, particularly in NGS ($p=0.005$). While this discrepancy is substantial between the two groups of countries, the percentages persist at a notably high level, underscoring an imperative for genetic training. Barriers to genetic testing included limited access, lack of knowledge, high costs, and delayed results.

Conclusion: Our survey highlights significant disparities in access to genetic testing and expertise between emerging and developed countries. Our findings emphasize the need for comprehensive global training in genetics for both developed and emerging countries. In emerging countries, the challenge is twofold: providing training in genetics and ensuring access to (NGS). These results underscore the urgent need for targeted training initiatives and resource allocation to bridge the gap and enhance the care of patients with autoinflammatory diseases worldwide.
Disclosure of Interest: None declared

Identifier: PO183

TO ASSESS HEALTH-RELATED QUALITY OF LIFE (HRQOL) IN PEDIATRIC PATIENTS WITH HEREDITARY AUTOINFLAMMATORY DISEASES (HAID) IN INDIA USING KIDSCREEN - 52 QUESTIONNAIRE - PILOT STUDY

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Introduction: HAID diseases could impact various domains of well-being in pediatric patients. The KIDSCREEN questionnaire is a validated tool designed to evaluate HRQoL in children and adolescents. It has been used in 252 studies for chronic illnesses like cystic fibrosis, diabetes, Familial Mediterranean Fever, Juvenile Idiopathic Arthritis, mental health disorders etc. However, its application in HAIDs remains limited to a single study from Europe on 25 children. The validated English and Hindi version of KIDSCREEN-52 is available from 'The KIDSCREEN Group' Germany, By interpreting scores relative to mean, the KIDSCREEN 52 provides insights into specific areas of well-being affected by HAID.
Objectives: To evaluate feasibility and assess HRQoL in patients diagnosed with HAID, utilising parent-reported KIDSCREEN-52 data in their preferred language (English, Hindi).
Methods: This cross-sectional pilot study was conducted from June 2024 to December 2024. The KIDSCREEN-52 Parent Form, available in Hindi and English was administered to parents of children diagnosed with HAID. The questionnaire assesses ten domains: physical well-being, psychological well-being, moods and emotions, autonomy, parent relations, social support, bullying, school environment, self-perception, and financial resources.
Descriptive statistics summarized findings. Standardised T-scores (normative average=50) and Z scores contextualised raw data, accounting for discrepancies in number of questions in each domain. Average ratings neutralize these differences, providing for a fairer assessment of HRQoL). T-scores higher than 50 indicate better than average HRQoL while Z-scores measured standard deviations from the mean, identifying outliers and variability across domains.
Results: Domains with Lowest T scores included:

- Physical Activities and Health (T-score = 30.99) reflecting significant limitations in physical functioning and mobility due to disease burden.
- Peer Relationships ("Friends") (T-score = 37.27) indicating challenges in social interactions.

Data was collected during physical visits(n=4) and virtually using Zoom platform(n=17). Parents of 21 children (males: n=10, females: n=11), aged 8 to 18 years, diagnosed with HAID at our centre, answered the questionnaire.

Highest scores were observed in

- "Free Time" (T-score = 61.30) indicating strong satisfaction with leisure opportunities.
- Emotional well-being, self-esteem, and family support, indicating resilience despite health challenges.

Variability: Standard deviations ranged from 0.77–1.39, suggesting consistency in experiences across domains.. The highest variability observed in the 'Money' domain (SD = 1.39), reflecting diverse perceptions of financial circumstances. These results show the wide-ranging impact of chronic illness on children's lives.

(Statistics table will be diaplayed in the poster)

Conclusion: Our study confirms the feasibility of KIDSCREEN-52 for assessing HRQoL in Indian pediatric patients and identifies the domains most affected in this pilot study.

Disclosure of Interest: None declared

Identifier: PO184

INSIGHTS FROM A ONE-YEAR INTERNATIONAL MONTHLY QUIZ ON AA AMYLOIDOSIS CAUSES: ENGAGING 2,567 VOTERS ACROSS FRENCH-SPEAKING COUNTRIES

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Introduction: Inflammatory (AA) amyloidosis is secondary to chronic inflammatory conditions. The discovery of an AA amyloidosis can reveal the underlying inflammatory disease, but the etiologic diagnosis can be challenging.

Considering this diversity of etiologies, we proposed the "AA Challenge": an international educational program aimed mainly at French-speaking physicians, thanks to financial support: Françoise Dubois Charlier Prize from the French Association of Amyloidosis Patients (AFCA).

Objectives:

The aim of the AA challenge was to teach and communicate the diversity of causes of AA amyloidosis in order to reduce diagnostic wandering.

Methods: From 2023 to2024, a monthly clinical case consisting of images with a short text was proposed to the French-speaking medical community under the name "AA challenge" via emails and social networks accounts of the French reference center for AA amyloidosis, the French association against amyloidosis, the international alliance against amyloidosis, a Facebook page and Instagram account "AA challenge". The questionnaire was developed using Eval&Go® software and distributed thanks to the twelve members of the AA challenge Steering Committee, each representing their French-speaking country. After the monthly challenge case, a 40-second educational video explaining the correct answer and the various elements that guide the diagnostic strategy is posted on social networks. We have also provided a monthly “literature review” on AA amyloidosis.
Results: A total of 12 clinical cases of AA amyloidosis were sent allowing to collect 2567 responses over one year. The medical specialties of participants were: internal medicine (n=1534, 60%), nephrology (n=470, 18%), rheumatology (n=199, 7%) and other specialties (cardiology, dermatology, gastroenterology, geriatrics pediatrics and infectious diseases (n=307,11%).

The top three participating countries with the highest number of voters in the 12 quizzes were Morocco (n=646), France (n=537) and Romania (n=420). The number of voters from the remaining countries were: Tunisia (n=273), Algeria(n=212), Belgium (n=147), Senegal (n=156), Lebanon (n=72), Switzerland (n=56) and Canada (n=48).

The pathologies studied in the different clinical cases and the percentage of correct answers were respectively in order of publication: 1-Mevalonate Kinase deficiency (57%), 2-Tuberculosis and bronchectasis (41%), 3-Familial Mediterranean Fever (73%), 4-Rheumatoid arthritis (80%), 5-Obesity (62%), 6-Primary hyperoxaluria (58%), 7-Castelman disease (60%), 8-Spondylarthritis (80%), 9- Multiple causes (70%), 10-Cryopyrinopathy (58%), 11-Crohn disease (88%), 12- non AA amyloidosis (29%).

For the monthly literature review, 25 articles on AA amyloidosis published between 2022 and 2024 were summarized. Topics covered were 10 rare causes of AA amyloidosis (variable common immune deficiency, hidradenitis suppurativa, inflammatory lymphomas, xanthogranulomatous pyelonephritis, sickle cell disease, PSTPiP1 mutations, anakinra, checkpoint inhibitors such as atezolizumab, Behçet's disease and hereditary epidermolysis bullosa), 6 on the epidemiology of AA amyloidosis in some countries (such as Brazil, Portugal, Algeria and Turkey), familial Mediterranean fever, anti-inflammatory cytokine biotherapies and disease progression or kidney transplantation; Only one involved inflammatory rheumatism (gout), a classic but declining aetiology of AA amyloidosis.

Conclusion: The "AA challenge" educational project brought together >10 French-speaking countries to discuss the various causes of AA amyloidosis. This project attracted more than 2500 colleagues from at least 8 different specialties.

The high number of responses to the questionnaire indicates an interest in the subject and in fun approaches to teaching.

Acknowledgments: French Association of Amyloidosis Patients (AFCA)
Disclosure of Interest: None declared

Identifier: PO185

CLINICAL FEATURES AND TREATMENT OUTCOMES IN VEXAS SYNDROME: A RETROSPECTIVE SINGLE CENTER EXPERIENCE

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Introduction: VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) syndrome is a monogenicautoinflammatory disease, accompanied by clonal hematopoiesis.
Objectives: This study aims to present clinical features, management strategies, and outcomes of 6 patients with VEXAS syndrome followed in a tertiary clinical center.
Methods: Data regarding clinical spectrum, genotype, treatment, histopathologic examinations, and outcomes were retrospectively collected from patient files.
Results: This study includes 6 male patients with VEXAS that with a mean follow-up duration of 16.2±9.5 months. The average age of patients was 70±10.8 years and the average age at the onset symptoms was 63±6.7 years. Mean diagnostic delay was 6.33±5.5 years. Most common pathogenic UBA1variant was p.Met41Thr (c.122T>C) (4/6) followed byp.Met41Leu (c.121A>C) (1/6) and c.121A>C (1/6). Initial diagnosis included RA (2/6), gout (1/6), infection (1/6),MGUS (1/6), MDS (1/6), Sweet syndrome (1/6), FMF (1/6), and Behcet's disease (1/6).

Patients experienced constitutional symptoms includingfatigue (6/6), fever (4/6), night sweats (4/6), lymphadenopathy (3/6), and weight loss (2/6). The most common hematological manifestations were macrocytic anemia (6/6), MDS (5/6), thrombocytopenia (5/6), and leukopenia (5/6). Most of the patients experienced severe arthralgia (5/6) and one patient had arthritis. Auricular chondritis was noted in one patient. Skin lesions such as erythematous papules (3/6), vasculitic lesions (2/6), neutrophilic dermatosis (1/6), and urticaria (1/6) were observed in all. Half of the patients exhibited ocular involvement, all manifesting as episcleritis. Pulmonary involvement was detected in 5 patients which included pulmonary infiltrates (5/6) and pleural effusion (2/6). Hepatosplenomegaly was present only in one patient.

Treatment modalities included high dose glucocorticoids (6/6), Anakinra (3/6), Azacytidine (3/6), Tocilizumab (2/6), Ruxolitinib (2/6), Methotrexate (1/6), Cyclosporin (1/6), and allogenic bone marrow transplantation (1/6). All patients were responsive to high dose glucocorticoids (6/6). Response rate to Anakinra and Azacytidine treatments was 1/3. None of the patients responded to Tocilizumab, Ruxolitinib, Methotrexate, Cyclosporin, and allogenic bone marrow transplantation.

Two patients died from complications related to the disease.

Conclusion: The patients experienced long diagnostic delays reflecting the challenges in recognition and the diagnosis of VEXAS. Moreover, the study demonstrated high mortality rates and low response rates to current treatment modalities, underscoring the challenges in managing VEXAS. These findings highlight the need for novel and effective treatment options to improve patient outcomes.
Disclosure of Interest: None declared

Identifier: PO186

IW-601, A FIRST-IN-CLASS CLINICAL-STAGE MONOCLONAL ANTIBODY TARGETING A NOVEL ADHESION CHECKPOINT ON MYELOID CELLS: POTENTIAL FOR TREATMENT OF AUTOINFLAMMATORY AND AUTOIMMUNE INDICATIONS

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Introduction: Monocytes and neutrophils are innate immune cells that are implicated in various autoinflammatory and autoimmune diseases, making them an attractive target for therapeutic intervention. IW-601 is a first-in-class monoclonal antibody (mAb) targeting MOSPD2, a novel adhesion checkpoint protein expressed on the surface of myeloid cells, but not lymphocytes. IW-601 binding to MOSPD2 increases Integrin β2 adhesion and leads to reduced cell motility, thereby blocking the ability of these innate immune cells to migrate towards inflamed tissue.
Preclinical studies previously demonstrated the involvement of MOSPD2 and efficacy of anti-MOSPD2 mAb in models of rheumatoid arthritis, inflammatory bowel disease and NASH. In the Experimental Autoimmune Encephalomyelitis (EAE) model for multiple sclerosis (MS), MOSPD2 deficiency or treatment with anti-MOSPD2 mAbs protected against disease development and restricted infiltration of monocytes into the CNS. The pathogenesis of Non-Infection Uveitis (NIU), a leading cause of vision loss in the developed world, typically involves the innate immune system. NIU is seen in the context of systemic autoinflammatory diseases such as Bechet's disease, sarcoidosis and spondyloarthropathies along with other neurologic manifestations. There is a major need for effective, safe, steroid-sparing, systemic targeted therapeutics for NIU. Blocking migration of monocytes & neutrophils to inflamed tissues is an appealing therapeutic approach.
Objectives: To study IW-601 as a potential novel systemic therapy in autoinflammatory and autoimmune diseases with neurologic and ocular manifestations.

Methods: Inflammation was studied using the EAE and Experimental Autoimmune Uveitis (EAU) mouse models. Following induction of EAE using pMOG35-55, animals were treated with anti-MOSPD2 or anti-VLA-4 antibodies. EAU was induced in wild-type (wt) or MOSPD2 knockout C57BL/6 mice by subcutaneous injection of human IRBP peptide 1-20 with complete freund's adjuvant containing Mycobacterium tuberculosis strain H37Ra. For analysis of human monocyte migration venous blood samples were drawn from MS patients or healthy controls. Peripheral blood mononuclear cells (PBMCs) were isolated using Leucosep tubes. CD14+ monocytes were isolated using magnetic microbeads. Monocyte migration was studied using transwell assay in the presence of IW-601 or IgG control antibody.
Results: In the EAE model for MS, in vivo treatment with anti-MOSPD2 was more effective than anti-VLA-4 (Integrin α4β1; the target of natalizumab) mAb. Furthermore, IW-601 was more effective than natalizumab and vedolizumab (anti α4β7) in inhibiting human monocyte migration ex-vivo. In human ex-vivo studies, IW-601 profoundly inhibited the migration of monocytes isolated from all tested subjects, regardless of disease severity, gender, or patient's active therapy. In the EAU model, incidence of uveitis was lower in MOSPD2 knockout mice than in wt controls (70% vs 100%, respectively). In addition, uveitis clinical score was significantly lower in MOSPD2 knockout animals compared to wt (0.475 vs 2.25 at day 24, $p<=0.001$).
Conclusion: MOSPD2 is a novel adhesion checkpoint protein that specifically regulates monocyte and neutrophil migration. Targeting MOSPD2 leads to profound reduction of CNS and ocular inflammation in various models. IW-601 also inhibited migration of monocytes isolated from MS patients ex-vivo. Taken together these results point to the potential of IW-601 as a therapeutic agent in the treatment of autoinflammatory conditions with neurologic and ocular manifestations such as Behcet's disease. IW-601 is currently being studied in a Phase 1 clinical trial in healthy subjects, whose Single Ascending Dose stage has been completed successfully. Full data are expected in year-end 2025.

Disclosure of Interest: I. Mendel Employee of: ImmuneWalk Therapeutics, N. Yakov Employee of: ImmuneWalk Therapeutics , O. Propheta-Meiran Employee of: ImmuneWalk Therapeutics, E. Feige Employee of: ImmuneWalk Therapeutics, T. Rachmilewitz Minei Employee of: ImmuneWalk Therapeutics

Identifier: PO187

KIKUCHI-FUJIMOTO DISEASE AS PRESENTING SIGN OF INBORN ERRORS OF IMMUNITY: A SINGLE CENTER EXPERIENCE FROM A COUNTRY AT LOW DISEASE PREVALENCE

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Introduction: Kikuchi-Fujimoto disease (KFD) is a rare, benign and self-limiting disorder characterized by acute or subacute necrotizing lymphadenitis. It generally affects young adults with a female preponderance, but it may develop in children with a slight male preponderance. An association with systemic lupus erythematosus has been described.
Objectives: To describe the clinical features of KFD in a geographical area with low disease prevalence and examine its association with immunological disorders.
Methods: We reviewed all records of pediatric patients with histologically confirmed KFD diagnosed at Gaslini Institute from 2014 to 2024. In all cases, the examined lymph node was obtained through excisional biopsy. Patients' data as age, gender, symptoms, laboratory tests, lymph node biopsy, genetic analysis and therapies were reviewed.
Results: A total of five patients were included. The median age at diagnosis was 8 years (range 2-14) and 3/5 (60%) patients were male. All patients presented with fever and cervical lymphadenopathy, which was bilateral in 3/5 (60%) patients. All patients had at least two sites of lymphadenopathy detected by physical examination or imaging: intraparotid (2 patients), supraclavicular (2 patients), or axillary (1 patient). Three patients (60%) underwent surgical excision after a long-lasting fever (>20 days) and presented a recurrence of fever after the surgery, which in one patient required oral steroids. Hepatomegaly and splenomegaly were noted in 3/5 (60%) patients. Other symptoms were abdominal pain, vomit, fatigue and pharyngitis. Laboratory tests showed leukopenia in 2/5 (40%) patients, hypertransaminasemia in 2/5 (40%) patients and raised C-reactive protein in 4/5 (80%) patients. The initial therapy was antibiotics in all the patients, whereas 2/5 (40%) patients were also treated with oral steroids. After the failure of initial treatments, all the patients carried out an imaging evaluation with ultrasound (5 patients), magnetic resonance (2 patients), and positron emission tomography (4 patients); three patients (60%) underwent a bone marrow evaluation with no signs of malignancy. Immunological disorders were subsequently diagnosed in 3/5 (60%) patients after a median follow-up period of 35 months (range 1-54): inborn errors of immunity were diagnosed in 2 patients (LRBA deficiency and activated PI3K delta syndrome) and one patient developed an autoimmune lymphoproliferative syndrome.
Conclusion: In countries with low KFD prevalence, inborn errors of immunity should be ruled out with long term follow-up and target genetic analysis.
Disclosure of Interest: None declared

Identifier: PO188

A QUANTITATIVE STANDARDIZED STRATEGY FOR CLINICAL APPLICATION OF TYPE I INTERFERON SIGNATURE

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Introduction: Type I Interferon Signature (IS) analysis is employed to detect pathological conditions characterized by type I Interferon (IFN) dysregulation and to guide therapeutic interventions. Nonetheless, the absence of a standardized procedure complicates comparisons across various time points or institutions.
Objectives: To formulate a reproducible protocol for the analysis of IS utilizing a synthetic control, and to assess the consistency of results derived from this method across the laboratories of two Italian hospitals.
Methods: Real-time PCR was employed to analyze the expression of six interferon-stimulated genes (ISGs): *IFI27, IFI44L, IFIT1, ISG15, RSAD2*, and *SIGLEC1* in peripheral blood. A synthetic control was employed to calculate the copy numbers of the chosen genes. The IS for each patient was determined as the geometric mean of the genes' copy counts, normalized with endogenous reference genes.

The cut-off value for IS was determined as the mean + 2 standard deviations of the IS from 40 healthy donors.

The approach was validated through the analysis of 39 patients with various inflammatory, autoimmune, and infectious diseases associated with Type I IFN or other inflammatory pathways (i.e. monogenic interferonopathies, systemic lupus erythematosus, juvenile dermatomyositis, periodic fevers, juvenile idiopathic arthritis).

Results: As predicted, our method showed a positive IS for IFN-driven inflammatory disorders. The test exhibited significant repeatability as evaluated through numerous analyses of the identical sample. Moreover, the IS derived from samples provided by two distinct laboratories yielded similar values.
Conclusion: The proposed procedure demonstrated great reproducibility across centers and effectively distinguished between IFN-related and non-IFN-related inflammation. The implementation of a synthetic control reduced inter-assay and inter-laboratory variability, thereby enhancing data exchange among centers to advance understanding of IFN-related inflammation and patient management.
Disclosure of Interest: None declared

Identifier: PO189

BRIDGING THE GAP: WHEN INSTAGRAM BECOMES A TOOL FOR PATIENT EDUCATION IN FAMILIAL MEDITERRANEAN FEVER

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Introduction: Familial Mediterranean Fever (FMF) is a rare monogenic autoinflammatory disease characterized by recurrent episodes of fever and serosal inflammation. Despite advances in the understanding and management of FMF, awareness and access to reliable educational resources for patients remain limited. Social media platforms have emerged as powerful tools for health education and patient engagement. In this context, we launched the first dedicated Instagram account entitled @FMF.reference aimed to provide educational content on FMF in French langage.
Objectives: The primary objectives were:
1. To create an accessible and interactive platform for FMF education.
2. To raise awareness about FMF and its impact on patients' lives.
3. To disseminate evidence-based information on pathophysiology, genetics, treatment, pregnancy, fertility, daily living, nutrition, and physical activity.
4. To foster a sense of community among FMF patients through a modern, user-friendly medium.
Methods: We established an Instagram entitled @FMF.reference account dedicated to FMF in April 2023. The account was designed for patients, caregivers, and healthcare professionals interested in FMF. Content was developed by a multidisciplinary team of physicians, and clinical research assistant specialized in FMF to ensure accuracy and relevance. Over a period of 20 months, we published over 50 posts covering the following themes:
- Pathophysiology: Simplified explanations of FMF mechanisms.
- Genetics: Information on MEFV gene mutations and inheritance patterns.
- Treatment: Updates on colchicine therapy and emerging treatments.
- Pregnancy and Fertility: Guidance on managing FMF during pregnancy and addressing fertility concerns.
- Daily Life: Tips for managing the disease in everyday scenarios.
- Nutrition and Physical Activity: Overall health and well-being recommendations.

The platform also included interactive features such as polls, quizzes, and article summaries. Metrics such as follower count, post reach, and user interactions were tracked to assess the account's impact.
Results: During 20 months, the Instagram account attracted over 300 followers, predominantly patients with FMF and their families. 60% of followers were aged 25-44, representing an active population balancing health and family responsibilities. Posts on daily life and work-life balance targeted their needs. 70% of followers were women; however, our content addressed the needs of all FMF patients, regardless of gender. Concerning the geographic distribution: 75% of followers were from France and 10% from North African French speaking countries, demonstrating growing interest in FMF-related there.
Concerning the posts: each received an average of 210 views and 20 likes. Instagram Stories with interactive features like polls and quizzes had an average of 100 views and a 12% participation rate.Visual posts (images, infographics, and videos) performed better than text-only posts, with an average of 320 views compared to 180, underscoring a preference for dynamic content. Feedback from followers emphasized the value of an FMF-dedicated platform. Many users reported feeling less isolated and more empowered in managing their condition. Notable achievements included successful polls and quizzes sessions addressing misconceptions about FMF and positive responses to posts on pregnancy management.
Conclusion: This initiative demonstrates the potential of social media as a tool for patient education in rare diseases like FMF. The success of our Instagram account highlights the importance of accessible, accurate, and engaging educational content tailored to patient needs.
Moving forward, we plan to incorporate multimedia content (videos and live sessions) and to conduct formal surveys to

evaluate the platform’s impact on patient knowledge and quality of life. Our experience suggests that social media is an effective tool in patient education strategies.

Disclosure of Interest: None declared

Identifier: PO190

SYSTEMIC AUTOINFLAMMATORY DISEASES IN UKRAINE: CHALLENGES, ACHIEVEMENTS, AND FUTURE PROSPECTS

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Introduction: The SAIDs are infrequent conditions representing up to 2% of all Ukrainian patients diagnosed with inborn errors of immunity. Despite spectacular progress over the last years in diagnosis, treatment, and management, this topic faces unprecedented challenges today.
Objectives: To provide an overview of the current situation with SAIDs in Ukraine identifying the burdens, achievements, and prospects.
Methods: Analysis of registry data, literature, and stakeholder input to assess the state of SAIDs in Ukraine
Results: Landscape of SAIDs in Ukraine. Medical literature includes only case reports (e.g., CAPS, PFAPA, FMF), without summarizing the overall picture. The unofficial registry lists 35 SAIDs patients, plus over 130 PFAPA cases. Patient numbers increased after 2018 due to improved genetic diagnosis, IL-1β treatment availability, and educational events, though true incidence remains unknown. Many conditions remain undiagnosed, with delays of months to over 10 years causing severe complications.

Local treatment protocols and state programs supporting patients with SAIDs. In 2018, IL-1β blockers were first purchased using state funds. In 2021, the Ministry of Health approved protocols for managing FMF, HIDS, TRAPS, and CINCA/NOMID and merged pediatric and adult programs to ensure continuity of care.

Role of NGOs. NGOs (professional organizations, patient organizations) played a pivotal role in unveiling the problem: organization of educative events (conferences, workshops, symposia, and webinars), advocation of patient rights, and implementation of treatment to state programs. Despite the absence of an official community of patients with SAIDs, they are part patient's NGO for primary immunodeficiencies and have good advocacy support.

Scientific research. Although opportunities for conducting research on SAIDs in Ukraine remain limited, Ukrainian clinicians have participated in international collaborative studies. These contributions include identifying novel genetic mutations in autoinflammatory diseases, elucidating the etiology of PFAPA syndrome, and drafting treatment protocols.

Internation collaboration. Collaboration with global experts has, as well as international patient organizations had an unprecedented impact on addressing SAIDs in Ukraine. From providing expert consultations to facilitating the treatment of Ukrainian patients in foreign clinics, these partnerships have directly benefited patients (genetic diagnostic, specific investigation, support with treatment etc.), and accelerated progress in the field.

SAIDs and war. The Russian invasion of Ukraine has severely disrupted progress achieved in recent years. The war poses significant risks to patients with SAIDs, including restricted access to healthcare facilities, forced internal displacement, and emigration. Educational activities have been paused, the state's funding for patient treatment has been curtailed, and patients' mental health has been profoundly affected.

Conclusion: SAIDs represent a pressing challenge as ultra-orphan diseases in Ukraine. The journey from diagnosing initial cases to understanding the depth of the problem and finding effective solutions has been marked by significant obstacles. International collaboration and partnerships with patient communities have been and will remain critical in addressing these challenges and supporting patients.
Acknowledgments: We thank the clinicians, Ukrainian MOH, patients, families, and communities for their contributions to addressing SAIDs.
Disclosure of Interest: None declared

Identifier: PO192

DATA FROM THE EUROFEVER REGISTRY FOR CENTRAL AND EASTERN EUROPEAN COUNTRIES: AN UPDATE

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Introduction: Autoinflammatory diseases (AID) are rare chronic conditions characterized by abnormal regulation of innate immunity. In countries with small populations, only few patients with AID are reported, making it impossible to carry out research and deepen the understanding of AID. To overcome this shortcoming, in 2010, a worldwide registry – the Eurofever registry was founded. The main aim was to link together all European centres that follow patients with AID. The first, and so far, the last demographic data from Central and Eastern European countries from the first 18 months of enrolment in the Eurofever registry was published in 2012.

Objectives: To collect and analyse AID demographic data for Central and Eastern European countries currently available in the Eurofever registry.

Methods: We requested data from the Eurofever registry for 16 Central and Eastern European countries – Albania, Bosnia and Herzegovina, Bulgaria, Croatia, Czech Republic, Estonia, Hungary, Latvia, Lithuania, Macedonia, Montenegro, Poland, Romania, Serbia, Slovakia, and Slovenia. We included data on gender, diagnosis, comorbidities, genetics, and age at the start of the symptoms, at diagnosis, and initial visit to the tertiary centre. The collection of the data and statistical analysis was done using the IBM SPSS Statistics (version 29.9.2.0).

Results: On October 29th, 2024, we received data for 11 of the 16 requested centres; Macedonia and Montenegro had no registered centres, and no data were available for Albania, Bosnia and Herzegovina, and Estonia. Within the other centres, 554 patients were identified: 5 (0.9 %) in Bulgaria, 36 (6.5%) in Croatia, 176 (31.8%) in the Czech Republic, 2 (0.4%) in Hungary, 4 (0.7%) in Latvia, 2 (0.4%) in Lithuania, 7 (1.3%) in Poland, 47 (8.5%) in Romania, 5 (0.9%) in Serbia, 247 (44.6%) in Slovakia, and 23 (4.2%) in Slovenia. Of these, 302 (55%) were male, and 528 (95%) were Caucasian. Thirty-six (6.5%) had co-morbidities, ranging across different systems of the body. We recorded 13 different diagnoses; the exact data is presented in Table 1. For 193 (35%), genetic analysis was available, results were positive for 159 (82%), negative for 9 (5%), and non-informative for 25 (13%) patients.

Table 1: Autoinflammatory disease diagnoses among patients

Diagnosis	N (%)	Diagnosis	N (%)
Behcet's disease	11 (2.0)	NLRP12-related disease	1 (0.2)
Blau's disease	1 (0.2)	PAPA[f]	13 (2.3)
CAPS[a]	25 (4.5)	PFAPA[g]	267 (48.2)
CRMO[b]	37 (6.7)	SURF[h]	36 (6.5)
DADA2[c]	7 (1.3)	TRAPS[i]	18 (3.2)
FMF[d]	117 (21.1)	Undefined	1 (0.2)
MKD[e]	20 (3.6)		

a CAPS – cryopyrin-related periodic syndromes, [b] CRMO – chronic recurrent multifocal osteomyelitis, [c] DADA2 – deficiency of adenosine deaminase 2, [d] FMF – familial mediterranean fever, [e] MKD – mevalonate-kinase deficiency, [f] PAPA – pyogenic sterile arthritis, pyoderma gangrenosum and acne syndrome, [g] PFAPA – periodic fever, aphthous stomatitis, pharyngitis, adenitis, [h] SURF – syndrome of undifferentiated recurrent fever, [I] TRAPS – tumor necrosis factor receptor-associated periodic syndrome

Identified patients ranged in age from zero to 60 years, with a median age of 2.5 years (IQR 1.0-6.4 years) at the start of symptoms, 5.6 years (IQR 2.9-14.0 years) at the time of diagnosis and 5.9 years (IQR 3.1-14.0 years) at the time of the initial visit to the tertiary centre. The diagnosis of AID was determined before coming to the tertiary centre in 118 (21%) patients. The median time from the start of the symptoms to the initial visit to the tertiary centre was 2.9 years (IQR 0.9-8.7 years). If the diagnosis had not been established before the initial visit, it was usually made during this visit, with a median time from the initial visit to the diagnosis of 0 days (IQR 0-134 days).

Conclusion: We report the most recent demographic data for 554 patients with AID from 11 Central and Eastern European countries from the Eurofever registry.
Disclosure of Interest: None declared

Identifier: PO193

AA AMYLOIDOSIS IN A FRENCH COHORT OF 312 PATIENTS: A COMPREHENSIVE STUDY ON ETIOLOGIES, DISEASE PROGRESSION AND MORTALITY

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Introduction: AA amyloidosis is a serious complication of chronic inflammatory diseases associated with the deposition of amyloid substances, mainly composed of serum amyloid A protein, in tissues, especially in the kidneys. The causes are varied. No data are available on cases of AAA amyloidosis in France.
Objectives: To describe histologically proven cases of AA amyloidosis in France to determine the distribution of causes, progression to dialysis and mortality.
Methods: A retrospective and prospective cohort of histologically proven cases of inflammatory amyloidosis was established in 2023 in the French center of AA amyloidosis, Paris, France to identify cases through the REDCAP® database. Ethical approval was obtained from the Ethics Committee of the Sorbonne University. After obtaining patient consent, anonymized data were collected in a redcap database. Statistics were performed usingEasymedstat® software.
Results: 312 patients were included, 47% of whom were women. The median age at inclusion was 60.2 years [min 18-max 97]. Patients were of Caucasian (n=119), Mediterranean (n=112), sub-Saharan African (n=27), Asian (n=9), and other (n=45) origin. Consanguinity was found in 23 patients (8.5%) and a history of monogenic autoinflammatory disease in 30 patients.

Regarding AA amyloidosis: The median age at onset of symptoms was 52 years [min 7-max 97] and the median age at diagnosis of AA amyloidosis was 51 years [min 6-max 92]. Symptoms at diagnosis were, in descending order: renal failure (n=201), proteinuria (n=177), nephrotic syndrome (n=149), lower limb edema (n=64), dialysis (n=42), thyroid goiter (n=27), renal transplant (n=15). Patients' median body mass index was 24.1 [min 12.8- max 57.8]. Median SAA at enrolment was 23 mg/L [min 0- max 1120] and CRP was 31 mg/L [min 0- max 389]. Median hemoglobin was 10.9 g/dL [min 6- max 16.4]. The median proteinuria/creatinuria ratio was 0.75 g/g [min 0- max 1382]. Hypogammaglobulinemia occurred in 14 patients.

Etiologies of AA amyloidosis were as follows, in descending order : autoinflammatory diseases (n=96; 30.8%) including 66 cases of Familial Mediterranean Fever (FMF), unknown (n=65, 20.8%), recurrent infections (n=59, 19.9% including 35 tuberculosis), chronic inflammatory rheumatism (n=58 ,16.6% including 20 rheumatoid arthritis and 16 spondyloarthropathies), obesity (n=37, 11.9%), chronic inflammatory bowel disease (n=14 including 11 Crohn's disease), cancer (n=15), hemopathy (n=14), HIV (n=7), drug addiction (n=6), hidradenitis suppurativa (n=5), Castleman's disease (n=3), other (n=6). Interestingly, 53 patients had 2 causes combined, 6 had 3, and 6 had more than 3.

The anti-inflammatory treatments received by the patients since the diagnosis were, in descending order: colchicine (n=94), corticosteroids (n=75), anti-interleukin-1 biotherapies (n=21), methotrexate (n=19) and anti-IL6 (n=12), anti-IL17 and/or anti-IL12/23 (n=4), anti-TNF (n=3), anti-JAK (n=2) biotherapies.

Progression to end-stage renal disease led to dialysis in a total of 102 patients (32.7%); 60 patients underwent kidney transplantation (19.2%) and 63 patients died (20%) at a median age of 64.7 [21.5-90.2] years.

Conclusion: This is the first large French cohort of AA amyloidosis, showing that the diseases has not disappeared in France. Among the causes, we note the high proportion of cases with uncertain aetiology and cases with no cause other than obesity. Among treatments, we note the high proportion of patients who received corticoids compared to biologics, which no longer seems appropriate in 2025. This rare disease is severe, with one third of patients requiring dialysis and one fifth dying before the median age of 65 years. The variety of causes requires careful investigation to tailor treatment to the specific aetiology. A prospective national survey is being established to complete this data collection.

Disclosure of Interest: None declared

Identifier: PO194

EMPOWERING PATIENTS WITH RARE AUTOINFLAMMATORY DISEASES: A PIONEER THERAPEUTIC EDUCATION PROGRAM FOR AMYLOIDOSIS, FMF, AND CAPS IN FRANCE

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Introduction: Rare autoinflammatory diseases like amyloid inflammatory conditions, Familial Mediterranean Fever (FMF), and cryopyrin-associated periodic syndromes (CAPS), challenge both patients and healthcare providers. These conditions require lifelong management, making patient education a cornerstone of effective care. Facing the need for tailored resources, we launched three therapeutic education programs dedicated to these diseases. Over three years, these programs have successfully trained 115 patients through interactive workshops providing essential knowledge and self-management tools.

Objectives: The primary goals were:

1 To enhance patients' understanding of their disease (causes, pathophysiology, symptoms, treatments, progression, and monitoring).

2 To empower patients to actively participate in their care and improve adherence to treatment.

3 To develop innovative educational tools tailored to each disease.

4 To assess patient satisfaction and identify areas for program improvement.

5 To establish a foundation for expanding these programs nationwide through e-therapeutic education platforms.

Methods: Three distinct therapeutic education programs were designed and implemented for amyloid inflammatory conditions, FMF, and CAPS. Each program included the following components:

1 Patient Recruitment: Participants were identified through specialized clinics and patient advocacy groups. Informed consent was obtained prior to enrollment.

2 Workshops: Interactive, in-person sessions were held, covering:

- Disease basics: Causes, genetics, and pathophysiology.
- Symptom management and treatment options.
- Long-term monitoring and follow-up strategies.
- Lifestyle adaptations (nutrition, physical activity).

3 Educational Tools: Tailored materials, such as brochures, videos, and interactive models, were developed to facilitate understanding.

4 Evaluation: Patients completed satisfaction surveys and provided feedback on the content, structure, and delivery of the workshops.

5 Follow-Up: Outcomes were reviewed periodically to ensure knowledge retention and program effectiveness.

Results: Over three years, 115 patients participated in the therapeutic education programs, with 28 patients enrolled in the Amyloidosis AA program, 64 in the FMF program, and 23 in the CAPS program.

Key findings include:

1 **High Satisfaction Rates**: Post-program surveys revealed overwhelmingly positive feedback, with participants reporting increased confidence in managing their condition.

2 **Enhanced Knowledge**: Patients demonstrated improved understanding of their disease, as reflected in pre- and post-workshop assessments.

3 **Community Building**: Participants appreciated the opportunity to connect with others facing similar challenges, fostering a sense of support and shared experience.

4 **Development of Educational Tools**: The creation of disease-specific materials provided long-lasting resources for patients and caregivers.

5 **Program Impact**: Several participants reported improved adherence to treatment plans and fewer disease-related complications, though further data is needed for comprehensive analysis.

Conclusion: By addressing the unique needs of patients with amyloid inflammatory conditions, FMF, and CAPS, these programs have filled a critical gap in patient education. The overwhelmingly positive feedback underscores the value of structured, disease-specific education initiatives.
The next step involves transitioning these programs to a digital format to reach a broader audience nationwide. E-therapeutic education platforms will enable flexible, scalable delivery while maintaining the interactive and personalized elements that have proved to be effective. This initiative serves as a model for integrating patient education into the comprehensive management of rare diseases, improving outcomes and quality of life for affected individuals.
Disclosure of Interest: None declared

Identifier: PO195

AUTOIMMUNE-LYMPHOPROLIFERATIVE IMMUNODEFICIENCIES: A MONOCENTRIC EXPERIENCE

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Introduction: Autoimmune lymphoproliferative syndromes are a group of disorders characterized by immunedysregulation with chronic benign lymphoproliferation, autoimmunity, increased susceptibility to infections, and increased risk of lymphoma. The most described disease is referred to as autoimmune lymphoproliferative syndrome (ALPS), caused by genetic defects impairing Fas-mediated apoptosis. The term paediatric autoimmune-lymphoproliferative immunodeficiencies (ALPID) was recently introduced to describe a broad and heterogeneous group of children with autoimmune disorders and/or cytopenia who did not meet diagnostic criteria for ALPS. The aim of this study was to describe the clinical and immunological phenotype and therapeutic response of a subgroup of children with ALPID

Objectives: The aim of this study was to describe the clinical and immunological phenotype and therapeutic response of a subgroup of children with ALPID

Methods: We report the B cell phenotype in 6 patients with a phenotype consistent with ALPID who did not fit the diagnostic criteria for ALPS. 45 children were used as age-matched controls.

Results: We described 6 patients, all males, with a clinical phenotype consistent with ALPID All patients exhibited systemic inflammation with fever and elevated inflammatory markers (median CRP 12.40 mg/dl, median ESR 79 mm/h). Peripheral cytopenia was observed in only one child, who had a mildly decreased white blood cell count during disease flares (WBC 2290 x 10^3/uL). Notably, significant lymphatic system involvement was detected in all cases through imaging techniques (ultrasound, CT, or MRI), with splenomegaly (80%), hepatomegaly (60%), and lymph node enlargement (100%). Lymph node biopsy was performed in 5 cases and revealed reactive hyperplasia without signs of malignancy. No patients met Oliveira's criteria for the diagnosis of ALPS. Double negative T lymphocytes were normal (0.6 to 1-5% on T lymphocytes). No specific inflammatory pathways were detected with interferon-gamma induced chemokines slightly increased (CXCL9 median value 497,5 pg/ml; CXCL10 median value 139 pg/ml) and normal values of IL-18 and type I IFN score. Frequency of B cells was similar between patients and controls. We observed a reduction in the frequency of immature transitional B cells (p=0.0052) and a trend towards a higher frequency of circulating plasmablasts (p=0.067) in patients compared to controls. Although the frequency of total memory B cells was similar between the two groups, the relative frequency of switched memory and IgM memory B cells was skewed in patients (p=0.034), with an expansion of switched memory B cells and reduction in IgM memory B cells compared to controls (p=0.052). Three children were initially treated with IL-1 inhibitors (two patients with anakinra and one patient with canakinumab) with partial control of inflammation but no regression of lymph node involvement. In five patients, tocilizumab, was administered (iv every four weeks). All patients experienced a complete resolution of febrile episodes, normalization of inflammatory markers and progressive reduction of lymphadenopathy. The last patient, due to low systemic inflammation, was treated with glucocorticoids and sirolimus with satisfactory response.

Conclusion: ALPID currently refers to a group of patients that remains very heterogeneous. In this study, we describe six children with a fairly homogeneous clinical and immunological phenotype, that associates enlargement of lymphoid organs, markedly elevated acute phase reactants, with a reduction in transitional B cells and an expansion of switched memory B cells and plasmablasts. This subgroup of ALPID patients is characterized by an excellent response to IL-6 receptor inhibition. Further studies on a larger group of patients with even more homogeneous characteristics will be essential to confirm this finding.

Disclosure of Interest: None declared

Identifier: PO196

EFFECTIVENESS OF IL1 INHIBITION WITH ANAKINRA IN ACUTE AND RECURRENT MYOCARDITIS IN CHILDREN

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Introduction: Myocarditis is defined as an inflammatory disease affecting the myocardium and in the paediatric population can be a challenging diagnosis to make. Viral infection remains the most prevalent cause, and analysis of myocardial tissue has shown the presence of specific viruses such as adenovirus, enterovirus, parvovirus B19 and human herpesvirus 6. More recently, during the coronavirus -19 (COVID) pandemic, signs of myocardial inflammation in children attributed to a Sars Cov 2 infection were observed. Non-infectious causes of myocarditis are also known to include autoimmunity, hypersensitivity and drugs. Recently the literature reports [1,2] a possible auto-inflammatory hypothesis, with an important role of the pro-inflammatory cytokine interleukin (IL)-1 in the pathogenesis of myocardial inflammation.

Objectives: The aim of this study was to evaluate the efficacy and safety of the antiIL-1 receptor anakinra in patients with active myocarditis refractory to standard therapy.

Methods: In this retrospective, observational study, we enrolled 4 patients, (all male with a median age of 16 years): 2 with recurrent active myocarditis and 2 with a first episode of acute myocarditis. The 4 patients received anakinra in addition to standard treatment. Response to treatment was assessed in terms of clinical symptoms (fever and thoracic pain) and laboratory tests [C-reactive protein (CRP), a high-sensitivity cardiac troponin T (cTnT), and Type B natriuretic peptide (BNP)]. All patients underwent cardiac magnetic resonance imaging (CMR) at diagnosis and 2 out of the 4 patients (those with recurrent myocarditis) underwent MRI at diagnosis and after a 5-month follow-up period.

Results: Among the 4 patients observed, 2 started anakinra therapy at the second episode of myocarditis, the other 2 at the first episode. All patients were symptomatic prior to the start of therapy and presented with fever, chest pain, increased markers of inflammation and cardiac enzymes (cTnT and Nt pro BNP) In one patient at the first episode, microbiological examinations showed an Ebstein Barr virus infection. Seven days after the start of anakinra, there was a marked improvement in clinical condition and laboratory parameters in all patients (table 1). MRI performed in 2 patients at diagnosis and after a follow-up period of 5 months showed reduction of oedema or late gadolinium enhancement and improvement of the left ventricular ejection fraction.

Table 1 CRP (mg/dl) , cTnT, BNP pre and post 7 days from the beginning of Anakinra

Patient	CRP pre	CRP post	cTnT pre	cTnT post	BNP pre	BNP post
Patient 1	1	0.05	200	18	48.4	18
Patient 2	4.9	0.5	883	13	251	125
Patient 3	5	0.93	575	59.3	57	36.3
Patient 4	1.19	0.4	741	6.6	124	50

Conclusion: Our results suggest that anakinra may be an effective treatment in active acute myocarditis by leading to an improvement in cardiac function and a reduction in systemic inflammation. Studies on a larger number of subjects are needed

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Disclosure of Interest: None declared

Identifier: PO197

CANADIAN AUTOINFLAMMATORY CASE ROUNDS: AN EDUCATION INITIATIVE TO FOSTER A COMMUNITY OF PRACTICE IN AUTOINFLAMMATION THROUGH CONNECTIVISM

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Introduction: Autoinflammation is consistently identified as an area of educational need among Canadian rheumatologists. Although some formal curricula exist in training programs, the rarity of cases and rapid advances in diagnostics and therapeutics renders autoinflammation diagnosis and management challenging for practising rheumatologists. In response, we launched an education initiative known as the CANadian Autoinflammatory Case (CANAC) Rounds in 2021.

Connectivism is a learning theory where learning is a process created through connections between learners and dynamic networks of evolving information, rooted in increasing use of digital technology. Connectivism is well-suited in our context to enhance evolving knowledge in autoinflammation through virtual interactions across Canada.

Objectives: We designed, delivered, and evaluated a virtual case-based curriculum on autoinflammation grounded in Connectivism learning theory.
Methods: The CANAC Rounds program was developed in partnership with the Canadian Rheumatology Association (CRA) Pediatrics committee informed by national needs assessments.

Curriculum Development

A steering committee, consisting of seven Canadian pediatric rheumatologists including one education scholar, planned two one-hour live sessions annually and recordings were available on-demand online to CRA members. Topics were identified by committee input and post-session surveys. Cases and presenters were solicited from Canadian and international pediatric rheumatology centers, with presenters paired with committee members to guide curriculum development aligning with Connectivism. Instructional design strategies focused on knowledge-building activities in specialized and changing information networks, and nurturing connections to facilitate continual learning in shifting realities.

Curriculum Evaluation

Post-session surveys were collected from session attendees. Quantitative data were analyzed descriptively while themes were identified from free text responses. Feedback was reviewed and incorporated iteratively to subsequent sessions.

Results: Since 2021, nine one-hour sessions were delivered. Topics covered included FMF, PFAPA, CAPS, TRAPS, Interferonopathies, RElopathies, APLAID, ARPC1B deficiency, CANDLE, and unusual and unsolved cases. Presenters were based in Canada (12) and internationally (1); and practiced as rheumatologist (10), immunologist (2), and geneticist (1). There were an estimated 418 total views (314 real-time, 104 on-demand) with an average of 46 views per session.

134 survey responses were collected. There is consistent attendance with geographic representation across Canada. 127/134 (95%) felt it met expectations, 99/134 (74%) changed practice as a result, and 125/134 (93%) would recommend it to colleagues.

Free text comments were generally positive. Some themes were acquiring new knowledge in diagnosis and testing, addressing evolving uncertainty and complexity, connecting with the community who faces similar challenges, engaging with experts, acknowledging variations in provincial and institutional resources, and appreciating diversity of approaches. One area for improvement was allocating more time for interactions.

Conclusion: CANAC Rounds is a Canadian education initiative on autoinflammation that successfully fostered a community of practice utilizing the learning principles of Connectivism. Evaluation demonstrated high educational value, indicating that virtual case-based learning networks are effective for advancing evolving knowledge in autoinflammation through connectivity. This approach may serve as a model in other educational contexts.
Disclosure of Interest: None declared

Identifier: PO198

SERUM CYTOKINE PROFILES IN NEUTROPHILIC DERMATOSES

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Introduction: Introduction:

Neutrophilic dermatoses are a heterogenous group of inflammatory skin diseases characterized by the accumulation of neutrophils in the skin in the absence of clinical infection. In most cases, neutrophilic dermatoses are associated with systemic disorders including hematological, autoimmune or autoinflammatory diseases. Patients present with polymorphic skin lesions including wheals, plaques, papules, nodules, pustules, abscesses, bullae and ulcers. Neutrophilic dermatoses are primarily mediated by the innate immune system, but the exact pathophysiology is largely unclear.

Objectives: Objective:

Characterization of serum cytokine profiles in neutrophilic dermatoses

Methods: Methods:

Patients with the following neutrophilic dermatoses were included: pustular psoriasis (n=21), hidradenitis suppurativa (n=21), nodulocystic acne (n=12), pyoderma gangraenosum (n=13), Behcet's disease (n=8), adult onset Still's disease (n=15), Schnitzler syndrome (n=12) and healthy controls (n=22). Sera were obtained and a multiplex assay including 45 secreted mediators was performed. The mediators were categorized into Th1/Th2, Th9/Th17/Th22/Treg cytokines, inflammatory cytokines, chemokines, and growth factors.

Results: Results:

Of the 45 mediators analyzed, 27 were significantly upregulated across all diseases. Hidradenitis suppurativa showed the most upregulated mediators (n=16), followed by pustular psoriasis (n=14), Schnitzler syndrome (n=13), pyoderma gangraenosum and Still’s disease (n=12 each), acne (n=10), and Behcet's disease (n=5). The Th1/Th2 cytokines IL-1 beta ($p < 0.0001$ to 0.014) and IL-2 ($p < 0.0001$ to 0.005) were consistently upregulated in all conditions. Except for Behcet's disease, IL-5, IL-9, IL-23, IL-31, TNF-beta, and VEGF-D were also significantly elevated across all diseases. Disease-specific upregulation was observed for IL-6 and MCP-1 in hidradenitis suppurativa IL-21 in Schnitzler syndrome, GM-CSF in pyoderma gangraenosum, IL-1alpha in acne, IL-18, IFN-gamma, and MIP-1beta in Still's disease, and IL-10 and GRO-alpha in pustular psoriasis. In Behcet's disease, IFN-alpha and Eotaxin were significantly elevated.

Conclusion: Conclusion:

The obtained disease-specific cytokine profiles offer valuable insights into the inflammatory environment of neutrophilic dermatoses. Our findings highlight the roles of individual mediators and their interactions in disease pathology. These findings will contribute to better patient stratification and support the development of targeted therapies.

Disclosure of Interest: None declared

Identifier: PO199

MUTATION OF X-LINKED INHIBITOR OF APOPOTOSIS (XIAP) IN A 14-YEAR-OLD GIRL: CHALLENGING MANAGEMENT OF INFLAMMATORY BOWEL DISEASE (IBD) IN XIAP-DEFICIENT FEMALE PATIENTS

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Introduction: XIAP deficiency is usually related to severe inflammatory bowel disease and hemophagocytic lymphohistiocytosis in males.
Objectives: This clinical case aims to shed a light on the possible clinical relevance of heterozygous XIAP mutations in female patients.
Methods: We present a case of anti-tumor necrosis factor (TNF) α refractory Crohn disease in a young girl with heterozygous XIAP mutation.
Results: A 14-year-old girl from Iraq was referred to hospital due to steroid-resistant and anti-TNFα refractory Crohn disease, associated with severe perineal disease and failure to thrive since the age of seven.
Laboratory investigations showed anemia, elevated inflammatory markers, hyperferritinemia and hypoalbuminemia, without other laboratoristic markers of macrophage activation syndrome. Endoscopy confirmed a severe pancolic Crohn disease (A1a, L2, p, G1). The patient underwent diverting ileostomy and was supported with parenteral nutrition, which gradually led to a complete healing of perineal disease and long-term clinical improvement. Immunological tests showed normal results. Pro-inflammatory cytokines profile detected elevated IL18 levels. Targeted IBD gene panel identified a heterozygous deletion of XIAP exon 2 and 3, classified as pathogenic for X-Linked Lymphoproliferative Disease 2. The protein expression was found to be normal in only 26% of NK and 43% of T cells, indicating a skewed X chromosome inactivation.
Conclusion: We describe a case of anti-TNFα refractory pancolic and perineal Crohn disease in a XIAP-deficient girl. Usually, non-random X-inactivation prevents females from developing the disease; in fact, asymptomatic carriers frequently display wild type allele in over 80% of their cells. In this case, reduced protein expression together with gene deletion are likely responsible for the patient's symptoms.
These findings underline the importance to investigate XIAP mutations even in female subjects when affected by severe drug resistant IBD. Since severe clinical manifestations may arise in female XIAP-carriers at any age, further studies focusing on the best diagnostic and therapeutic approach are needed.
Disclosure of Interest: None declared