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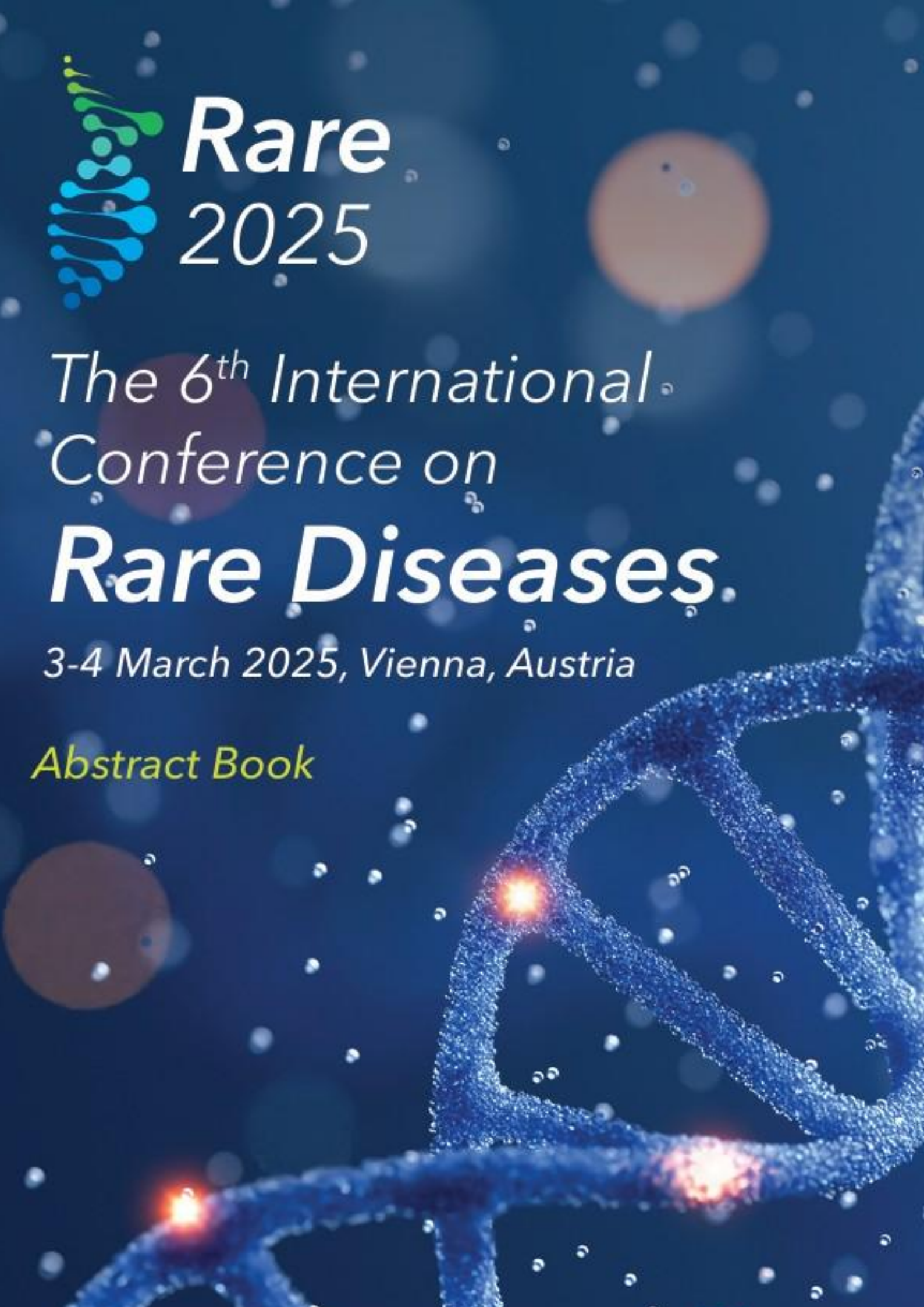
Abstract Book



Poster 50

Relations between rare diseases and common disorders

UNRAVELING THE COMPLEXITIES: EXPLORING RARE DISEASE CO-OCCURRENCE IN HYPERMOBILE EHLERS-DANLOS SYNDROME

Victoria Daylor[1], Molly Griggs[1], Matthew Huff[1], Taylor Petrucci[1,2], Rebecca Byrd[1], Amy Weintraub[1], Sunil Patel[2], Cortney Gensemer[1,2], Russell A. Norris[1,2]

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Background: The Ehlers-Danlos Syndromes (EDS) represent a broad spectrum comprising 14 hereditable connective tissue disorders, with hypermobile EDS (hEDS) emerging as the most prevalent subtype. Despite its prevalence, hEDS often remains underdiagnosed and perceived as rare, contributing to challenges in clinical management and research.

Objectives: Research on hEDS and its associated multisystemic manifestations remains relatively underexplored. This study seeks to deepen our understanding by investigating the intersection of hEDS with rare diseases and examine their co-occurrence through an extensive online survey.

Methods: Over a duration of six months, we conducted a global, cross-sectional survey-based study. The survey elicited anonymous responses encompassing diagnostic history, symptoms, and patient experiences. Among 3,360 hEDS participants meeting inclusion criteria, comprehensive 194-question surveys were completed. Comparative and statistical analyses against external databases were performed to provide relevance of findings.

Results: Analysis of survey data revealed a notable elevation in the prevalence of specific rare diseases among hEDS patients compared to reported figures from external sources. These include Addison's disease (0.36%), pure autonomic failure (0.42%), myasthenia gravis (0.42%), hemophilia (0.45%), systemic mastocytosis (0.57%), and Cushing's disease (0.65%).

Discussion: Our survey findings shed light on the multisystemic nature of hEDS, with co-occurring rare conditions spanning diverse body systems and medical specialties. This underscores the importance of acknowledging the heterogeneous presentations of hEDS in clinical settings and the potential for complex comorbidities within this patient population. Such insights will improve diagnostic accuracy and optimize patient care strategies tailored to the unique needs of individuals with hEDS.

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General challenges in rare disease

COMPARATIVE ANALYSIS OF CARDIOVASCULAR RISK FACTORS IN FABRY DISEASE AND HEALTHY CONTROL

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Background. The aim of the study was to assess the prevalence of coronary heart disease risk factors and the risk of cardiovascular incidences occurrence in patients with Fabry diseases as the prediction of health state in adults with metabolic defect compared to general population. The main risk factors were analysed: hypertension, smoking, age, elevated levels of lipid fraction, glucose, premature occurrence of cardiovascular incidences in the family history and obesity.
Material and methods. 23 subjects, aged 21-66 years, were enrolled in the study. The group of 23 healthy individuals without metabolic defect, matched according to gender and age, were selected from this population. The correlation of main risk factors occurrence in this group were determined.

Results. Diabetes was primarily treated in 2 pts (8,69%) patients with FD compared to 4 pts (17,36%) in control group, p
Conclusions. High prevalence of coronary heart disease risk factors in the patients with FD was determined and thus it is necessary to investigate and actively eliminate risk factors of coronary heart disease in this age group in order to prevent cardiovascular events in patients with rare metabolic defect.

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Rare syndromes

BASELINE CHARACTERISTICS OF A COHORT STUDY OF FAMILIAL HYPERCHYLOMICRONEMIA IN CHINA

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Objective: To observe the clinical characteristics of Chinese patients with Familial chylomicronemia syndrome (FCS). To explore the diagnostic criteria of FCS which is suitable for clinical practice in China.

Method: We screened 6,856 patients with triglyceride (TG) ≥10 mmol/L from 9 hospitals in China between January 2010 and December 2023. The overall clinical information was colected among 102 patients with high suspicion of FCS, who also underwent FCS-related gene testing. Demographic characteristics were analyzed and FCS diagnosis was drafted.

Results: In this study, the diagnostic criteria for FCS in Chinese population were drafted based on European and American diagnostic criteria and Chinese clinical practice: (1) Fasting TG ≥ 10 mmol/L (~880 mg/dL) after standard lipid-lowering treatment; (2) One of the requirements listed below: Positive detection of FCS related genes; Family history of hypertriglyceridemia pancreatitis; History of pancreatitis in adolescence or adult hypertriglyceridemia pancreatitis; History of repeated hospitalization with unexplained abdominal pain. According to this criterion, 60 were preliminarily diagnosed with FCS from the 102 patients enrolled (age 43.0±8.6 years, 70% male, TG 20.0±15.0 mmol/L). FCS related gene mutations were detected in 6 patients, all of which were lipoprotein lipase gene mutations.

Conclusion: The clinical and genetic characteristics of Chinese patients with FCS are consistent with those of European and American patients. The diagnostic criteria for FCS in Chinese population drafted in this study can be further verified and popularized.

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Relations between rare diseases and common disorders

THE PECULIARITIES OF THE ADAPTIVE-COMPENSATORY MECHANISMS OF ADULT RATS' CARDIOMYOCYTES IN THE MODEL OF ALLOXAN INDUCED DIABETES

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Background: In mammals, hepatocytes and cardiomyocyte's ability of polyploidization is considered to be a protective evolutionary mechanism developed in response to variable environmental factors and stress, and serves to maintain the functional activity of the tissue. On the other hand, in the case of heart muscle, the low proliferative activity of highly ploidy cardiomyocytes is considered a limiting factor for regeneration.

Purpose: study the peculiarities of adult rats' cardiomyocytes adaptive-compensatory mechanisms in the model of Alloxan induced diabetes.

Materials and Methods: heart left ventricle of adult white rats, model-alloxan induced diabetes, staining with hematoxylin-eosin and Fiolgen's reagent; determination of DNA with program Image-J.

Results: No reliable quantitative changes of protein - NT-proBNP was detected in cardiomyocytes of adult rats at different time points (24h, 48h, 96h) after alloxan injection. At the same time, there are no changes in the areas of cardiomyocytes and their nuclei.

24 h after Alloxan injection, the amount of tetraploid (4C) cells is significantly increased, while the number of binucleated octaploid (4Cx2) and tetraploid (2Cx2) cells is decreased significantly compared to control group animals.

At the 96th hour after the injection, the intensity of TNF-alpha immunostaining increases visibly.

Conclusion: In response to alloxan injection and the activation of inflammatory processes, at the initial stage of cardiomyopathy the percentage ratio of highly ploidy cardiomyocytes is changed in the left ventricle of adult rats. This is manifested in the quantitative increase of 4c cells.

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Patients focused aspects in rare diseases

BRIDGING DIVIDES: EMBRACING THE PATIENT-SCIENTIST COLLABORATION TO ADVANCE EHLERS-DANLOS SYNDROME RESEARCH

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Background: Ehlers-Danlos Syndromes (EDS) pose significant challenges in genetic connective tissue disorders, historically under-researched and misunderstood. Our aim is to deepen understanding of EDS and develop effective solutions for patients.

Objectives: Acknowledging the pivotal role of patient perspectives, our lab leads in innovative patient-scientist collaborations. By integrating those directly affected by EDS into our research, we accelerate discoveries, empower disabled researchers, and cultivate a robust community of experts.

Methods: The Norris Lab initiated two pioneering programs for patient-scientists: the Gensemer hEDS Internship Program (HIP) and the Visiting Scholars Program. Implementation involved distributing RedCap surveys through local advocacy groups and global social media platforms. Applicants were required to meet two key prerequisites: a personal connection to EDS and a dedicated commitment to advancing understanding and research in the field of EDS through their future careers. Eligible candidates underwent streamlined interviews for acceptance.

Results: Over four years, 26 patient-scientists from 164 applicants participated in these programs, supported by 10 lab members with EDS. These initiatives yielded significant outcomes, with alumni assuming key roles in healthcare, advocacy, and academia, including admission to prestigious MD and PhD programs. Media coverage highlights the growing interest in the patient-scientist model`s potential to reshape research and medical practices.

Conclusion: The Norris Lab`s patient-scientist initiatives signal a paradigm shift in EDS research, engaging patients as collaborative partners. The resounding success of these initiatives underscores the imperative for other institutions to emulate similar programs, empowering individuals with rare diseases to actively shape the trajectory of research in their respective fields.

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Patients focused aspects in rare diseases

REGISTRY FOR ARTHROGRYPOSIS: FEDERATED MODEL TO EXPAND FROM NORTH AND CENTRAL AMERICA TO EUROPE

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Arthrogryposis multiplex congenita (AMC) is a term describing multiple congenital contractures, which affects individuals' function and quality of life. To better understand AMC, i) a multisite registry for children with AMC, and ii) a structure for international expansion were developed. First, a multisite AMC registry was implemented across eight sites across Canada, USA and Mexico. Patient-reported outcomes, phenotypic description and whole genome sequencing aim to broaden the knowledge, address the gaps and identify new causes, treatments and future directions in this group of rare conditions. Second, an international AMC consortium was started in 2020 and contributed to a set of 541 consensus-based common data elements (CDEs) using a Delphi methodology with experts from North America, Europe, and Australia. Human Phenotype Ontology (HPO) was used for phenotypic terms to standardize language. To create an International AMC Registry, a data management and sharing infrastructure were developed that adopts the CDEs as standard data model and supports federation of databases. This poster will describe i) findings on 500 children with AMC; ii) standard REDCap schema using the CDEs and HPO concept mapping to support the Shriners AMC Registry data. The schema has been deployed on the Shriners enterprise REDCap instance and is being translated to multiple languages using a hybrid LLM and human review process for deployment by the International AMC consortium. The federated data platform will allow access of REDCap data sources in the International AMC Consortium without intermediate data storage and based on local security and privacy regulations.

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Single gene diseases

A CASE REPORT: HYPOPHOSPHATEMIC RICKETS, A NOVEL VARIANT OF XLH GENE (IN A FAMILY WITH NEGATIVE DISEASE HISTORY)

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Introduction: Hypophosphatemic rickets (HR) is a rare genetic disorder marked by renal phosphate wasting, leading to defective bone mineralization and rickets. This case report highlights the diagnostic journey and management of HR in a pediatric patient, emphasizing clinical presentation, diagnostic challenges, and treatment outcomes.

Case Presentation: A 2year and half-old female presented with growth retardation, bone pain, and progressive bowing of the legs. Family history was negative for Rickets. Initial laboratory evaluations revealed hypophosphatemia, elevated alkaline phosphatase, and high urine phosphate. Radiographs confirmed rickets. Genetic testing for PHEX gene mutation confirmed the diagnosis of X-linked hypophosphatemia (XLH). A novel Dominant variant of the gene was detected, a Novel variant of PHEX gene NM_000444.6, C1724GT p.(Gly575Val), Heterozygous, dominant pattern.

Management and Outcome: The patient was initially treated with oral phosphate supplements and active vitamin D analogs (calcitriol). This regimen improves biochemical parameters, and growth velocity, reduces bone pain, and corrects limb deformities supported by orthopedic devices.

Discussion: This case underscores the importance of early recognition and appropriate management of HR. While conventional treatments can stabilize phosphate levels, they might carry significant side effects, so they should be followed carefully. Burosumab is a novel therapy that effectively normalizes phosphate metabolism and improves clinical outcomes, presenting a favorable safety profile.

Conclusion: HR requires a high index of suspicion for diagnosis. Genetic testing is pivotal for confirmation. A negative family history does not exclude the XLH. Long-term treatment and follow-up of these patients are still recommended.

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Patients focused aspects in rare diseases

CHARACTERIZING PAIN IN RARE CONGENITAL CONDITIONS: RESULTS OF A NORTH AMERICAN PEDIATRIC REGISTRY ON ARTHROGRYPOSIS

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Purpose: Arthrogryposis Multiplex Congenita (AMC) is a large, rare group of congenital conditions characterized by multiple joint contractures. Pain is a common complaint in AMC with heterogenous profiles based on severity of joint deformities and surgical and rehabilitation management strategies. The purpose of this study was to: 1) describe the intensity, location, quality of pain; and 2) characterize various levels of pain among a pediatric population with AMC.

Methods: Data on 207 children with AMC (age 0-21 years) from a North American AMC registry across eight hospital sites was used. Pain was assessed cross-sectionally using the Adolescent Pediatric Pain Tool (APPT) and the Patient Reported Outcome Measurement Information System (PROMIS) Pain Interference (PROMIS-PI).

Main findings: Mean pain intensity score was 1.6 (range= 0, 10). Majority (84%) reported at least one body area as painful (range= 0,14). Pain was highest on extremities (29%), back (13%) and abdomen (11%) and lowest on chest (5%), and head/neck (3%). Using pain descriptors was highest in sensory dimension (35%) and lowest in affective dimension (4%). Mean PROMIS-PI T-score was 46.2 (range=32,73.2), which was weakly correlated with evaluative and temporal pain quality descriptors. Pain was characterized into: “No-Pain” cluster (n=68, 33%): male dominance; “Slight pain” cluster (n=115, 56%): age 7-13 years with equal male/female ratio with mean number of 3 orthopedic surgeries; “Moderate Pain” cluster (n=23, 11%): Mainly age 18 years, females dominance, mean number of 8 orthopedic surgeries and frequent (61%) history of non-orthopedic surgeries.

Conclusion: Our findings will help identify subgroups of affected individuals to tailor personalized management strategies and care pathways incorporating various individual factors in AMC.

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LIPEMIA RETINALIS IN AN INFANT ASSOCIATED WITH A NOVEL MISSENSE VARIANT p.Cys291Tyr(c.872GA) IN EXON 6 OF LIPOPROTEIN LIPASE GENE

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An infant presented to the pediatric emergency department with failure to thrive. Bedside fundus examination revealed a bilateral salmon-colored retina with creamy vasculature, characteristic of lipemia retinalis. Pale pink venous blood samples and markedly elevated serum triglyceride levels (12,100.7 mg/dL) corroborated the clinical suspicion. Exome sequencing revealed a novel homozygous missense variant, pCys291Tyr (c.872GA), in exon 6 of the Lipoprotein lipase (LPL) gene, establishing the diagnosis of lipoprotein lipase deficiency. The infant was managed with dietary modifications, including a low-fat diet and was scheduled for follow-ups. The infant showed significant clinical improvement, however, the creamy retinal vasculature persisted. This case highlights the importance of early fundus examination and genetic testing in diagnosing lipemia retinalis.

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Single gene diseases

THE NIPBL-GENE MUTATION OF A CORNELIA DE LANGE SYNDROME PATIENT CAUSES DEFICITS IN THE HEPATOCYTE DIFFERENTIATION OF INDUCED PLURIPOTENT STEM CELLS VIA ALTERED CHROMATIN-ACCESSIBILITY

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The Cornelia de Lange syndrome (CdLS) is a rare genetic disease, which is characterized by a cohesinopathy. Mutations of the NIPBL gene are observed in 65% of CdLS patients. A novel iPSC (induced Pluripotent Stem Cell) line was reprogrammed from the leukocytes of a CdLS patient carrying a missense mutation of the NIPBL gene. A mutation-corrected isogenic iPSC-line and two iPSC-lines generated from the healthy parents were used as controls. The iPSC lines were differentiated along the hepatocyte-lineage. Comparative immunofluorescence, RNA-seq and ATAC-seq analyses were performed on undifferentiated and differentiated iPSCs. In addition, chromatin organization was studied by ChIP-Seq analysis on the patient derived iPSCs as well as the respective controls. Relative to the mutation-corrected and the healthy-parents iPSCs, the patient-derived counterparts are defective in terms of differentiation along the hepatocyte-lineage. One-third of the genes selectively up-regulated in CdLS-derived iPSCs and hepatic cells are non-protein-coding genes. By converse, most of the selectively down-regulated genes code for transcription factors and proteins regulating neural differentiation. Some of the transcriptionally silenced loci, such as the DPP6 gene on chromosome 7q36.2 and the ZNF gene cluster on chromosome 19p12, are located in closed-chromatin regions. Relative to the corresponding controls, the global transcriptomic differences observed in CdLS undifferentiated iPSCs are associated with altered chromatin accessibility, which was confirmed by ChIP-Seq analysis. Thus, the deficits in the differentiation along the hepatocyte lineage observed in our CdLS patient is likely to be due to a transcriptional dysregulation resulting from a cohesin-dependent alteration of chromatin accessibility.

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Single gene diseases

LONG-TERM CLINICAL OBSERVATION OF PATIENTS WITH HETEROZYGOUS KIF1A VARIANTS

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Background

KIFIA(kinesin family member 1A)-related disorders (KRDs) encompass recessive and dominant variants with wide clinical variability. Recent genetic investigations have expanded the clinical phenotypes of heterozygous KIF1A variants. However, there have been a few long-term observational studies of patients with heterozygous KIF1A variants.

Objectives

To clarify the long-term clinical characteristics of KRD and find clues for diagnosis and management.

Method

A retrospective chart review of consecutive patients diagnosed with spastic paraplegia at Miyagi Children`s Hospital from 2016 to 2O2O identified six patients with heterozygous KIF1A variants. To understand the long-term changes in clinical symptoms, we examined these patients in terms of their characteristics, clinical symptoms, results of electrophysiological and neuroimaging studies, and genetic testing.

Results

The median follow-up period was 30 years (4-44 years). This long-term observational study showed that early developmental delay and equinus gait, or unsteady gait, are the first signs of disease onset, appearing with the commencement of independent walking. ln addition, later age-related progression was observed in spastic paraplegia, and the appearance of axonal neuropathy and reduced visual acuity were characteristic features of the late disease phenotype. Brain imaging showed age-related progression of cerebellar atrophy and the appearance of hyperintensity of optic radiation on T2Wl and FLAIR imaging.

Conclusion

Long-term follow-up revealed a pattern of steady progression and a variety of clinical symptoms, including spastic paraplegia, peripheral neuropathy, reduced visual acuity, and some degree of cerebellar ataxia. Clinical variability between patients was observed to some extent, and therefore, further studies are required to determine the phenotype- genotype correlation.

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Rare syndromes

CASE REPORT: 1P36 DELETION SYNDROME ASSOCIATED WITH MYELODYSPLASTIC SYNDROME

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Abstract:

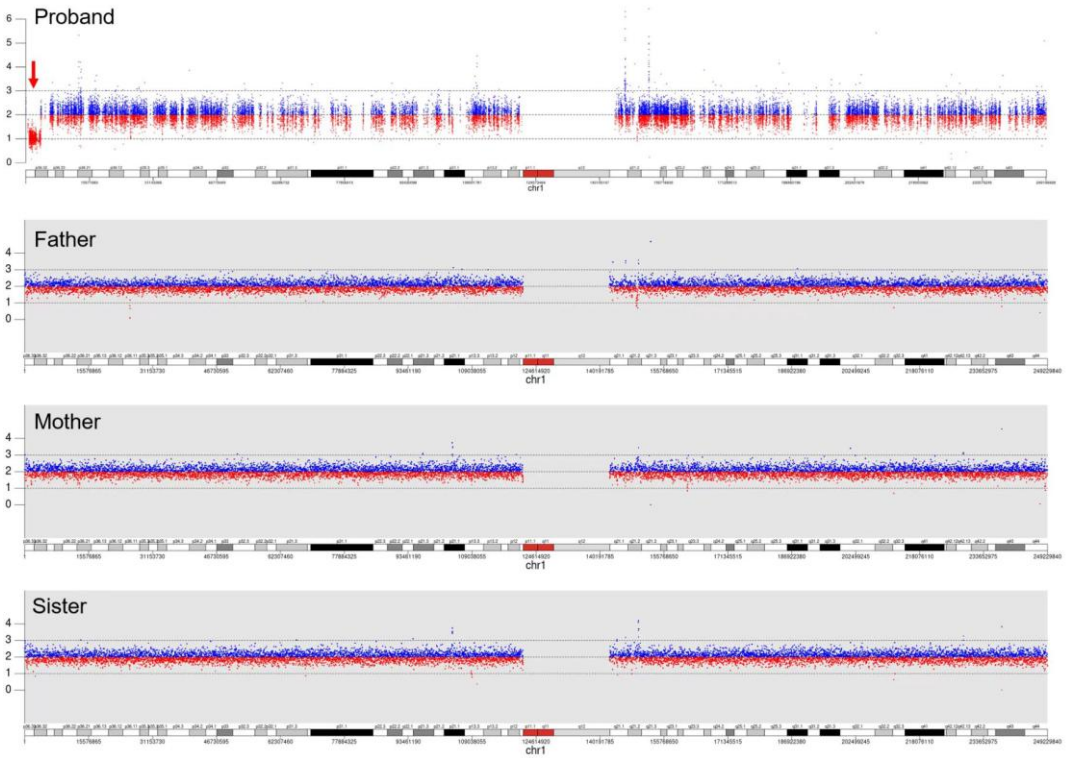
Background: 1P36 deletion syndrome is considered one of the most common terminal microdeletion syndromes, which is characterized by early developmental delay, intellectual retardation, cardiac disease and special facial features. Different deletion lengths may lead to phenotypic diversity. However, there are few reports of hematologic abnormal phenotypes in patients with 1P36 deletion syndrome.

Objectives: To provide a further understanding of the hematological phenotype of 1P36 deletion syndrome.

Methods: A case of Marfan body, developmental retardation, intellectual retardation, dilated cardiomyopathy, pulmonary hypertension was presented with anemia, thrombocytopenia (clinically diagnosed myelodysplastic syndrome) and performed whole-exon testing of whole family.

Results: Copy number variation analysis showed that there was a copy number deletion of about 2.82 Mb in size in the short arm of chromosome 1, 1p36. 33p36. 32. After cyclosporine A treatment, the child`s transfusion dependence was significantly improved.

Conclusion: This child has myelodysplastic syndrome, a rare phenotype of 1P36 deletion syndrome. The deletion fragments of 1p36. 33-1p36. 32, especially the deletion of GNB1 gene and TNFRSF4, are related to myelodysplastic syndromes. Whole exon sequencing is an important diagnostic tool in the diagnosis of diseases whose clinical manifestations involve multiple systems. Therefore, the cyclosporine A may have a significant improvement in transfusion dependence caused by 1p36 deletion syndrome.



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Single gene diseases

GENETIC TESTING IN ADULTS WITH NEPHROCALCINOSIS ENABLES PRECISION DIAGNOSIS

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Background and Aims: Nephrocalcinosis (NC), the parenchymal form of nephrolithiasis (NL), had multifactorial etiology, including genetic component. Molecular analysis in patients with NC enables an appropriate evaluation. Our single center study reports genetic and clinical characteristics of patients with NC, on whom we perform genetic testing.

Methods: We report a retrospective observational study that included adults with diagnosis of nephrocalcinosis, on whom we performed a genetic test, using nephrolithiasis panel, from two commercial genetic laboratories. The study was conducted between September 2020 – December 2024 in the Nephrology Department, Fundeni Clinical Institute.

Results: The study included 13 adult patients, 6 males and 7 females, with the mean age at the time of recruitment 33.0 ± 10.3 years, and the mean age of the first diagnosis 20.1 ± 10.9 years. Nine patients (69.2%) had NC associated with NL, and 4 patients had isolated medullary NC. We found a Mendelian disease in 10 (patients: distal renal tubular acidosis (SLC4A1; n=3), Dent disease (CLCN5; n=2), infantile hypercalcemia type 1 (CYP24A1; n=2), familial hypomagnesaemia with hypercalciuria and NC (CLDN16; n=1), primary hyperoxaluria type 1 (AGXT; n=1), Bartter syndrome type 2 (KCNJ1; n=1). A summary of manifestations in patients with positive genetic test included hypercalciuria, distal renal tubular acidosis, and young age of onset. In addition, 10 patients had chronic kidney disease.

Conclusion: Genetic testing should be considered in all patients with nephrocalcinosis. Genetic testing enables accurate diagnoses, changes in disease management, and precision medicine, that could significantly influence the long-term outcomes.

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Lysosomal storage disorders

LYSO-GB3 MODULATES PODOCYTE PROTEINS AND IMMUNE MARKERS IN FABRY NEPHROPATHY

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Background: Fabry nephropathy is characterized by progressive podocyte injury driven by the accumulation of globotriaosylceramide (Gb3) and its bioactive metabolite, Lyso-Gb3. This accumulation induces structural and immunological alterations in podocytes, exacerbating glomerular dysfunction.

Objectives: To evaluate the effects of Lyso-Gb3 on the expression of podocyte-specific proteins and immunological markers, elucidating its role in Fabry nephropathy progression.

Methods: Human immortalized podocytes were exposed to Lyso-Gb3 (100 nM) for 2, 6, and 24 hours. The mRNA expression levels of key podocyte proteins (PODXL, CD2AP, nephrin, synaptopodin, WT-1, and ACTN4) and immunological markers (CD80, TLR1, TLR2, TLR4, TGF-β1, and VDR) were quantified using RT-qPCR. Statistical analysis was performed to determine significant differences compared to untreated controls.

Results: Lyso-Gb3 induced time-dependent alterations in podocyte-specific proteins. Nephrin, synaptopodin,ACTIN4 and podocalixin showed significant upregulation at 2 hours, followed by a marked reduction at 6 and 24 hours (p 0.05). CD2AP levels decreased significantly after 6 hours. Immunological markers revealed sustained TLR4 upregulation and increased TGF-β1 expression at 24 hours, suggesting chronic inflammatory and fibrotic responses. CD80 was transiently elevated at 2 hours but declined at later time points, while TLR2 levels decreased significantly at 24 hours.

Conclusion: Lyso-Gb3 drives both structural and immunological dysregulation in podocytes, contributing to glomerular dysfunction in Fabry nephropathy. These findings underscore the importance of targeting Lyso-Gb3-mediated pathways for potential therapeutic interventions.

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Patients focused aspects in rare diseases

DEMOGRAPHIC, CLINICAL AND THERAPEUTIC INSIGHTS INTO PYODERMA GANGRENOSUM: THE 2024 PISA COHORT

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Background

Pyoderma Gangrenosum (PG) is a rare, immune-mediated dermatological disorder characterized by painful ulcers and variable clinical presentations. Understanding the demographic and clinical profiles of affected individuals is crucial for optimizing management.

Objectives

This analysis aimed to describe the demographic, clinical, and therapeutic characteristics of 21 patients with PG, followed in Pisa in 2024, to identify relevant comorbidities and evaluate treatment outcomes.

Methods

A cross-sectional review of medical records was performed to gather data on sex, age, body mass index (BMI), lifestyle habits, comorbidities, family histories, lesion characteristics, and treatment regimens. Frequencies, means, and standard deviations were calculated where applicable.

Results

The cohort was predominantly female (71%), with a mean age of 57.9 ± 16.3 years. Smoking was reported by 71.4%, and 47.6% consumed alcohol. Comorbidities included diabetes mellitus (57.9%), psoriasis (26.3%), and inflammatory bowel diseases (19%). Family histories frequently involved solid neoplasms (52.6%). Mean onset of PG was 53.3 ± 15.6 years, most commonly presenting with non-confluent pustules (31.6%). Active disease was noted in 4.8% of patients, with 61.9% achieving complete re-epithelialization. Treatments included anti-TNF-α (28.6%), IL-23 inhibitors (28.6%), IL-17 inhibitors (9.5%), oral corticosteroids (33.3%), and dapsone (19.0%). The average number of biologic switches was 0.67 per patient, with a maximum of four.

Conclusion

These findings highlight the clinical heterogeneity and potential complexity of PG management. A thorough evaluation of comorbidities, personal and family histories, and therapeutic response is essential to tailor effective treatment strategies and improve patient outcomes. Further multicentre investigations should explore targeted interventions to optimize management.

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General challenges in rare disease

SYSTEMIC IMMUNE-INFLAMMATION INDEX (SII) AS A MARKER OF IMFLAMMATION IN PYODERMA GANGRENOSUM

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INTRODUCTION

The systemic immune-inflammation index (SII) is a novel inflammation biomarker, increasingly applied in clinical practice. SII is calculated based on three parameters—platelet count, lymphocyte count, and neutrophil count in peripheral blood—and serves as an indicator of both inflammatory status and immune response. Pyoderma gangrenosum (PG) is a neutrophilic dermatosis characterized by a high inflammatory burden, with its etiology involving complex interactions among genetic, immune, and environmental factors. This study aims to investigate the SII levels in PG patients.

METHODS

A retrospective analysis was conducted on 16 patients diagnosed with PG. Blood samples were collected from all patients. Lymphocyte, neutrophil, monocyte, and platelet counts were measured as x10^3 cells/µL, and the SII was calculated using the formula: (platelet count x neutrophil count) / lymphocyte count.

RESULTS

The population includes 16 patients: 11 females (68.75%) and 5 males (31.25%), the average age is 59,68 with a standard deviation of 9. SII medium value is 6.689 with a standard deviation of 500.555.

CONCLUSION

SII values in patients with PG were higher than those typically observed in other chronic inflammatory skin diseases. The consistently elevated SII levels in PG highlight the potential for establishing a clinical cut-off value, which could aid in monitoring disease progression and tailoring treatment strategies. Further studies with larger cohorts are warranted to validate these results and determine a precise SII threshold for clinical application.

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New treatment modalities

MANAGING PATHERGY IN PYODERMA GANGRENOSUM: TIMING DEBRIDEMENT TO ENABLE HOMOLOGOUS SKIN GRAFTING

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Introduction

Pyoderma gangrenosum (PG) is a rare neutrophilic dermatosis characterized by painful, rapidly progressing ulcers. Its management is complicated by the pathergy phenomenon, where trauma exacerbates the lesions. This case report demonstrates the successful application of the PG-TIME algorithm in facilitating wound healing in PG, underscoring the critical importance of timing for mechanical interventions.

Case Report

A 67-year-old male presented with a PG ulcer on the left heel. Previous mechanical debridement had aggravated the condition due to pathergy. Initial evaluations revealed a wound area of 42 cm^2, a Wound Bed Score (WBS) of 3/16, a Visual Analog Scale (VAS) pain score of 9/10, and a Dermatology Life Quality Index (DLQI) of 27/30. Treatment followed the PG-TIME protocol, combining local wound care with systemic prednisone and dapsone. After achieving sufficient inflammatory control, surgical debridement was performed to remove biofilm and excise the necrotic exposed tendon, which was delaying wound healing and fostering bacterial colonization. Post-debridement, wound bed improvement was significant (WBS 9/16), with a reduction in wound area by 10 cm^2, VAS decreased to 3/10, and DLQI improved to 11/30. This progression facilitated a homologous skin graft.

Conclusion

This case highlights the effectiveness of a multimodal approach in managing pyoderma gangrenosum. Transitioning to a non-inflammatory phase allowed safe surgical interventions without pathergy-related complications, enabling successful debridement and homologous grafting. The marked improvements in wound healing, pain reduction, and patient quality of life underscore the importance of timely and coordinated interventions in the treatment of this challenging disease.

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Single gene diseases

BOOSTING THE UNFOLDED PROTEIN RESPONSE AS A THERAPEUTIC STRATEGY IN HUNTINGTON'S DISEASE AND OTHER NEURODEGENERATIVE DISEASES

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Background: No efficient therapy is available for Huntington's disease (HD) nor for other neurodegenerative diseases, including Alzheimer's, Parkinson's and many rare diseases. No disease-modifying approaches exist. A common pathological mechanism underlying these disorders is cytotoxicity induced by endoplasmic reticulum (ER) stress. This stress disrupts cellular protein homeostasis and contributes to neurodegeneration.

Objectives: We aimed to develop and explore the therapeutic potential of small molecules designed to modulate the unfolded protein response (UPR), mitigating ER stress and improving disease outcomes.

Methods: We developed MK-28, a small molecule designed to activate PKR-like ER kinase (PERK), a key regulator of the UPR. MK-28 was tested in HD cellular models and the aggressive R6/2 HD mouse model. The effects of the compound on PERK activation and downstream cellular pathways were assessed, with a focus on eIF2α phosphorylation and its role in inhibiting protein translation and reducing damaged protein accumulation. Physiological responses, motor performance, and survival rates of treated R6/2 mice were monitored to evaluate therapeutic efficacy.

Results: MK-28 effectively activated PERK, increasing eIF2α phosphorylation and enhancing UPR activity. This led to a reduction in ER stress and improved cellular homeostasis. In R6/2 mice, MK-28 treatment significantly improved motor performance, physiological metrics, and survival. These findings suggest that PERK activation delays the onset and progression of HD symptoms.

Conclusion: Boosting PERK activity through MK-28 represents a promising therapeutic strategy for HD and conceivably opens a new approach for recovery of protein homeostasis breakdown in other common and rare neurodegenerative diseases.

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Patients focused aspects in rare diseases

ELEVATING PATIENT VOICES ON LABOR AND DELIVERY FOR BIRTHING PEOPLE WITH RARE CONGENITAL AND ACQUIRED BLADDER ANOMALIES

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Background:

Patients with bladder exstrophy, a rare birth defect where the bladder develops outside the body, commonly undergo reconstructive surgery, as do patients with spina bifida or other conditions causing impaired bladder control. Complex post-surgical anatomy can prompt providers to recommend cesarean delivery (CD) to avoid theoretical risk from vaginal delivery (VD) or emergent CD. One-third of US pregnancies deliver by CD, which is associated with significantly increased morbidity and mortality compared to VD.

Objectives:

This study aimed to describe provider practices regarding delivery counseling and obstetric outcomes for patients with bladder surgery.

Methods:

18 pregnancies in 13 patients with reconstructive bladder surgery who delivered at an academic center between 2004-2024 are described. Manual chart review was performed.

Results:

Patients had diagnoses of bladder exstrophy (53.9%), spina bifida (30.8%), neurogenic bladder (7.7%) and bladder rhabdomyosarcoma (7.7%). 4 patients (30.8%) also reported vaginal surgery. 61.1% of included pregnancies and 100% of pregnancies with vaginal surgery had counseling recommending CD secondary to anatomy. 55.6% of all pregnancies ended in CD, including 72.7% of patients counseled toward CD, with 27.2% of counseled patients undergoing VD.

Conclusion:

Bladder surgery patients have significantly higher rates of CD compared to the general population. Many CD occurred after directed counseling due to theoretical risks of VD, though almost half of all reviewed pregnancies resulted in uncomplicated VD, including nearly one-third of patients recommended CD. Shared decision-making guided by obstetric providers may enable safer pregnancy outcomes for these high-risk patients, and caution should be used in adhering to unilateral care recommendations from specialists.

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Patients focused aspects in rare diseases

PATIENTS` MOTIVATIONS TO PARTICIPATE IN CLINICAL TRIALS FOR GAUCHER DISEASE – A QUALITATIVE INQUIRY

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· Background
Patients` motivations to participate in clinical trials vary and include altruism, personal benefits such as access to medications they could not otherwise afford, and more. Reasons for non-participation include concerns about side effects, apprehension about being assigned to the placebo group, and the potential loss of workdays.
· Objectives
Studies have explored patients` motivations for participating in clinical trials for diseases such as cancer, heart disease, and HIV. However, no research has examined the reasons for participation among patients with Gaucher disease (GD). This is the focus of our study.
· Methods
Adult patients with GD who participated in at least one GD-related clinical trial were invited to participate in this pilot, explorative qualitative study. All participants signed informed consent prior to enrolling. Semi-structured interviews were conducted on Zoom, all recorded, transcribed, and analyzed through thematic analysis. The institutional IRB approved the study design (0053-24-SZMC). The first author has an extensive experience in qualitative research.
· Results
The participants (N=13), aged 37–81 (9 women), are followed at the Gaucher Unit, Shaare Zedek Medical Center, which serves ~500 active patients annually, ~40% of whom have participated in clinical trials. Eight joined one trial and the other - more than one. For most interviewees, the time range since their participation in a clinical trial was 20–30 years.The interviewees expressed strong trust in the medical team, often participating in trials due to the close relationships built. Their motivations included contributing to science, trying convenient medications, receiving free treatment, and helping others. Most described the experience positively, though some mentioned the burden of participation affecting their decision to continue. One patient expressed regret.
· Conclusion
Our study is the first to explore the motivations of patients with GD to participate in clinical trials. In the era of gene therapy trials for GD and for GBA-related Parkinson’s disease, it is important to understand patients` reasons for joining or avoiding trials, as well as what encourages them to stay or withdraw, to optimize research recruitment. The findings from this exploratory study will provide the foundation for future qualitative research in this area, ultimately contributing to more patient-centered approaches in clinical trial design and implementation.

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General challenges in rare disease

INSTRUMENTS TO MEASURE THE HEALTH-RELATED QUALITY OF LIFE IN EPIDERMOLYSIS BULLOSA: A SCOPING REVIEW

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Background:
Epidermolysis Bullosa (EB) is a group of rare inherited skin diseases. The assessment of health-related quality of life (HRQoL) is key to understanding the psychosocial and emotional impact on patients and their family relatives and caregivers (FC).

Objectives:
To identify which instruments are in use to evaluate the HRQoL of people with EB and their FC.

Methods:
A Scoping review (ScR) was carried out that followed the PRISMA criteria. The protocol was developed according to the Joanna Briggs Institute for ScR methodology. The research question was: “What measurement tools are available for the assessment of HRQoL in EB?” A search was performed in PubMed, Scopus and WOS. Articles were collected in Zotero, and independently reviewed by two authors. Discrepancies were resolved by the third author. PRISMA flowchart was built to show the results and the inclusion process.

Results:
290 records were identified from databases (PUBMED:74; SCOPUS:139 and WOS:77). After removing 116 duplicates, 128 articles were revised by title and abstract, and 42 proceeded to full-text peer review. The final analysis was carried out on 31 articles. The independent reviewers obtained a good strength of agreement (Kappa 0.73) and authorship biases were not identified. QoLEB questionnaire is the most used for EB patients. In FC, FDLQI and EB-BoD are more often employed.

Conclusion:
This ScR has provided an overview of the evidence on the use of HRQoL instruments, both in patients and in their FC. These results will enable professionals to better understand the health and well-being of EB patients.

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Genetic Parkinson’s disease

ALPHA-SYNUCLEINOPHATIES IN GAUCHER DISEASE: A MULTICENTER LONGITUDINAL STUDY

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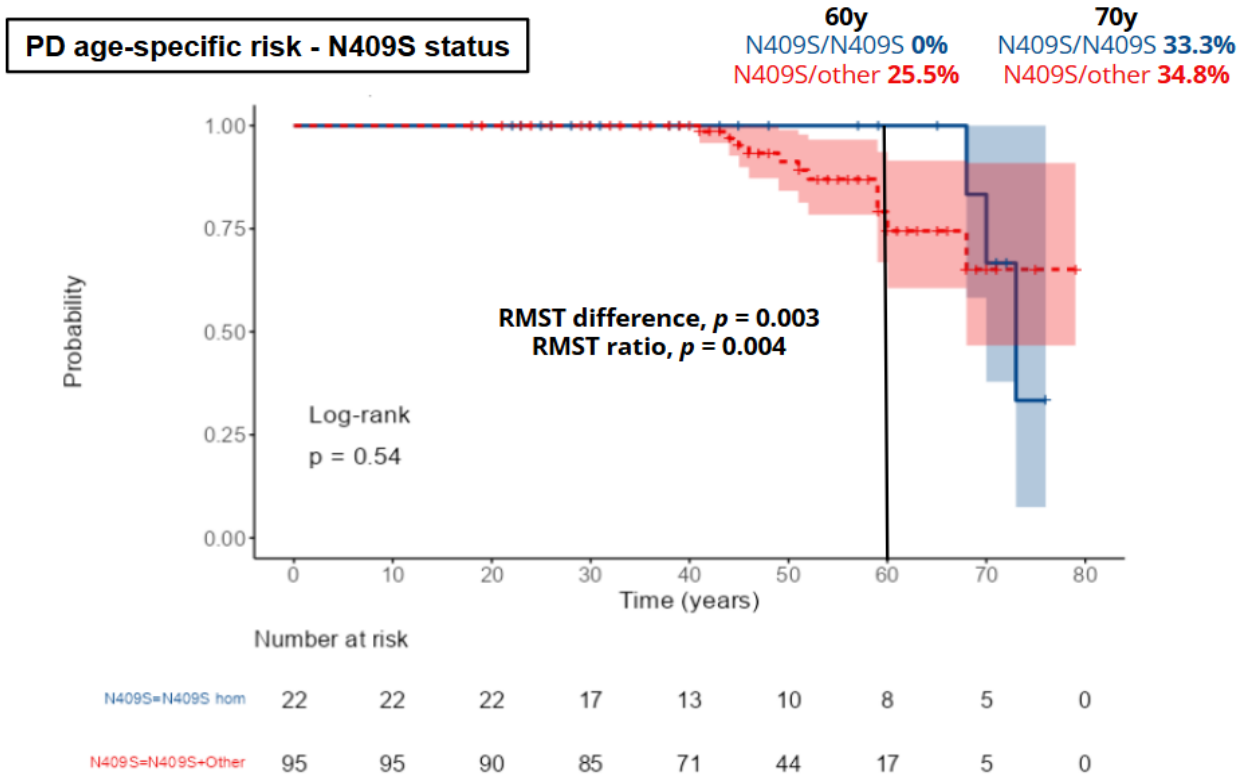
BACKGROUND: Gaucher disease (GD) is a lysosomal storage disorder caused by biallelic GBA1 variants, which represent the most common genetic risk factor for Parkinson’s disease (PD) and dementia with Lewy bodies (DLB).

OBJECTIVES: To investigate the occurrence of PD and DLB in a cohort of type 1 and type 3 GD patients (GD1, GD3), and to identify possible predictors of PD or DLB phenoconversion in these patients.

METHODS: GD patients from multiple centers were consecutively evaluated by neurologists with expertise in movement disorders at two different time-points (T0, at baseline; T1, after 4±2y).

RESULTS: One-hundred-thirty-six GD1 and 13 GD3 patients were evaluated at T0 (mean age-at-T0 47.6±15.6y). The mild N409S variant in compound heterozygosity with another GBA1 variant (N409S/other) was the most frequent genotype (72.1%). Diagnosis of PD and DLB was reached in 18 (13.2%) and two (1.5%) GD1 patients, respectively. Fifty-four GD1 and five GD3 patients were re-evaluated at T1. PD and DLB phenoconversion were observed in four (7.4%) and seven (13%) GD1 patients, respectively. Two (15.4%) GD3 patients developed PD. PD diagnosis preceded that of GD in six (4.4%) GD1 patients. The lifetime risk to develop PD was 25.5% in N409S/other GD1 patients and 0% in homozygous N409S patients at 60y ($p = 0.003$), 34.8% and 33.3% respectively at 70y ($p = 0.54$) (Fig.1).

CONCLUSIONS: This study highlights the potential of close follow-up of GD patients to identify possible predictors of phenoconversion to PD or DLB.


PD age-specific risk - N409S status
60y
N409S/N409S 0%
N409S/other 25.5%
70y
N409S/N409S 33.3%
N409S/other 34.8%
Probability
1.00
0.75
0.50
0.25
0.00
RMST difference, p = 0.003
RMST ratio, p = 0.004
Log-rank
p = 0.54
0
10
20
30
40
50
60
70
80
Time (years)
Number at risk
N409S=N409S hom 22 22 22 17 13 10 8 5 0
N409S=N409S+Other 95 95 90 85 71 44 17 5 0

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General challenges in rare disease

PIONEERING GENOMIC NEWBORN SCREENING: INTERIM RESULTS OF BABYDETECT PROJECT

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Background: Newborn Screening (NBS) has come a long way since its first introduction to the public health system back in the 1960's. The advent of new technologies has paved the path for progressive inclusion of more metabolic, endocrine and rare disorders, resulting in saving thousands of children from severe disability and/or early death. In the context of NBS, 26 genomic newborn screening projects using targeted Next-Generation Sequencing (tNGS), Whole-Exome Sequencing or Whole-Genome Sequencing have been initiated worldwide.

Objective: In September 2022, research project BabyDetect (ClinicalTrials.gov NCT05687474) started aiming to explore feasibility and acceptability of first-tier genomic NBS in Liege, Belgium. The study focuses on identifying actionable genetic variants and their impact on neonatal health.

Method: In BabyDetect tNGS is used and the panel consists of 405 genes responsible for 165 severe, pediatric and treatable diseases.

Results: As of now, 5,442 newborns have been enrolled in the study with a 90.5% consent-rate and those have been sequenced with a screen-positive rate of 1.8%. 97 positive cases have been identified, 29 of which were not detected by conventional NBS, with G6PD deficiency being the most frequent.

Conclusion: The data demonstrate the high acceptability of genomic newborn screening in a properly informed population. These interim results indicate the feasibility of mid-scale targeted genomic NBS, highlighting the importance of combining biochemical and genomic methods in NBS.

Lysosomal storage disorders

CARDIOVASCULAR EVENTS IN PATIENTS WITH FABRY DISEASE: DATA FROM A MULTICENTRIC NATIONWIDE STUDY

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Clinical presentation of Fabry cardiomyopathy can vary significantly, but cardiovascular (CV) events are a major cause of morbidity and mortality among affected patients. Although specific therapies are available, these events may still occur, particularly when treatment begins at a later disease stage. This study aims to describe the occurrence of CV events in a cohort of patients with Fabry disease who have distinct GLA gene mutations, using data from a multicentric nationwide study.

In forty-nine patients (18 male, mean age 52), CV events were reported in 13 (27%) patients. These events included: 4 cases of heart failure, 9 arrhythmias, one CV-related death, one pacemaker implantation and 3 strokes. Seven patients experienced two or more CV events. Events occurred in 71% of patients in stage III.

Before the first CV event, seven patients were already receiving treatment, either with enzymatic or oral medications for Fabry, initiated between two months and 17 years prior to the event.

In conclusion, our data highlight the significant impact of CV events in patients with Fabry disease, emphasizing the importance of early treatment and the relevance of disease staging for prognostic assessment.

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Lysosomal storage disorders

FABRY DISEASE SCREENING IN PATIENTS WITH IDIOPATHIC HCM OR IDIOPATHIC LVH: DATA FROM THE MULTICENTRIC NATIONWIDE F-CHECK STUDY

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Fabry disease (FD) is a rare lysosomal storage disorder caused by mutations in the X-linked GLA gene, with hypertrophic cardiomyopathy (HCM) being its most common cardiac manifestation. Due to its non-specific presentation, systematic screening in patients with compatible phenotypes, especially HCM, is crucial for improving diagnosis rates. This multicenter study reports findings from the F-Check screening initiative in Portugal, aimed at determining FD incidence.

Methods: Screening focused on centers in northern Portugal, excluding the F113L founder-effect area. Patients with idiopathic HCM (left ventricular wall thickness ≥15 mm), idiopathic left ventricular hypertrophy (LVH ≥13 mm), dilated-phase HCM (dHCM), or dilated cardiomyopathy (DCM) with inferolateral late gadolinium enhancement (LGE) were included. Testing involved Dried Blood Spot (DBS), genetic testing, or both, from January 2021 to December 2024. Exclusion criteria included cardiomyopathy before age 30 or male-to-male transmission.

Results: Among 265 patients (61.5% male, median age 65 years), FD was diagnosed in 10 (3.8%) with 6 distinct GLA mutations (4 F113L, 2 N215S, 4 other pathogenic variants). Reduced enzyme activity on DBS was observed in 17 patients, with genetic confirmation in 7. Cardiovascular symptoms were present in 90% of FD patients, with higher QRS duration, more frequent right bundle branch block (66.7%), fascicular block (33.3%), and inferolateral LGE (70.0%) compared to non-FD patients.

Conclusion: FD was identified in 3.8% of screened patients, with 60% involving non-F113L mutations, underscoring the value of screening in patients with HCM or idiopathic LVH.