22ND | INTERNATIONAL SYMPOSIUM OF THE PORTUGUESE SOCIETY FOR METABOLIC DISORDERS

THE FUTURE OF INBORN ERRORS OF METABOLISM: DECODING COMPLEXITY, DELIVERING INNOVATION

HOTEL VILA GALÉ, COIMBRA

18th-20th March

spdm SOCIEDADE PORTUGUESA DE DOENÇAS METABÓLICAS

WELCOME LETTER

Dear Colleagues and Friends,

On behalf of the Organizing Committee, it is with great pleasure that I welcome you to the 22nd International Symposium of the Portuguese Society for Metabolic Disorders (SPDM).

This year´s programme will focus on "The Future of Inborn Errors of Metabolism: Decoding Complexity, Delivering Innovation", with the aim of exploring recent therapeutic advancements and future perspectives in the field of Inherited Metabolic Disorders (IMD).

The Symposium programme has the privilege to count on the participation of outstanding experts from national IMD reference institutions, as well as several international experts, who will present you the most recent scientific advances in the main fields of IMD, including lysosomal storage disorders, mitochondrial diseases, amino acid catabolism disorders, and glycogen storage disorders. We will also have a pre-symposium course addressing emergencies in IMD and a special Masterclass session which will provide a broad and longitudinal overview on the topic of Phenylketonuria.

We hope that participants can get together in person, so important for exchange of ideas in an informal environment.

The Vila Galé Hotel offers ideal conference conditions in a modern and pleasant atmosphere, located near the Mondego River and the historic center of Coimbra.

This meeting has been made possible by the continued support of the sponsors, which we acknowledge. We are delighted to be hosting the 2026 SPDM Annual Symposium, hoping that it will be a success, and very much look forward to welcoming all of you in Coimbra.

João Durães and Sónia Moreira
Symposium Chairpersons

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PROGRAMME

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SCIENTIFIC PROGRAMME

WEDNESDAY, 18TH MARCH

14:00--18:00	**Pre-Congress Course: Emergencies in IEM: Practical Protocols and Interdisciplinary Management**
18:00--19:00	**SPDM Working groups meeting**
19:00--20.00	**SPDM Nutrition groups meeting**

THURSDAY, 19TH MARCH

08:30	**Secretariat Opening**
09:00	**Symposium Opening** *João Durães (Coimbra) and Sónia Moreira (Coimbra)*
09:20	**Session I - New avenues for diagnosis and treatment of Neurometabolic diseases** *Chairpersons: Maria Carmo Macário (Coimbra) and Arlindo Guimas (Porto)*
09:20	**From Disease Discovery to Treatment in DEGS1 leukodystrophy** *Aurora Pujol, Barcelona, Spain*
09:40	**New therapy advancements in Metachromatic Leukodystrophy** *Cutillo Gianni, Milan, Italy*
10:00	**Usefulness of blood tests in the diagnosis of GLUT1 deficiency syndrome** *Hana Pavlú Pereira, Lisbon, Portugal*
10:20	Discussion
10:40	Coffee Break
11:10	**Session II - Managing and treating lysosomal storage disorders** *Chairpersons: Ana Cristina Ferreira (Lisbon) and João Gomes (Coimbra)*
11:10	**New therapeutic approaches in Fabry disease** *Patrício Aguiar, Lisbon, Portugal*
11:30	**Management of pregnancy in lysosomal storage disorders** *Derralynn A Hughes, London, UK*
11:50	**Hematopoietic Stem Cell Gene Therapy for Mucopolysaccharidosis Type I: clinical outcomes** *Matilde Cossutta, Milan, Italy*
12:10	Discussion
12:30	**IMMEDICA Symposium: Accumulated clinical experience in the management of patients with urea cycle disorders: Long-term impact on patients' lives. New therapeutic options** *Elisa Leão Teles, Porto, Portugal* *Esmeralda Rodrigues, Porto, Portugal*
13:15	Lunch
14:30	**Session III - Mitochondrial diseases: are we ready for innovative therapies?** *Chairpersons: Célia Nogueira (Porto) and Margarida Paiva Coelho (Porto)*
14:30	**Three decades of translational research in Leber's Hereditary Optic Neuropathy: what have we learned?** *Manuela Grazina, Coimbra, Portugal*
14:50	**Recent advances in diagnosis and treatment of TK2 Deficiency** *Cristina Dominguez-González, Madrid, Spain*
15:10	**Small molecules as a therapeutic strategy in mitochondrial diseases** *Paulo Oliveira, Coimbra, Portugal*
15:30	Discussion
16:00	Coffee Break & Posters communications

16:40	**Session IV - Masterclass PKU - Past, Present, and Future Perspectives** *Chairpersons: Luísa Diogo (Coimbra) and Esmeralda Martins (Porto)* Discussion *Rita Jotta (Lisbon, Portugal), Carla Carmona (Porto, Portugal), Nanci Baptista (Coimbra, Portugal), Elisabete Almeida (Porto, Portugal)*
17:45	**SPDM General Assembly**

FRIDAY, 20TH MARCH

09:00	**Session V - Oral Communications** *Chairpersons: Ana Paula Leandro (Lisboa) and Teresa Almeida Campos (Porto)*
10:00	**Session VI - Recent therapeutic advances in Glycogen Storage Diseases** *Chairpersons: Helder Esperto (Coimbra) and Anabela Bandeira (Porto)*
10:00	**Hepatic outcomes in adult patients with glycogen storage disease type III** *Kevin Kuriakose, Manchester, UK*
10:20	**Bempedoic acid prolongs fasting time in patients with GSD type 1a** *Anibh Das, Hannover, Germany*
10:40	**New avenues to treat Neutropenia in GSD type Ib and G6PC3-deficient patients** *Maria Veiga da Cunha, Leuven, Belgium*
11:00	Discussion
11:20	Coffee Break & Posters communications
12:00	**Session VII - Advances and Challenges in Therapeutic Approaches for Inherited Amino Acid Catabolism Disorders** *Chairpersons: Ana Oliveira (Coimbra) and Manuela Ferreira De Almeida (Porto)*
12:00	**Therapy for Urea Cycle Disorders: Current Practice and Future Prospects** *Julien Baruteau, London, UK*
12:20	**Liver Transplantation in Aminoacidopathies and Organic Acidemias: The Portuguese Experience** *Sara Ferreira, Coimbra, Portugal*
12:40	Discussion
13:00	Lunch
14:00	**Session VIII - Oral communications** *Chairpersons: Hugo Rocha (Porto) and Mariana Pintalhão (Porto)*
15:00	**Session IX - Therapeutic and Technological Innovation in Inherited Metabolic Diseases** *Chairpersons: Joana Rosmaninho Salgado (Coimbra) and Anabela Oliveira (Lisbon)*
15:00	**Targeted Nanomedicine in Inherited Metabolic Diseases** *Jose Alvarez Gonzalez, Santiago de Compostela, Spain*
15:20	**Metabolic Reprogramming in Metabolic Diseases** *Paulo Gameiro, Lisbon, Portugal*
15:40	**Gene therapy in Inherited Metabolic Diseases** *Rui Nobre, Coimbra, Portugal*
16:00	Discussion
16:20	Coffee Break & Posters communications
16:50	**Session X - SPDM grants** *Chairpersons: Dulce Quelhas (Porto) and Isabel Rivera (Lisbon)*
16:50	**Validation of a questionnaire to assess eating disorders in inherited metabolic disease patients requiring dietary treatment** *Inês Curvelo Mendes*
17:30	**Closing Session & awards** *João Durães (Coimbra) and Sónia Moreira (Coimbra)*

SPEAKERS

SOCIEDADE PORTUGUESA
DE DOENÇAS METABÓLICAS

ANIBH MARTIN DAS
GERMANY

Anibh Martin Das

Prof. Das is head of Paediatric Metabolic Medicine at the Department of Paediatrics, Hannover Medical School.
After undergraduate studies of medicine at Göttingen University he was a scholar of the 'Max-Planck Society' in Göttingen (Germany) where he worked in respiratory physiology, followed by a postdoctoral fellowship at the Department of Biochemistry, University of Oxford (UK) where his focus of research was the regulation of cardiac energy metabolism. Prof. Das trained in Paediatrics at Hannover Medical School and University Clinics Hamburg-Eppendorf (Germany). His special interest is in Inborn Errors of Metabolism and Neuropaediatrics with a research focus on energy metabolism, amino acid metabolism and lysosomal storage diseases. He has also obtained experience in Newborn screening at the 'Screening Laboratory Hannover' for several years. Prof. Das has (co)-authored more than 200 scientific papers and book articles.
Prof. Das is member of the scientific advisory board of the 'German Society for Muscle Diseases', the 'Centre for Systems Neurosciences' in Hannover and the 'Centre for Rare Diseases' as well as the 'Ethical Review Board' at Hannover Medical School.

AURORA PUJOL
SPAIN

Aurora Pujol

Professor Aurora Pujol is a clinical and laboratory geneticist, board certified in France and the United States, and Professor of Genetics and Neuroscience. She obtained her MD from the University of Barcelona (Spain), her PhD from Heidelberg University (Germany), and completed her postdoctoral training and clinical specialization in genetics in Strasbourg (France).
Since 2005, she has led a translational research team, the Neurometabolic Diseases Lab at IDIBELL (Barcelona, Spain), focused on improving the diagnosis and treatment of leukodystrophies. By integrating computational algorithms with clinical and functional genomics, her team has provided diagnoses to over 600 previously unsolved families and discovered 14 novel ultrarare diseases. Her work has uncovered fundamental roles of lipid and energy metabolism in brain health.
Her studies of adrenoleukodystrophy have revealed key pathogenic pathways, enabling the repurposing of several approved drugs—including pioglitazone, temsirolimus, dimethyl fumarate and fingolimod—and accelerating their translation toward clinical application.

CARLA M. CARMONA
PORTUGAL

Carla Maria Carmona

Clinical Psychologist at Serviço de Genética Médica - Centro de Genética Médica Doutor Jacinto Magalhães, ULS de Santo António, E.P.E. - Porto, Portugal
In 1986 - started her professional career at the Jacinto de Magalhães Medical Genetics Center as a member of the team that followed-up cases under the National Neonatal Screening Program.
Made her MsC at College of Psychology and Educational Sciences - Oporto University on the theme "Phenylketonuria and self-control: exploratory studies".
Made her PhD at Institute of Education and Psychology – University of Minho on the theme "Classical Phenylketonuria: psychological factors in adapting to a chronic illness".
The neuropsychological assessment of patients with phenylketonuria, and the understanding of the factors modelling their adaptation to this condition throughout the different life stages, has been an important contribution to the characterization of this population, making it possible to set guidelines for the follow-up of these patients providing them with the most appropriate psychosocial support.
The multidisciplinary teamwork and extensive experience on neuropsychological evaluation of neurodevelopmental disorders, have enabled the collaboration not only in areas such as hereditary metabolic diseases but also in the field of medical genetics.
Her main professional activity is the provision of clinical care, followed by clinical research, supervision of master's projects in different areas as well as publishing articles in national and international journals.

CRISTINA D. GONZÁLEZ
SPAIN

Cristina Domínguez González

Dr. Domínguez-González is a neurologist specializing in neuromuscular and mitochondrial diseases. She leads a multidisciplinary clinical and research group at University Hospital 12 de Octubre in Madrid, Spain, where she has worked in the Neuromuscular Unit since 2004. The unit is a National Reference Center for rare neuromuscular and mitochondrial disorders.
Her expertise focuses on genetic myopathies, particularly those of metabolic and mitochondrial origin. In 2020, she obtained her PhD from Complutense University of Madrid, with a doctoral thesis focused on the treatment of TK2 deficiency using non-GMP nucleosides.
Dr. Domínguez-González is a principal investigator at the i+12 Research Institute and has led multiple research projects and clinical trials. She has authored over 120 scientific publications, including 15 publications on TK2 deficiency. Her research interests include clinic-molecular characterization of mitochondrial diseases, biomarker validation, and the use of quantitative muscle MRI in mitochondrial myopathies.

DERRALYNN HUGHES
UNITED KINGDOM

Derralynn Hughes

Prof. Derralynn Hughes is Professor of Experimental Haematology at the University College London, Director of Research and Innovation at the Royal Free London NHS Foundation Trust Group. She is co-clinical Director of the NCL cancer Alliance. She has clinical responsibilities in the area of Haematology and Lysosomal Storage Disorders. She directs the research programme in the LSD unit where interests include understanding the pathophysiology of phenotypic heterogeneity in Fabry Disease and bone related pathology in Gaucher disease and malignancy. Prof Hughes is Principal Investigator of a number of clinical trials examining the efficacy of new agents in the treatment of Gaucher, Fabry, Pompe and MPS disorders including gene therapies. Particular interests relate to the clinical and biological effects of bone disease and malignancy in Gaucher disease and the effects of Fabry disease in women; developing access standards for diagnosis and therapy for rare disorders; reducing inequalities in time to diagnosis of rare disorders using AI/ algorithms in primary care to suggest candidates for genomics; accelerating clinical research including gene therapy for rare disorders. She is an author of over 200 papers in the area of macrophage biology and lysosomal Storage Disorders.

GIANNI CUTILLO
ITALY

Gianni Cutillo

Gianni Cutillo, MD is a neurologist and PhD candidate at IRCCS San Raffaele Scientific Institute, Milan, with clinical and research interests focused on leukodystrophies, pediatric neurology, and clinical epileptology. His work lies at the interface between rare neurogenetic disorders and electrophysiology, with particular attention to the neurological manifestations and monitoring of inherited encephalopathies and white-matter diseases.

His current research is primarily centered on metachromatic leukodystrophy and other leukodystrophies, where he contributes to longitudinal clinical cohorts investigating disease progression and therapeutic outcomes in the era of emerging disease-modifying treatments, including gene therapy. Within this context, he focuses on the development of multimodal biomarkers that integrate clinical features, neuroimaging, electrophysiological data, and biochemical markers to better characterize disease trajectories and support diagnosis and monitoring.

HANA P. PEREIRA
PORTUGAL

Hana Pavlu Pereira

Hana Pavlů-Pereira is a molecular biologist and biochemist specializing in inborn errors of metabolism, with international research experience. At Charles University in Prague, she gained expertise in lysosomal storage disorders and contributed to the characterization of the intermediate A/B form of Niemann-Pick disease. She has had experience with, and maintains professional contacts at, several institutions in the field.

She is currently a researcher at the Faculty of Pharmacy, Universidade de Lisboa in Portugal, focusing on the molecular basis of inherited metabolic disorders. Her work provided a comprehensive description of the complete cohort of Portuguese patients with pyruvate dehydrogenase complex deficiency, as well as extensive structural and functional characterization of pathogenic variants. She is also involved in developing and optimizing innovative diagnostic approaches and exploring emerging therapeutic strategies for metabolic disorders.

JOSÉ V. A. GONZÁLEZ
SPAIN

José Víctor Álvarez González

José Víctor Álvarez González is a researcher in the field of inherited metabolic diseases and advanced therapies. He currently works as a Miguel Servet Researcher at the Health Research Institute of Santiago de Compostela, integrated into the Neonatology Service of the Clinical University Hospital of Santiago de Compostela. He holds a PhD in Drug Research and Development from the University of Santiago de Compostela and has a background in Pharmacy, as well as a master's degree in Pharmaceutical Technology and the Development of New Medicines. Throughout his scientific career, he has conducted research at several renowned institutions, including Nemours Children's Health in the United States, where he carried out postdoctoral research for several years.

His research mainly focuses on inherited metabolic diseases and lysosomal disorders, with a particular emphasis on the development of new therapeutic strategies, biomarkers, and diagnostic methods. He is the author of several scientific articles published in high-impact international journals and participates in multiple national and European research projects, some of them as principal investigator.

In addition to his scientific activity, he has contributed to knowledge transfer through patent registrations and regularly participates in international scientific conferences. He also collaborates in supervising academic work and in the training of young researchers.

MANUELA GRAZINA
PORTUGAL

Manuela Grazina

Doutorada em ciências biomédicas e (Neuro)Cientista. Professora Auxiliar com nomeação definitiva na Faculdade de Medicina e Investigadora Principal no CIBB/Universidade de Coimbra. Coordena o subgrupo de investigação "Bigenómica Mitocondrial e Teranóstica". Tem dezenas de publicações e mais de cinco centenas de comunicações científicas e de comunicação de ciência, colaborando ativamente na divulgação científica. Foi premiada diversas vezes como "Melhor docente" da Faculdade de Medicina da Universidade de Coimbra. Em maio de 2023, no âmbito de uma EEA Grant (projeto Mit.OnOff), lançou o livro "As avarias da fábrica de energia", como ferramenta de literacia em ciência e saúde. É uma das 12 mulheres que foram retratadas no Livro "Mulheres Incomuns" (Ed. Vida Económica, 2023). É uma das autoras que escreveu um capítulo para o Livro "O que se passa na infância não fica na infância. Tomo II (Ed. Editora d'Ideias, 2025; coordenação João Pedro Gaspar e Paulo Guerra).

Tem uma experiência profissional sólida de mais de 30 anos, nomeadamente como docente universitária (29), investigadora (34), Geneticista Laboratorial Clínica (31), como comunicadora de ciência (20) e como mentora científica (3). É uma investigadora ativa, com orientação de mais de 55 teses (mestrado, doutoramento, licenciatura), dezenas de publicações e mais de 500 de comunicações científicas, colaborando ativamente na escrita de artigos na imprensa no âmbito da divulgação científica. É responsável pela Coordenação e lecionação de 25 Cursos Avançados. Co-coordena o curso Livre Caminhos de Cultura, Arte e Ciência. Refira-se a participação em 30 Projetos de Investigação (1 na área da Pedagogia e 1 na área de Comunicação de Ciência) dos quais é/foi Investigadora Responsável em 15, incluindo a bolsa SPDM 2014.

É uma comunicadora de ciência dinâmica, multipremiada, que promove a literacia científica e em saúde e ela acredita firmemente que a instrução e o conhecimento são os melhores indicadores para o desenvolvimento, para a preparação de melhores profissionais e para a melhoria das condições de saúde das populações. O AEV (Advertising Equivalent Value) da sua atividade é superior a 3,7 milhões de euros.

(Neuro)Cientista, professora universitária. É uma Ativista social e considera-se uma Influencer científica. Ensina e comunica a sorrir. Promove ativamente a literacia. Gosta de desvendar os segredos da genética, do cérebro e das mitocôndrias. É defensora da ciência para todos. Acredita que conhecimento é liberdade e que a coisa mais importante da infância é o amor incondicional.

MARIA V. CUNHA
BELGIUM

Maria Veiga da Cunha

Maria is both a senior FRS-FNRS researcher at the de Duve Institute and an assistant professor at the School of Biomedical Sciences, UCLouvain, in Brussels, Belgium. She holds a degree in bioengineering from UCLouvain and a PhD from the University of Oxford. For the past 30 years, her research has focused on various inborn errors of metabolism together with her mentor Prof. Emile Van Schaftingen. Together, they explored various aspects of intermediary metabolism, focusing on the molecular identification and regulatory mechanisms of multiple enzymes. A key achievement of their work was pioneering research on metabolite repair, beginning with the identification of L-2-hydroxyglutarate deficiency as the first inborn error in this field. Importantly, she has made two major contributions to the field of GSD1b: (1) the discovery of the gene encoding the glucose-6-phosphate transporter of the endoplasmic reticulum (SLC37A4), which is mutated in GSD1b patients. This discovery enabled genetic screening for GSD1b. (2) The elucidation of the mechanism underlying neutropenia in GSD1b and G6PC3 deficiency, which led to the repurposing of the commonly used antidiabetic drug empagliflozin to treat neutropenia, first in a mouse model and subsequently in patients.
Together with Dr. Saskia Wortmann and other collaborators, she played a key role in initiating the use of empagliflozin to treat neutropenia in GSD1b patients. This work also led her to identify SGLT5, the renal transporter responsible for the reabsorption of 1,5-anhydroglucitol, a polyol whose presence in blood is responsible for these patient's neutropenia. Since then, she has continued to focus part of her research on better understanding the toxicity of 1,5-anhydroglucitol on the neutrophils of GSD1b patients, with the goal of further improving available treatments.
She is also a specialist in hexokinase regulation and is actively investigating the mechanisms underlying two newly identified neurometabolic disorders with brain anomalies: PGM2L1 deficiency and NEDVIBA, caused by de novo mutations in hexokinase 1.
Affiliations
- Group Leader, de Duve Institute
- Associate Professor, UCLouvain
- Research Associate, F.R.S. – FNRS

MATILDE COSSUTTA
ITALY

Matilde Cossutta

Is a pediatric immuno-hematologist at the Pediatric Immunohematology and Bone Marrow Transplant Unit of IRCCS San Raffaele Hospital in Milan, Italy.
She is currently a PhD candidate in Immunology, Molecular Medicine and Applied Biotechnologies at the University of Rome Tor Vergata and conducts translational research at the SR-TIGET laboratory in Milan.
Her clinical and research interests focus on hematopoietic stem cell transplantation and innovative ex vivo gene therapy approaches for non-oncological pediatric disorders, with particular emphasis on lysosomal storage diseases and inborn errors of immunity.

PAULO OLIVEIRA
PORTUGAL

Paulo Oliveira

Paulo J. Oliveira is a Principal Investigator with "Agregação" at the Center for Neuroscience and Cell Biology, University of Coimbra (UC), Portugal. He is the current leader of the "Mitochondria, Metabolism and Disease" group and of the MitoXT: Mitochondrial Toxicology and Experimental Therapeutics laboratory. He completed his PhD in Cellular Biology at UC in 2003. After completing his PhD, Paulo Oliveira spent more than three years working at the University of Minnesota Medical School, Duluth, USA, where he collaborated with several researchers and contributed to the publication of several peer-reviewed manuscripts. Paulo Oliveira's current research focuses on mitochondrial metabolism, namely alterations resulting from aging and lifestyle-related diseases, and on investigating strategies to preserve mitochondrial function across the lifespan for a healthy aging. Paulo has over 350 peer-reviewed papers, is currently the coordinator of the EU-funded projects PAS GRAS and Excelscior, and has maintained a consistent primary role in the organization of national and international scientific meetings, including the International Courses in Toxicology (2005-2010), Annual Meeting of the European Society for Clinical Investigation (2013 and 2019, Coimbra, Portugal), the 2014 Meeting of the Portuguese Biochemical Society, and FEBS Advanced Lecture Courses in Oncometabolism (2017 and 2019). Paulo Oliveira was also President of the European Society for Clinical Investigation (2019-2022) and is a reviewer for more than 40 scientific journals and over 10 different funding agencies, including the European Commission (Research Executive Agency) and the Portuguese Foundation for Science and Technology. Since 2020, Paulo is Vice-President of the CNC – Center for Neuroscience and Cell Biology, UC, Portugal.. As an entrepreneur, Paulo is also co-founder of the start-up MitoTAG, which develops mitochondria-directed antioxidant with applications in cosmetics and human health, and is co-inventor in several patents.

SARA FERREIRA
PORTUGAL

Sara Ferreira

Sara Ferreira, MD, graduated in Medicine from the Faculty of Medicine of the University of Coimbra in 2007 and completed her Pediatrics residency at the Pediatric Hospital of Coimbra in 2014. Since 2021, she has worked as a Pediatrician focusing on inherited metabolic diseases, as part of the Reference Center for Inherited Metabolic Diseases at ULS Coimbra. She is involved in clinical and research activities in this field and serves on the plenary committee of the Inherited Metabolic Diseases Section of the Portuguese Society of Pediatrics. She has been attending the Special Study Cycle in Pediatrics on Inherited Metabolic Diseases since 2025. Additionally, she is a guest lecturer in Biochemistry for the Integrated Master's

SESSION I _

NEW AVENUES FOR DIAGNOSIS AND TREATMENT OF NEUROMETABOLIC DISEASES

CHAIRPERSONS

MARIA CARMO MACÁRIO (COIMBRA)

ARLINDO GUIMAS (PORTO)

New therapy advancements in Metachromatic Leukodystrophy

Cutillo Gianni
IRCCS San Raffaele Scientific Institute, Milan, Italy

Metachromatic leukodystrophy (MLD) is a rare lysosomal storage disorder caused by deficiency of the enzyme arylsulfatase A (ARSA), leading to progressive accumulation of sulfatides within the central and peripheral nervous systems and resulting in widespread demyelination. The disease is characterized by marked clinical heterogeneity and is traditionally classified according to age at onset into late-infantile, early-juvenile, late-juvenile, and adult forms. Early-onset variants, particularly the late-infantile phenotype, are associated with a rapidly progressive course characterized by motor regression, cognitive decline, epilepsy, and severe disability.Historically, therapeutic options for MLD have been extremely limited. For symptomatic patients, management has largely relied on supportive and palliative interventions, including multidisciplinary rehabilitation, treatment of spasticity and epilepsy, and nutritional and respiratory support. Allogeneic hematopoietic stem cell transplantation has been explored in selected patients, particularly in pre symptomatic or very early juvenile forms, but outcomes have been variable and the procedure is associated with significant morbidity and mortality. In recent years, however, the therapeutic landscape of MLD has dramatically changed with the development of hematopoietic stem cell gene therapy. Atidarsagene autotemcel (arsa-cel) is an autologous ex vivo gene therapy in which the patient's CD34+ hematopoietic stem cells are transduced with a lentiviral vector encoding functional ARSA and subsequently reinfused following myeloablative conditioning. Clinical studies have shown that this approach can restore ARSA activity and significantly modify the natural history of the disease when administered at pre-symptomatic or very early symptomatic stages, preserving motor and cognitive functions in a substantial proportion of treated patients. With new therapy advancements newborn screening protocols have been developed across Europe and the US and has been established collaborative group of physicians working on MLD to aid in complex cases management.

Usefulness of blood tests in the diagnosis of GLUT1 deficiency syndrome

Early Detection Matters: Launching Blood-Based GLUT1 Testing in Portugal

Hana Pavlú Pereira

Laboratory of Metabolism and Genetics, Department of Pharmaceutical Sciences and Medicines, Faculty of Pharmacy, Universidade de Lisboa, Lisbon, Portugal
Metabolism, Genetics and Proteins in Health & Disease Group at iMed.ULisboa, Faculty of Pharmacy, Universidade de Lisboa, Lisbon, Portugal

GLUT1 Deficiency Syndrome (GLUT1DS) is a rare but treatable neurometabolic disorder caused by impaired glucose transport across the blood-brain barrier. Its clinical presentation is highly heterogeneous and may include epilepsy, paroxysmal movement disorders, developmental delay, and speech or cognitive impairment. The symptoms evolve with age and diagnosis is often delayed for many years. This diagnostic gap is particularly concerning given that early initiation of ketogenic diet therapy can significantly improve neurological outcomes and prevent irreversible brain injury.

Traditional diagnostic approaches rely on lumbar puncture to demonstrate hypoglycorrhachia and subsequent molecular analysis of the SLC2A1 gene. These procedures may postpone the clinical decision. Recently, a simple blood-based assay (METAglut1) has emerged as a minimally invasive tool. Based on quantification of GLUT1 receptors at the erythrocyte surface, this simple test allows early identification of patients with suspected GLUT1DS.

Real-world experience in France has demonstrated increasing clinical adoption of this simple blood test, with a positivity rate of approximately 2- 3% among patients tested for compatible phenotypes and a measurable reduction in the median age at testing. Importantly, this approach has enabled the identification of new cases among the patients with atypical clinical presentations who might otherwise remain undiagnosed. Health-economic modelling based on the French real-world data further suggests that earlier diagnosis through simplified testing strategies may substantially reduce the costs associated with prolonged diagnostic pathways while improving patient management.

We will review the clinical spectrum of GLUT1DS, discuss the diagnostic challenges, review key findings from French experience, and outline guidance for integrating blood-based testing into routine practice. By highlighting the test's usefulness, we aim to raise clinician awareness and promote earlier, more accurate diagnosis of GLUT1DS in Portugal.

SESSION II _

MANAGING AND TREATING LYSOSOMAL STORAGE DISORDERS

CHAIRPERSONS

ANA CRISTINA FERREIRA (LISBON)

JOÃO GOMES (COIMBRA)

Management of pregnancy in lysosomal storage disorders

Derralynn A Hughes
Royal Free Hospital and University College, London, United Kingdom

Thymidine kinase 2 deficiency (TK2d) is a mitochondrial DNA (mtDNA) depletion and deletion syndrome caused by pathogenic variants in TK2, which encodes the enzyme responsible for the first phosphorylation step of deoxycytidine and thymidine within mitochondria. Impairment of this nucleotide salvage pathway leads to defective mtDNA synthesis, resulting in mtDNA depletion and accumulation of multiple mtDNA deletions and duplications, predominantly affecting skeletal muscle.

TK2d presents as a continuous clinical spectrum. Infantile-onset disease is characterized by rapid motor regression and a median age at death of 1.8 years. In a cohort of nearly 200 patients with onset before 12 years, 90% achieved independent sitting and 80% independent walking prior to disease onset; however, over 80% experienced subsequent motor regression, with 40% losing four or more motor milestones. Late-onset patients (onset after 12) typically present with progressive muscle weakness and early respiratory involvement, the leading cause of morbidity and mortality. Forced vital capacity in this subgroup declines by approximately 8% per year, while independent ambulation is often preserved, with a median survival of 15–20 years after disease onset.

Several biomarkers correlate with disease severity and prognosis. Muscle mtDNA copy number is the strongest prognostic factor, correlating with age at onset and time to mechanical ventilation. Circulating GDF15 and serum creatinine levels correlate with motor and respiratory involvement, while muscle MRI shows a characteristic pattern of selective involvement, with quantitative fat replacement correlating with functional outcomes.

Oral pyrimidine nucleoside therapy, initially validated in TK2d mouse models, enhances residual TK2 activity and activates alternative metabolic pathways, enabling restoration of mtDNA levels. Clinical studies funded by UCB in more than 100 patients—predominantly with onset before 12 years—demonstrated an 87–95% reduction in mortality risk and significant recovery of motor milestones, leading to FDA approval in November 2025. The most frequent adverse event was dose-dependent diarrhea, generally well tolerated and not leading to treatment discontinuation; no other clinically relevant adverse events were identified. Preliminary data from an ongoing adult trial show significant reductions in GDF15 levels by six months, with improvements in motor function reaching statistical significance by three months despite long-standing disease, supporting pyrimidine nucleoside therapy as the first effective disease-modifying treatment for TK2d, with substantial survival benefit in pediatric patients and early evidence of functional and biomarker improvement in adults.

Hematopoietic Stem Cell Gene Therapy for Mucopolysaccharidosis Type I: clinical outcomes

Matilde Cossutta
San Raffaele Hospital, Milan, Italy

Mucopolysaccharidosis type I Hurler syndrome (MPS-IH) is a severe lysosomal storage disorder caused by alpha-L--iduronidase (IDUA) deficiency, resulting in glycosaminoglycan (GAG) accumulation and progressive multisystem disease. Early allogeneic hematopoietic stem cell transplantation (allo-HSCT) represents the current standard of care, as donor-derived cells can partially restore enzyme activity through cross-correction. However, allo-HSCT is limited by donor availability, transplant-related morbidity, immune complications and variable, often suboptimal, metabolic correction, particularly in hard-to-reach tissues such as the central nervous system, bone and connective tissues.
Autologous hematopoietic stem cell gene therapy (HSC-GT) has been developed to overcome these limitations by enabling stable engraftment of genetically corrected autologous cells capable of producing supraphysiological levels of IDUA, with the potential to achieve more effective and sustained metabolic correction.
A phase 1/2 clinical trial (NCT03488394; EU CT 2024-514870-29-00) was conducted at IRCCS San Raffaele Hospital in Milan, Italy, evaluating OTL-203, an investigational autologous HSC-GT, in eight young children with MPS-IH (median age at treatment: 2.0 years).
Patients received autologous CD34+ hematopoietic stem and progenitor cells transduced ex vivo with a lentiviral vector encoding the human IDUA gene and were followed for up to 5 years.
Long-term assessments included biochemical correction, neurodevelopmental outcomes, neuroradiological findings and skeletal manifestations evaluated by imaging and functional measures.
All patients are alive and show durable engraftment of gene-corrected cells at 5 years post-treatment. Sustained supraphysiological IDUA activity in peripheral blood resulted in long-term normalization or near- normalization of urinary GAG levels. IDUA activity was detected in the cerebrospinal fluid within 3 months after treatment and persisted over time, leading to marked reduction of CSF GAGs and supporting effective central nervous system correction. Importantly, beyond neurological stabilization, patients demonstrated favourable skeletal outcomes, including stabilization or improvement of motor function, longitudinal growth within age-appropriate ranges and improvement of specific skeletal abnormalities such as hip dysplasia. These findings contrast with the residual and progressive skeletal disease commonly observed after allo-HSCT. Results from this investigator-led phase 1/2 study demonstrate that autologous HSC-GT with OTL-203 provides durable metabolic correction and appears to offer a meaningful advantage over allo-HSCT in the control of skeletal and neurological disease, major unmet clinical needs in MPS-IH. Ongoing phase 3 studies directly comparing OTL-203 with allo-HSCT will further clarify the potential superiority of gene therapy over transplantation.

SESSION III _

MITOCHONDRIAL DISEASES: ARE WE READY FOR INNOVATIVE THERAPIES?

CHAIRPERSONS

CÉLIA NOGUEIRA (PORTO)

MARGARIDA PAIVA COELHO (PORTO)

Three decades of translational research in Leber's Hereditary Optic Neuropathy: what have we learned?

Manuela Grazina

FMUC - Faculty of Medicine; CIBB - Centre for Innovative Biomedicine and Biotechnology; Laboratory of Mitochondrial Biomedicine and Theranostics (LBioMiT), CNC-UC - Center for Neuroscience and Cell Biology. University of Coimbra, Portugal

Diagnosis of OXPHOS diseases is complex given the heterogeneity in clinical presentation and two genomes' involvement. Tissue specificity is critical. Optic atrophies, particularly LHON1, have been extensively studied and many cases remain without a genetic cause identified2. However, our GenEye24 test allowed an improvement in genetic diagnosis and increased the probability in defining the genetic alteration underlying disease in a maximum of 24h3. A scientific gap in LHON remains, persisting the key question about genetic causes: if and how is nuclear genome involved. Recent discoveries point to intracellular network failures that may reveal novel mechanisms and possible therapeutic targets.
Biochemical evaluation of OXPHOS complexes' activities is performed by double wavelength spectrophotometry4. Genetic screening of both genomes is currently performed by NGS and extensive bioinformatics' analysis. For understanding functional impact of genetic alterations, biochemical/functional studies are performed5.
During the last 31 years, we have studied more than 7,000 samples of OXPHOS disease cases, including 182 patients with optic atrophy, suspected of LHON as first diagnostic hypothesis. Genetic results are heterogeneous, including identification of typical mutations, but also pointing to bigenomic causes, including in LHON. NGS approaches allows identification of a growing number of genetic alterations, but a new challenge arises: gathering data for demonstrating functional impairments underlying the energy failure.
Genetic information underlying the disease is essential for genetic counseling, but recent technological advances bring additional difficulties in validating novel mutations. The most recent developments and guidelines include functional studies, in which biochemical genetics approaches play a key role for clarifying pathogenicity. Furthermore, in face of the results, it is worth to hypothesize that LHON may be not a single disease, but instead a "spectrum" of optic neuropathies. Our most recent projects include the exploitation of the intracellular networking, involving inter-organelle communication. To explore inter- and intra-cellular communication, which might help to further elucidate the variable penetrance and the specific disease mechanisms of LHON, we are researching the role of mitochondrial microproteins, namely MOTS-c. Using fibroblasts and lymphoblast under cell stress models and plasma/serum samples we are exploring differences between patients, controls and carriers in mitonuclear communication, plus if treatment with these peptides might ameliorate the phenotype. Because of dysregulation of cross-organellar dysfunction in LHON, particularly between ER and mitochondria and activation of ER-UPR, we predicted that a global attenuation of protein synthesis in patients' cells and possibly, increased in carriers as a compensatory mechanism, in order to restore protein-folding homeostasis. To this end, Click-iT assays and western blotting are being used to assess protein translation in the cells. Our team is also exploring genomic, proteomic and metabolomic alterations in fibroblasts derived from LHON patients, asymptomatic LHON mtDNA pathogenic sequence variants (PSVs) carriers and healthy controls. Using an integrated multi-omics strategy focused on oxidative phosphorylation (OXPHOS) dysfunction and stress responses involving the Golgi apparatus and endoplasmic reticulum, we aim to identify nuclear genetic variants that may act synergistically with PSVs to drive disease manifestation. By correlating genomic data with proteomic and metabolomic alterations, the project aims to clarify the molecular basis of the incomplete penetrance observed in LHON and to uncover pathways contributing to disease expression. These findings may provide biomarkers relevant for diagnosis and prognosis, while supporting improved genetic counselling and the identification of new therapeutic targets.

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Recent advances in diagnosis and treatment of TK2 Deficiency

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Thymidine kinase 2 deficiency (TK2d) is a mitochondrial DNA (mtDNA) depletion and deletion syndrome caused by pathogenic variants in TK2, which encodes the enzyme responsible for the first phosphorylation step of deoxycytidine and thymidine within mitochondria. Impairment of this nucleotide salvage pathway leads to defective mtDNA synthesis, resulting in mtDNA depletion and accumulation of multiple mtDNA deletions and duplications, predominantly affecting skeletal muscle.

TK2d presents as a continuous clinical spectrum. Infantile-onset disease is characterized by rapid motor regression and a median age at death of 1.8 years. In a cohort of nearly 200 patients with onset before 12 years, 90% achieved independent sitting and 80% independent walking prior to disease onset; however, over 80% experienced subsequent motor regression, with 40% losing four or more motor milestones. Late-onset patients (onset after 12) typically present with progressive muscle weakness and early respiratory involvement, the leading cause of morbidity and mortality. Forced vital capacity in this subgroup declines by approximately 8% per year, while independent ambulation is often preserved, with a median survival of 15–20 years after disease onset.

Several biomarkers correlate with disease severity and prognosis. Muscle mtDNA copy number is the strongest prognostic factor, correlating with age at onset and time to mechanical ventilation. Circulating GDF15 and serum creatinine levels correlate with motor and respiratory involvement, while muscle MRI shows a characteristic pattern of selective involvement, with quantitative fat replacement correlating with functional outcomes.

Oral pyrimidine nucleoside therapy, initially validated in TK2d mouse models, enhances residual TK2 activity and activates alternative metabolic pathways, enabling restoration of mtDNA levels. Clinical studies funded by UCB in more than 100 patients—predominantly with onset before 12 years—demonstrated an 87–95% reduction in mortality risk and significant recovery of motor milestones, leading to FDA approval in November 2025. The most frequent adverse event was dose-dependent diarrhea, generally well tolerated and not leading to treatment discontinuation; no other clinically relevant adverse events were identified. Preliminary data from an ongoing adult trial show significant reductions in GDF15 levels by six months, with improvements in motor function reaching statistical significance by three months despite long-standing disease, supporting pyrimidine nucleoside therapy as the first effective disease-modifying treatment for TK2d, with substantial survival benefit in pediatric patients and early evidence of functional and biomarker improvement in adults.

Small molecules as a therapeutic strategy in mitochondrial diseases

Paulo Oliveira

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Mitochondria are central organelles in eukaryotic cells, best known for their role in ATP production through oxidative phosphorylation (OXPHOS). However, their biological relevance extends far beyond energy conversion. Mitochondria are crucial regulators of intermediary metabolism, calcium homeostasis, redox balance, apoptosis, innate immunity, and cellular differentiation. Because of this broad functional picture, mitochondrial dysfunction has pleiotropic consequences and can affect virtually every tissue, with particularly severe impact on high-energy-demand organs such as the brain, skeletal muscle, heart, liver and kidney.
Mitochondrial dysfunction is a hallmark of many diseases. These include primary mitochondrial diseases, a heterogeneous group of inherited disorders caused by pathogenic variants in mtDNA or nuclear genes encoding mitochondrial proteins, affecting OXPHOS, gene expression, dynamics, quality control, transport, or cofactor biosynthesis. Mitochondrial dysfunction also contributes to common age-related disorders, including neurodegeneration, diabetes, obesity, cardiovascular disease, cancer, and inflammation, making mitochondria an important therapeutic target.
Despite major advances in genetic diagnosis, effective treatments for mitochondrial diseases remain limited and are largely supportive. In this context, small molecules have emerged as a particularly promising therapeutic strategy. Small molecules may act through distinct mechanisms, including enhancement of mitochondrial bioenergetics, reduction of oxidative stress, stabilization of mitochondrial membranes, stimulation of mitochondrial biogenesis, modulation of mitophagy and quality control, bypass of metabolic bottlenecks, or correction of redox imbalance.
Non-targeted small molecules, including drugs such as metformin and carvedilol, may improve mitochondrial function by modulating metabolism, redox balance, and cellular stress responses. Other examples include antioxidants, NAD+ boosters, and compounds that promote mitochondrial biogenesis. Although these agents are not designed to accumulate in mitochondria, they can still improve mitochondrial function. In parallel, mitochondria-targeted molecules are being developed to act more selectively. Examples include MitoQ, SS peptides, and newer compounds such as AntiOXCIN4 and AntiOXBEN2, which aim to reduce oxidative damage, stabilize mitochondrial membranes, and improve bioenergetic efficiency. By acting on mitochondria, these agents may overcome key limitations of conventional therapies.
Together, small molecules form a promising and expanding therapeutic option for mitochondrial diseases. Combining repurposed drugs with targeted agents may offer a more effective strategy to address the complexity of both primary hereditary mitochondrial disorders and other diseases driven by mitochondrial dysfunction.

Funding: Research at the PO laboratory is supported by the European Union (project PAS GRAS: De-risking metabolic, environmental and behavioural determinants of obesity in children, adolescents and young adults, ID: 101080329). Also funded by the European Regional Development Fund (ERDF) through the COMPETE 2030 - Innovation and Digital Transition Operational Programme under project COMPETE2030-FEDER-0067550, and by the EU Recovery and Resilience Facility and Portuguese national funds via FCT – Fundação para a Ciência e a Tecnologia, under projects, LA/P/0058/2020 [DOI: 10.54499/LA/P/0058/2020], UID/PRR/4539/2025 [DOI: 10.54499/UID/PRR/04539/2025] and UID/04539/2025.

SESSION IV _

MASTERCLASS PKU – PAST, PRESENT, AND FUTURE PERSPECTIVES

CHAIRPERSONS

LUÍSA DIOGO (COIMBRA)

ESMERALDA MARTINS (PORTO)

Discussion-Abstract

Carla Maria Carmona

Serviço de Genética Médica - Centro de Genética Médica Doutor Jacinto Magalhães, ULS de Santo António, E.P.E. - Porto, Portugal

Phenylketonuria (PKU; McKusick #261600), was the first inborn error of amino acid metabolism to be identified as a biochemical cause for intellectual impairment and the first genetic condition to be treated effectively, allowing its patients to live a fulfilling life. Caused by a deficiency in the activity of the hepatic-based enzyme Phenylalanine hydroxylase (PAH), it represents the most common inborn error of amino acid metabolism in Europe with more than 1.000 PAH pathological variants in the PAH gene. PAH is responsible for converting the essential amino acid phenylalanine (Phe) into tyrosine (Tyr), in the presence of of the co-substrate tetrahydrobiopterin (BH4). Untreated, PKU results in increased brain Phe levels, decreased tyrosine brain influx, and reduced cerebral protein synthesis. Newborn screening and early initiation of treatment with a Phe restricted diet, complemented with protein substitutes and special low protein foods, has successfully prevented severe neurological and neurocognitive impairments.

Historically, we have observed differences in treatment paradigms across different countries regarding the definition of optimal Phe levels for normal physical and neurocognitive development, as well as regarding the age at which the diet should be liberalised or discontinued. With the evidence of a significant relationship between poor long-term Phe control and general intellectual abilities, significantly impaired complex executive functions and neuropsychiatric symptoms for early-treated PKU, the need of a more restricted diet was addressed. In the last years we have witnessed the move towards lifelong dietary control. In Portugal, the dietary treatment has never been discontinued.

We studied 139 PKU patients aged 2 to 37 years, early diagnosed at the neonatal screening and without additional disorders and followed at our Reference Centre. The neonatal screening blood Phe concentrations were considered as independent variable: we considered three groups of PKU patients according to screening values - hyperphenylalaninemia [2,5 mg/dL – 5,9 mg/dL], moderate PKU [6,0 mg/dL to 20 mg/dL] and classical PKU >20 mg/dL. Patient's outcome was evaluated according to the global developmental quotient (QD) or intelligence quotient (IQ), the quality of dietetic control (QDC), their educational level and school curriculum, their professional carrier and comorbidities. We considered 4 groups of patients aged 1 to 6 years, 7 to 12 years, 13 to 17 and ≥ 18 years. Differences between groups were analysed. The Statistical Package for Social Sciences (SPSS 26.0 for Windows) was used for data analysis.

We observed that during the first two years, most part of our PKU patients had a good dietary control regardless the disease's severity. Significant differences between groups, after the age of 3 ($p<.001$) were observed, having the patients with the classical form of the disease the higher Phe values. These results draw attention to the importance of considering the severity of the disease as a risk factor for greater difficulty in complying with treatment. Despite normal global QD/IQ values, high blood Phe levels were negatively correlated with neurocognitive and psychosocial impairments and potentially interfered with school performance and socio-affective behaviour in all groups considered. In adulthood, higher Phe values were also associated with the rise of adverse effects on attention, specific executive functions and mood. The group of patients with hyperphenylalaninemia were the only one who maintain a good dietetic control throughout life.

From the year of 1992 some significant changes were introduced in the follow up of our PKU patients, namely, the definition of safety Phe levels ≤ 6 mg/dL up to the age of 12 years, the access to a greater diversity of special low protein foods freely available for life, and a more regular follow up. Evaluating the results of these changes on QDC, comparing patients born before and after 1993, a clear improvement in the quality of lifelong dietetic control were observed in the mild and classical PKU patients, with significant decreases in annual median PHE values. These differences were significant ($p < .05$) between the age of 4 to 21 years.

Our date supports the need of lifelong treatment for PKU while providing a regular follow-up to optimize their quality of dietetic control, neurocognitive outcomes and, consequently, their mental health and quality of life.

SESSION V _

ORAL COMMUNICATIONS

CHAIRPERSONS

ANA PAULA LEANDRO (LISBOA)

TERESA ALMEIDA CAMPOS (PORTO)

CO01

Initial Findings from the first four Patients Enrolled in OTC-Hope Clinical Trial: No Hyperammonemic Events in First Participant to Complete 24-Week Study

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Introduction
Neonatal onset ornithine transcarbamylase deficiency (OTCD) typically presents in hemizygous males with severe enzymatic deficiency. Infants can become hyperammonemic in the first 48-72 hours of life and develop progressive encephalopathy. If misdiagnosed or left untreated, death typically occurs within the first week of life. Despite adherence to management including protein restriction and nitrogen scavenging agents, recurrent clinical decompensation can occur. Currently, liver transplant is the only curative standard of care option for these patients.

Methods
OTC-HOPE (NCT06255782) is a 24-week, first in human, Phase 1/2/3, global, trial designed to assess the safety and efficacy of ECUR-506 in male participants with neonatal-onset OTCD who are < 9 months of age. Pre-dose observations of all enrolled participants through 08 Apr 2025 are reported.

Results/Case report
All 4 participants enrolled experienced an initial hyperammonemic event (HAE) within the first week of life and then stabilized. Participants were transitioned to standard of care (SOC) therapy (oral nitrogen scavenger and dietary protein restriction) but subsequently experienced HAEs despite SOC therapy. Following their initial HAE, the four participants have thus far experienced a total of 5 additional HAEs over a combined duration of 22 months, thereby averaging one HAE every 4.4 months while on SOC therapy and prior to receiving ECUR-506. Participant 1, who experienced HAEs at 1 week and 5.5 months of age, was dosed with ECUR-506 (1.3 x1013 GC/kg) at 6.5 months of age. Grade 3 transaminitis was observed between Weeks 4-8 post-infusion, which resolved with immunosuppression. Participant 1 experienced no HAEs during the 6-month period following the administration of ECUR--506.

Conclusion
These data represent initial findings of the first four participants enrolled in the OTC-HOPE trial. These observations support the continued evaluation of in vivo gene insertion as a possible treatment option for neonatal onset OTC deficiency.

Palavras-chave: Editing Gene Therapy, Urea Cycle Disorders, Ornithine Transcarbamylase Deficiency (OTCD, Neonates), Hyperammonemic Event

CO02

Development of Functional and Stable Human Phenylalanine Hydroxylase (hPAH)–Enzymosomes

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Introduction
Phenylketonuria (PKU) is a rare metabolic disorder caused by human phenylalanine hydroxylase (hPAH) deficiency, leading to neurotoxic phenylalanine (Phe) accumulation. Conventional management relies on strict dietary restrictions, which often compromise quality of life. Reposition of the deficient hPAH (Enzyme reposition therapy; ERT) offers a promising approach to restore Phe metabolism, providing a potential higher efficacy.
Herein, we report the development and characterization of hPAH-enzymosomes as a potential novel delivery system for ERT in PKU.

Methods
Recombinant hPAH was expressed in E. coli and purified via two chromatographic steps. Functional tetramers were SATA-modified at optimized ratios and deacetylated. Thiol-exposed hPAH was conjugated to maleimide-PEG-PE liposomes. Enzymosomes were evaluated for size, zeta potential, loading, lipid content, activity, and thermostability.

Results/Case report
SATA-modified hPAH was successfully isolated and characterized. Enzymatic activity was largely preserved, with a slight increase in melting temperature (Tm). Increasing PAH:SATA (1:8 and 1:14) led to higher modification rate but greater pI shifts, reduced activity, and loss of tetramers; 1:14 ratio was optimal to maintain structure and function. Modified hPAH was stable under selected storage conditions (-80 °C) and conjugation to maleimide-PEG-PE liposomes was sensitive to buffer composition, and hPAH:liposome 400:10 has the highest incorporation. Time-stability assays showed that after 70 days of storage at -80 °C, the higher maintenance of enzyme activity was obtained for hPAH-enzymosome when compared to naked hPAH.
These results demonstrate that hPAH-enzymosomes can be produced while preserving enzymatic activity, thermostability, and quaternary structure, providing a basis for further preclinical evaluation.

Conclusion
Covalent conjugation of hPAH to PEGylated liposomes stabilizes the enzyme's regulatory domain while preserving its essential tetrameric structure. The optimized 1:14 SATA modification ratio ensures a balance between conjugation number (protein modifications) and catalytic performance. By maintaining superior long-term activity compared to the free enzyme, hPAH-enzymosomes demonstrate significant potential as a stable and functional platform for enzyme replacement therapy.
These findings offer a promising strategy to enhance therapeutic efficacy and patient adherence in PKU management.

Acknowledgements
This work was supported by FEDER and Fundação para a Ciência e a Tecnologia, I. P. through iMED.ULisboa (Projects UID/04138/2025), research project PTDC/MED-QUI/29712/2017 and research grant 2021.08870.BD (to Raquel Lopes).

CO03

Decoding Lipidome Plasticity in Medium – And Long-Chain Fatty Acid Oxidation Disorders: Dried Blood Spot Lipidomics For Prognostic Innovation

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Introduction
Fatty acid oxidation disorders (FAOD) are inborn errors of metabolism marked by impaired mitochondrial β-oxidation and accumulation of specific acylcarnitines (CAR) and FA. While CAR enable diagnosis, mechanisms underlying clinical heterogeneity and long-term complications remain unclear. Decoding lipidome plasticity may uncover pathways linked to disease progression and comorbidities, supporting innovation in prognostic biomarker discovery [1].

Methods
In this study [2], dried blood spots (DBS) from patients with MCADD, LCHADD and VLCADD (total of 16 patients) and controls were analysed by LC-MS-based lipidomics. Variations in lipid species were identified through multivariate and univariate statistical analyses to characterize FAOD-specific lipid signatures.

Results/Case report
Significant alterations in CAR corroborated diagnostic profiles. Beyond these markers, distinct lipid remodeling patterns were observed. All FAOD showed variations in specific phosphatidylcholine (PC) lipid species, particularly up-regulation of LPC 16:1, potentially linked to a higher risk of cardiovascular disease. LCHADD and VLCADD showed increased levels of odd-chain PC species (PC 33:0, 35:4, 37:4). VLCADD displayed elevated odd-chain triacylglycerides (TG) and LCHADD demonstrated increased levels of ceramide Cer 41:2;O2. Previous studies associated the increase in the Cer class to neurodegeneration. MCADD exhibited upregulation of ether-linked PC species, namely plasmenyl species that suggest an adaptive antioxidant response to oxidative stress. These findings reveal disorder-specific lipidome plasticity extending beyond CAR biomarkers.

Conclusion
Overall, DBS-based lipidomics decodes metabolic complexity in FAOD by revealing shared and disease-specific lipid remodelling. Identified lipid signatures may serve as candidate prognostic biomarkers linked to cardiovascular and neurodegenerative risk. This integrative approach supports precision monitoring strategies and advances innovation in the management of inborn errors of metabolism.

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Acknowledgements
The authors acknowledge to FCT/MCTES the financial support to CESAM (UID Centro de Estudos do Ambiente e Mar (CESAM) + LA/P/0094/2020) and LAQV/REQUIMTE (UID/50006 - Laboratório Associado para a Química Verde - Tecnologias e Processos Limpos) through national funds and, where applicable, co-financed by the FEDER, within the PT2020 Partnership Agreement and Compete 2020. Inês M. S. Guerra (2021.04754.BD; doi:10.54499/2021.04754.BD) is grateful to FCT for the PhD grant. The authors are thankful to the COST Action EpiLipidNET, CA19105-Pan-European Network in Lipidomics and EpiLipidomics. The authors acknowledge Molecular Discovery Ltd. for the Lipostar version 2.1.5 license.

CO04

Palliative Care in Children with Inherited Metabolic Diseases (IMD)

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Introduction
Children with inherited metabolic disorders (IMD) have palliative care needs due to multisystemic, progressive conditions for which curative treatment is often unavailable. About 15% of children with life-limiting conditions in pediatric palliative care (PPC) present an IMD. Palliative care provides symptom management, comfort, and comprehensive support for families.

Objective
To describe the needs of children with IMD followed by a Pediatric Palliative Care Team (PPCT).

Methods
A single-center retrospective cohort study was conducted. The authors included pediatric patients referred to the PPC between 2020 and 2025 with an inborn error of metabolism. A descriptive quantitative approach was used to analyze clinical data, diagnoses and the physical, psychological, and social needs of the children and their families.

Results/Case report
Seventeen children with IMD are followed by the PPCT (16% of all patients). Ten children are alive and seven have died. Ten have a lysosomal disease (six of whom have died); the others include one urea cycle disorder, one cobalamin metabolism disorder, one PMM2-CDG (deceased), one serine biosynthesis disorder, and three mitochondrial disorders.
Age at referral to PPCT varied from the first year of life to 15 years of age; those referred before 1 year of age had a significantly shorter period of care and died earlier. Three children were referred due to acute clinical exacerbations.
All six lysosomal patients died before the age of 4 years (four gangliosidoses, one metachromatic leukodystrophy, and one galactosialidosis); the PMM2-CDG patient died at 14 years of age. The ages of surviving children range between 2 and 17 years; the oldest are patients with Niemann–Pick type C disease.

Conclusion
All children have neurological impairment, including difficulty moving, seizures, and spasticity; all are followed by a neuropediatric team and receive chronic neurological medication. Respiratory symptoms are present in almost all children, and seven benefit from home noninvasive ventilation. Feeding difficulties are present in most patients, with 11 having a gastrostomy button. Pain is present in all children; it is often difficult to recognize and manage. Psychological and spiritual support is provided to all family members, including parents, grandparents, and healthy siblings. Discussions about advance care planning were conducted at least once. All deaths occurred in hospital.

IMD represents a significant proportion of children referred to PPCT. The complexity of these diseases requires a multidisciplinary approach to alleviate suffering and to promote timely end-of-life care planning discussions.
Palliative care focuses on improving the quality of life of children and their families, managing metabolic crises, and supporting families through rare, complex, and severe neurological diseases such as IMD.

Palavras-chave: Palliative care, neurodegeneration

C005

First Newborn Screening Program for Pompe Disease and Mucopolysaccharidosis Type I in Spain

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Introduction
Newborn screening for Pompe disease and mucopolysaccharidosis type I (MPSI) enables early identification of patients who may benefit from disease-specific therapies; however, it also poses important challenges in result interpretation. The presence of enzymatic pseudodeficiencies (Ps-def.) and variants of uncertain significance reduces diagnostic specificity, particularly in MPS I, while in Pompe disease the detection of late-onset forms introduces prognostic uncertainty and complicates follow-up. We present the results of the first newborn screening program for these disorders in Spain.

Methods
GAA and IDUA activities were measured in dried blood spots using the NeoLSDTM MS/MS kit, which simultaneously quantifies ABG, ASM, GAA, GALC, GLA and IDUA. Samples with enzyme activity < 5th percentile and ≥3 abnormal ratios were considered screen-positive and prompted second-tier glycosaminoglycan (GAG) analysis and molecular testing.

Results/Case report
A total of 20,384 newborns were screened.
Four newborns showed reduced GAA (range 0.8-2.3 µmol/L/h). Enzymatic ratios were also decreased, supporting a positive screening result. One infant presented elevated creatine kinase (CK) levels (273 UI/L). Molecular analysis confirmed Pompe disease in all four cases, including genotypes consistent with late-onset forms. Overall, biochemical findings demonstrated concordantly low GAA with altered enzyme ratios and minimal early clinical involvement.
Nine newborns showed reduced IDUA (range 0.15–1.12 µmol/L/h) with altered enzymatic ratios. Only one infant presented markedly elevated GAG (dermatan sulfate 121; heparan sulfate 417), consistent with confirmed MPS I. The remaining eight cases had normal GAG profiles and were classified as Ps-def. or carriers. These findings highlight the high frequency of Ps-def. among screen-positive cases and demonstrate the key role of second-tier GAG quantification in improving specificity and reducing false positives in MPS I newborn screening.

Conclusion
Newborn screening for Pompe disease showed strong diagnostic accuracy with high specificity and consistent molecular confirmation. In MPS I, pseudodeficiencies remain a significant limitation; however, the combination of enzymatic assessment and second-tier GAG quantification substantially reduces false positives and enhances diagnostic precision. These findings support the implementation of second-tier GAG testing and underscore the clinical benefit of early detection strategies.

Palavras-chave: tandem mass spectrometry, newborn screening, lysosomal diseases, Pompe disease, MPS I

SESSION VI _

RECENT THERAPEUTIC ADVANCES IN GLYCOGEN STORAGE DISEASES

CHAIRPERSONS

HELDER ESPERTO (COIMBRA)

ANABELA BANDEIRA (PORTO)

Bempedoic acid prolongs fasting time in patients with glycogen storage disease type 1a

Anibh M. Das

Paediatric Metabolic Medicine, Hannover Medical School and Centre for Rare Diseases and Center for Systems Neurosciences, Hannover, Germany

Introduction

In patients with glycogen storage disease type1a (GSD1a), hypoglycaemia is a key clinical and biochemical finding, which is based on several pathophysiological mechanisms. The underlying deficiency of glucose 6-phosphatase leads to reduced glycogenolysis on one hand and elevated glucose 6-phosphate levels, which promote synthesis of malonyl-CoA, on the other hand. Malonyl-CoA is a potent inhibitor of mitochondrial influx of long-chain fatty acids, thus reducing the capacity of mitochondrial fatty acid oxidation (FAO). As a consequence, there is reduced ketone body production in the liver and reduced energy production in several organs which both contribute to hypoglycaemia. Standard treatment in GSD1a consists of frequent feedings rich in carbohydrates, preferably raw cornstarch at night, to prevent hypoglycaemia.

Bempedoic acid (BA) was primarily developed for the treatment of hyperlipidaemia in adults, which is also a feature in GSD1a. BA reduces the synthesis of malonyl-CoA, thus allowing more hepatic ketone body and systemic energy production via FAO.

We hypothesized that BA improves metabolic control, especially the tendency to hypoglycaemia, in patients with GSD1a.

Patients and methods

We report a case series of 4 females with GSD1a (age 20-47 years at start of treatment), who were treated with oral BA (180mg/d) for 2-5 years in our center. Lactate, alanine, triglycerides, uric acid and ketone bodies in blood and lactate in urine were monitored at visits in our outpatient clinics.

Results

All four patients could extend their fasting time (maximum additional 2 hours during daytime and maximum additional 2 hours during nighttime). All patients reported an improved quality of life with increased stamina. One patient experienced deterioration of fasting time after temporary discontinuation of BA due to shortage of medication.

Parameters monitored in blood were generally stable, in some patients, ketone body production increased. Lactate in plasma dropped by 52% on average. No clinical side effects under treatment were reported. Uric acid may increase under BA, in our study 2 patients showed a mild increase in uric acid concentrations in blood.

Conclusion

BA can presumably release the malonyl-CoA block of FAO in GSD1a-patients. Clinically, this resulted in extended fasting times, increased stamina and improved quality of life. No clinical or biochemical side-effects were observed.

New avenues to treat Neutropenia in GSD type Ib and G6PC3-deficient patients

Maria Veiga da Cunha
Duve Institute; School of Biomedical Sciences, UCLouvain, Brussels, Belgium

Following our elucidation of the mechanism underlying neutropenia in G6PC3-deficient and GSD1b patients, current therapeutic strategies target this defect using SGLT2 inhibitors. These agents promote the urinary excretion of 1,5-anhydroglucitol, thereby lowering its concentration in the blood. This reduction leads to a substantial decrease in intracellular 1,5-anhydroglucitol-6-phosphate, a potent inhibitor of hexokinase that accumulates in patients' neutrophils and underlies both neutropenia and neutrophil dysfunction. Although this treatment is generally effective, a subset of GSD1b patients responds suboptimally due to insufficient lowering of circulating 1,5-anhydroglucitol. Enhancing the efficacy of this approach would therefore benefit all patients, particularly those with an incomplete therapeutic response

Our recent findings show SGLT5 is the main kidney transporter of 1,5-anhydroglucitol, preventing its urinary excretion and retaining it in the body. Consequently, it now appears that SGLT2 inhibitors work indirectly by increasing glucose in kidney primary tubules, which in turn inhibits SGLT5-mediated reabsorption of 1,5-anhydroglucitol.

Our results show that SGLT5-knockout mice exhibit very low blood levels of 1,5-anhydroglucitol (<3 µM). Furthermore, when these mice were crossed with neutropenic G6PC3-deficient mice to get double knockout mice , levels of 1,5-anhydroglucitol-6-phosphate normalized and neutropenia was fully corrected. This indicates that targeting SGLT5 is a promising strategy to improve neutropenia treatment.

Based on this, we investigated whether (1) mannose supplementation or (2) remogliflozin, a less selective SGLT2-inhibitor, could impact neutropenia in a G6PC3-knockout mouse model.

Our rationale for testing mannose comes from earlier findings showing that in cell lines SGLT5 also transports this sugar. Additionally, oral mannose is an approved therapy for MPI-CDG, a congenital disorder of glycosylation caused by phosphomannose isomerase deficiency, where it bypasses the metabolic block. Here, we show that mannose administered in drinking water at various concentrations (0.4% - as used in MPI-CDG treatment - and at 2- and 5-fold higher doses) lowers blood 1,5-anhydroglucitol levels and protects G6PC3-knockout mice from developing neutropenia, minimally impacting GDP-mannose in white blood cells. We directly compare the effects of mannose and empagliflozin treatments in G6PC3-knockout mice.

Remogliflozin was tested due to its higher affinity for SGLT5 compared to empagliflozin or dapagliflozin, and its superior inhibition of 1,5-anhydroglucitol uptake in SGLT5-overexpressing cell lines. When administered in drinking water at clinically relevant doses, remogliflozin reduced blood 1,5-anhydroglucitol levels twice as effectively as empagliflozin or dapagliflozin. While its effect on neutropenia in mice remains to be tested, these results suggest potential for improved patient outcomes.

Our results are the final proof of concept that (1) neutropenia and (probably all immunological-related defects in GSD1b and G6PC3-deficiencies) are directly related to the accumulation of toxic 1,5-anhydroglucitol-6-phosphate in white blood cells, (2) remogliflozin or specifically designed SGLT5-inhibitor molecules may outperform SGLT2 inhibitors in treating neutropenia in these disorders.

SESSION VII _

ADVANCES AND CHALLENGES IN THERAPEUTIC APPROACHES FOR INHERITED AMINO ACID

CHAIRPERSONS

ANA OLIVEIRA (COIMBRA)

MANUELA FERREIRA DE ALMEIDA (PORTO)

Liver Transplantation in Aminoacidopathies and Organic Acidemias: The Portuguese Experience

Sara Ferreira
ULS Coimbra, Portugal

Liver transplantation (LTx) has been increasingly used as an elective therapeutic option in intoxication-type inherited metabolic disorders, including urea cycle disorders (UCDs), maple syrup urine disease (MSUD), and organic acidemias (OAs). In MSUD and UCDs, LTx may provide a metabolic cure by replacing the defective enzymatic activity. In OAs, LTx improves metabolic stability and may enhance neurological outcomes, particularly when performed early. Nevertheless, there is a residual risk of metabolic crises due to the persistence of the metabolic defect in extra-hepatic tissues. LTx may also be useful in the management of late complications, such as chronic kidney disease in Methylmalonic Acidemia and cardiomyopathy in Propionic Acidemia. In Tyrosinemia type I, since the introduction of nitisinone therapy, LTx is mainly reserved for acute liver failure, progressive liver disease, or hepatocellular carcinoma. Advances in multidisciplinary LTx management have improved outcomes and long-term survival, shifting LTx from a lifesaving procedure to a life-improving therapy. However, standardized management protocols are still lacking.

Paediatric liver transplantation in Portugal began in 1994. It is performed at a single national centre in the ULS of Coimbra. Inherited metabolic diseases (IMDs) represent the second most frequent indication, accounting for 43 of the 285 transplanted children (15%).

We present the Portuguese experience of liver transplantation in paediatric patients with aminoacidopathies, UCDs, and OAs: 27 patients (63% of IMD cases who underwent transplantation). In this group, MSUD was the most frequent underlying diagnosis (n = 8), followed by Tyrosinemia type I (n = 6), Ornithine Transcarbamylase deficiency (n = 4), Argininemia (n = 3), Methylmalonic Acidemia (n = 3), Propionic Acidemia (n = 2), and Citrullinemia type I (n = 1). Except for Tyrosinemia type I, where the indication was suspicion of malignancy, frequent metabolic decompensations were the most common indication for LTx. The median age at transplantation was 9.6 years (range 1.4–17.5 years), although there was considerable variability depending on the underlying diagnosis.

The majority of patients experienced an improvement in metabolic control, increasing natural protein tolerance at least to the level of the RDA recommendations. Ammonia scavengers were discontinued in UCD patients, nitisinone in Tyrosinemia type I patients, while carnitine therapy was maintained in OA patients.

Transplant-related complications occurred in 22 patients, and two patients required liver retransplantation. The overall survival rate in our cohort was 93% (2 deaths), reflecting the generally favorable outcomes of paediatric liver transplantation in patients with IMDs.

The retrospective nature of this review, along with the fact that patients are followed in multiple national centres, represents the main limitation of this study.

SESSION VIII

ORAL COMMUNICATIONS & SELECTED POSTERS

CHAIRPERSONS

ANA OLIVEIRA (COIMBRA)

MARIANA PINTALHÃO (PORTO)

CO06

Management of Ornithine Transcarbamylase Deficiency in Pregnancy: A Report of Two Cases

Carlos Grijó[1]; Adriana Costa[1]; Carla Ramalho[2]; Sílvia Pinhão[3]; Teresa Cardoso[4]; Paulo Castro Chaves[4]; Mariana Pintalhão[4]

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Introduction
Ornithine transcarbamylase (OTC) deficiency poses significant risks during pregnancy due to increased catabolic stress. This elevates the risk of life-threatening hyperammonemia during intercurrent illness, labor, and the postpartum period. Currently, evidence-based guidelines for optimal peripartum management remain limited.

Methods
We describe the clinical management of two pregnancies in women with OTC deficiency. Management was centered on structured biochemical surveillance, dietary optimization, and a standardized peripartum protocol. Patient A was previously diet-controlled; Patient B required diet and ammonia scavengers.

Results/Case report
Patient A presented to our clinic at 7 weeks' gestation. Monthly ammonia and urinary orotic acid levels were normal. Managed with an adapted low-protein plan and a standardized peripartum protocol, she experienced no metabolic decompensations. Following an uncomplicated spontaneous vaginal delivery at term, she initiated breastfeeding uneventfully. The infant's genetic screening was negative.
Patient B conceived via IVF with pre-implantation genetic testing. At 12 weeks, she experienced transient hyperammonemia (84 µmol/L) following a viral illness and high protein intake. This was managed with dietary optimization and sodium benzoate dose titration. Subsequent ammonia levels remained normal, although late pregnancy showed mildly raised orotic acid. Due to prolonged labor, she underwent an uncomplicated term cesarean section. In both cases, fetal development was normal.

Conclusion
Both pregnancies were managed through monthly ammonia and orotic acid monitoring, with rapid responses for catabolic stress or protein excess via diet adjustments, arginine and ammonia scavenging (sodium benzoate). A predefined delivery pathway, including early epidural anesthesia, 10% dextrose infusion, capillary glucose monitoring, and serial ammonia measurements ensured favorable outcomes. Additionally, cord-blood DNA was collected for neonatal testing. Structured multidisciplinary care is essential to facilitate successful pregnancy and delivery in patients with OTC deficiency.

Palavras-chave: Ornithine transcarbamylase, Pregnancy, Orotic acid, Catabolic stress

CO07

Clinical Remission in Severe AIP Following Givosiran: A Case Report

Joana Ramos[1]; Ana Saraiva[1]; André Abreu[1]; Hélder Esperto[1]; Sónia Moreira[1]

[1] ULS Coimbra

Introduction

Acute Intermittent Porphyria (AIP) is a rare metabolic disorder caused by a porphobilinogen deaminase enzyme deficiency, leading to the accumulation of toxic porphyrin precursors. Givosiran has recently emerged as the first treatment approved for the chronic management of AIP in adult patients with recurrent attacks. We report the one-year clinical evolution of a patient treated with Givosiran, one of the two patients in Portugal on this medication. We aim to discuss the therapeutic progression and the impact of this siRNA-based therapy on the patient's clinical and biochemical stability.

Results/Case report

We present a 46-year-old female patient with AIP, whose clinical presentation required Intensive Care Unit admission due to acute polyneuropathy and respiratory failure necessitating invasive mechanical ventilation. Her clinical course involved 2-4 attacks per year, leading to cumulative organ damage and chronic symptoms. Acute crises typically presented as severe recurrent abdominal pain. Over time, this cumulative burden led to persistent chronic abdominal pain and progression of chronic kidney disease and severe peripheral neuropathy. ALA (aminolevulinic acid) and PBG (porphobilinogen) levels were initially elevated only during attacks but became persistently high over time. 15 days after Givosiran was initiated, complete normalization of both was observed. Since the introduction of this therapy, the patient remained free of acute crises and showed improvement of chronic symptoms.

Conclusion

This case highlights a patient with high disease activity where Givosiran successfully eliminated recurrent acute attacks and alleviated debilitating chronic symptoms. In the Portuguese clinical context, where experience with this orphan drug is still emerging, sharing this successful one-year evolution is crucial. It provides evidence that Givosiran is not only effective in preventing acute crises but also instrumental in managing the chronic symptoms that define the most severe phenotypes of AIP, ultimately restoring clinical stability and quality of life.

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Palavras-chave: Givosiran; acute intermittent porphyria

CO08

Long-Term outcome of Sapropterine treatment in Phenylketonuria

Joana Correia[1]; Manuela Ferreira De Almeida[1,2,3,4]; Anabela Bandeira[1]; Rosa Ribeiro[1]; Arlindo Guimas[1]; Sara Rocha[1]; Rute Martins[1]; Sofia Pinto[1]; Margarida Paiva Coelho[1]; Vânia Magalhães[1]; Catarina Sousa Barbosa[1]; Esmeralda Martins[1,3,4]

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Introduction
Sapropterin dihydrochloride is approved for responsive phenylketonuria patients, reducing blood phenylalanine (Phe) concentrations and improving Phe tolerance. Between 2015 and 2016, responsiveness to sapropterin was assessed in patients with Phenylketonuria (PKU) aged >4 years, followed at a Portuguese Reference Center. True responders continued therapy, allowing evaluation of its long-term real-world effectiveness.
This study aimed to determine whether initial improvements in natural protein and Phe intake were sustained over time.

Methods
Retrospective review of medical records of PKU patients-sapropterin responders who initiated therapy between 2015 and 2017. Nutritional data were collected at two time points: end of 2018 and 2025. Good metabolic control was defined as blood Phe levels ≤6 mg/dL (<12 years) and ≤8 mg/dL (≥12 years).

Results/Case report
Seventeen patients were included (82% female; 13 with mild PKU, 4 classical PKU). Median age at baseline was 17 years (range 8–35), including 9 pediatric patients.
All patients remained on sapropterin (median dose 13.2 mg/kg/day; range 7.6–21.7); median treatment duration 118 months.
From 2018 to 2025, mean natural protein intake remained stable (0.96±0.24 vs 0.90±0.31 g/kg/day, p=0.38). Mean Phe intake showed non-significant increase (2426±884 to 2704±936 mg/day, p=0.089), while protein substitute use tended to decrease (0.69±0.36 to 0.55±0.30 g/kg/day, p=0.098). Two mild PKU patients were managed with protein restriction alone.
Median annual blood Phe increased significantly from 5.8 (4.8–6.3) to 7.3 (5.5–8.5) mg/dL (p=0.003). Seven patients had levels above target (8.3–10.4 mg/dL) in 2025 vs none in 2018.
One female patient continued sapropterin during pregnancy with good outcome

Conclusion
Critical ongoing evaluation is essential during long-term follow-up of sapropterin-responsive patients.
The increase in phenylalanine tolerance achieved with sapropterin was largely sustained, with stable natural protein intake. However, median blood Phe levels increased over time, with more than 40% of patients exceeding target ranges in 2025. In such cases, adherence to pharmacological and/or dietary treatment should be carefully reviewed and therapeutic adjustments considered. If no improvement is observed, the clinical benefit of continuing sapropterin therapy should be reassessed.

CO09

Why Mitochondrial Mimics Mimic: Clinical Confounders and Convergent Mitochondrial Disruption of Mitochondrial Homeostasis

Matilde Oliveira Pinto[1]; Célia Azevedo[2]; Ana Rita Soares[2]; Maria Abreu[2]; Cristina Garrido[3]; Sónia Figueiroa[3]; Anabela Bandeira[1]; Joana Correia[1]; Esmeralda Martins[1]; Margarida Coelho[1]

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Introduction
Primary mitochondrial disease (PMD) is frequently suspected in children presenting with multisystem neurological and metabolic abnormalities. However, a substantial proportion ultimately receive alternative genetic diagnoses. These "mitochondrial mimics" not only phenotypically overlap with PMD but may also converge mechanistically on mitochondrial homeostasis. We aimed to characterise the clinical and biochemical features leading to mitochondrial suspicion and to explore the biological basis underlying genetic mimics.

Methods
Within a longitudinal cohort of 178 children investigated for suspected PMD, we analysed 28 patients with confirmed alternative genetic diagnoses. Clinical, metabolic, neuroimaging and MDC score data were systematically reviewed.

Results/Case report
Mimics spanned neurosynaptic disorders, channelopathies, autophagy/lysosomal disease, vesicular trafficking, DNA/RNA and repair pathways, chromatin/transcriptional regulation, neuromuscular/structural disorders, imprinting or or chromosomal abnormalities.
Hyperlactatemia occurred in 60.7% and alanine elevation in 25%. MRI showed basal ganglia (17.6%), cerebellar (41.2%), white matter (23.5%) and brainstem involvement (11.8%).
Although none met "definite" MDC criteria (≥8), 71% were classified as "possible" and some as "probable"; 36% scored ≥2 in the metabolic domain.
Respiratory chain alterations were observed in 54.5% of non-PMD biopsied patients, similar to PMD (43.5%). Muscle biopsy was diagnostically decisive in 14.3% of non-PMD. Most diagnoses followed nondiagnostic mitochondrial-focused testing, frequently via whole-exome sequencing.

Conclusion
Genetic mimics of mitochondrial disease frequently reproduce metabolic and neuroimaging features traditionally interpreted as markers of primary bioenergetic failure. Mechanistically, diverse genetic defects converge on pathways influencing mitochondrial homeostasis, including disrupted Ca^{2+} signalling, impaired mitophagy, altered ER–mitochondria crosstalk, and dysregulated nuclear control of protein expression. Recognising these confounders is essential to refine diagnostic reasoning and avoid prolonged mitochondrial-focused investigations in inherited metabolic practice.

CO10

NBGenS: Pilot Study of Genomic Newborn Screening. Preliminary Results

Lluis Miquel Lis Lopez[1]; Catalina Lopez-Lopez[2]; Laura Lopez-Valverde[2]; Bruno K. Rodiño-Janeiro[2]; J. Victor Alvarez[2,3]; Cristobal Colon-Mejeras[2,3]; Maria Eugenia Vazquez-Mosquera[2,3]; Maria-Luz Couce-Pico[2,3]

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Introduction
Genomic newborn screening represents a complementary approach to conventional screening, enabling the detection of treatable pediatric genetic disorders not identifiable through specific biochemical markers. This study aimed to develop and evaluate the feasibility, diagnostic yield, and clinical impact of a pilot genomic newborn screening program in Spain.

Methods
DNA from dried blood spot samples of 550 recruited newborns was analyzed using whole-exome sequencing. Libraries were prepared using KAPAHyperPrep and KAPAHyperExome kits and sequenced on a NovaSeq6000 platform, followed by bioinformatic analysis included alignment, detection and annotation of SNV, indel, and CNV.

Results/Case report
To date, application of a 549-gene virtual panel of clinically actionable pediatric conditions identified seven cases(1.3%) with pathogenic or likely pathogenic findings, which were managed according to the predefined suspicious case protocol. Participants with findings in COL4A4(n=1), LDLR(n=1), COL1A1(n=1), F8(n=1), APOB(n=1), and GAA(n=2) were classified as suspicious. The GAA cases were confirmed as late-onset Pompe disease. The remaining cases received genetic counseling and are under clinical follow-up, with familial segregation studies ongoing. Intervention plans were implemented for both affected participants and relatives with confirmed segregation, and these data will inform subsequent cost-effectiveness analyses.

Conclusion
For the first time in Spain, this pilot study demonstrates the feasibility of genomic newborn screening for the early detection of treatable pediatric genetic diseases, enabling timely clinical management. Moreover, NBGenS has laid the groundwork for the ongoing national multicenter CRINGENES project.

Acknowledgements
With the collaboration of the CRINGENES consortium (PMPER24/00011). Carlos III Health Institute.

Palavras-chave: Newborn Screening, Whole-exome Sequencing, Actionable pediatric conditions, Variant interpretation, Gene virtual panel

SESSION IX _

THERAPEUTIC AND TECHNOLOGICAL INNOVATION IN INHERITED METABOLIC DISEASES

CHAIRPERSONS

JOANA ROSMANINHO SALGADO (COIMBRA)

ANABELA OLIVEIRA (LISBON)

Targeted Nanomedicine in Inherited Metabolic Diseases

J. Victor Alvarez, Ph.D.[1,2], Susana B. Bravo Ph.D[2], Cristóbal Colon MD, Ph.D[1,2], Francisco Otero-Espinar Ph.D[3], Maria L. Couce MD, Ph.D[1,2]

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Background
Among the treatments used for lysosomal storage diseases are hematopoietic stem cell transplantation and enzyme replacement therapy (ERT), administered via weekly intravenous infusions. ERT has limited efficacy due to its inability to reach critical tissues such as the brain and bone. To address these limitations, this study explores a novel method to improve drug delivery to target organs and simplify administration: oral administration of enzymes encapsulated in nanostructured lipid carriers (NLCs).

Methods
Nanoparticles encapsulating [1] laronidase (the reference enzyme for this work) were prepared using a rapid double emulsification method (water-in-oil-in-water; W/O/W). The nanoparticles were then spray-dried to construct a gastric coating. Fibroblast cell cultures and glycosaminoglycan (GAG) loading were performed, followed by glycosaminoglycan analysis studies in cell models and alpha-L-iduronidase activity assays. Cell function studies were conducted through proteomics, and finally, in vivo studies of biodistribution and enzymatic activity in tissues were performed.

Results
Encapsulating ERT in NLCs enabled efficient oral administration [2,3], using the enzyme L-iduronidase for mucopolysaccharidosis type I (MPS-I) as a reference. In vitro analysis demonstrated that our NLC formulation was as effective as intravenous ERT in correcting enzyme activity and reducing GAG accumulation in fibroblasts of MPS-I patients when administered periodically. Permeability studies confirmed passage across the intestinal barrier. Proteomic analyses demonstrated the normalization of protein expression in energy pathways related to hexose metabolism, as well as significant improvements in protein dysregulation in the cytoskeleton, cell trafficking, lysosomal function, GAG biosynthesis and degradation, and the extracellular matrix. Furthermore, in vivo studies in MPS-I knockout mice demonstrated the biodistribution of enzymes encapsulated in NLCs to all tissues affected by the disease, including passage across the blood-brain barrier and access to poorly vascularized bone.

Conclusion
These findings suggest that oral administration of ERT via NLC encapsulation represents a significant advance in the treatment of MPS-I, allowing drug delivery to previously inaccessible areas. This study opens important avenues of research for future therapeutic strategies targeting LSDs.

Support: NA

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SESSION X _

SPDM GRANTS

CHAIRPERSONS

DULCE QUELHAS (PORTO)

ANABELA OLIVEIRA (LISBON)

CLOSING SESSION & AWARDS

CHAIRPERSONS

JOÃO DURÃES (COIMBRA)

SÓNIA MOREIRA (COIMBRA)

Poster session I – 19th March - 15h50

POP01 - Urinary metabolomic signature of renal involvement in primary mitochondrial disease: 1-methylnicotinamide as a potential biomarker
POP02 - Inflammatory biomarkers in patients with propionic and methylmalonic acidemias under L-carnitine treatment
POP03 - Is 3D Printing a Promising Tool for Improving Metabolic Control in IEM?
POP04 - Evidence of Altered Translational Activity in Leber's Hereditary Optic Neuropathy
POP05 - Tracking the Thiol Cascade: Methodological Advances for Accurate Plasma Glutathione Assessment
POP06 - Deciphering the Molecular Basis of Multiple Acyl-CoA Dehydrogenase Deficiency Through Protein Analysis

Poster session II - 19th March - 15h50

POP07 - Unlocking the potential of Lipidomics: A powerful approach for biochemical validation of GM2A variants
POP08 - Long-term follow-up of a patient with LCHAD deficiency submitted to heart transplantation due to severe cardiomyopathy
POP09 - Critical role of determining trans configuration in myopathic CPTII deficiency for accurate genetic counseling and follow-up
POP10 - TANGO2 Deficiency: A Rare and Challenging Metabolic Disorder Presenting with Neurological Manifestations
POP11 - The effect of FAD supplementation on the activity and thermal stability of the most common variant of medium-chain acyl-CoA dehydrogenase
POP12 - How effective can one carbon be? – a Clinical Case

Poster session III - 20/03/2026 11h20

POP13 - Treatment of Glucose Transporter 1 Deficiency with a Ketogenic Diet: From Concept to Practice
POP14 - Betaine as an option for the treatment of Aspartylglucosaminuria: a case report
POP15 - Imaging patterns in cholesterol metabolism disorders with neurological involvement: the examples of SPG5 and CTX
POP32 - Early Diagnosis and Clinical Outcomes in Tyrosinemia Type I
POP16 - Sapropterine Loading Test Responsiveness - Experience of a Reference Centre

Poster session IV- 20/03/2026 11h20

POP17 - Neonatal cardiac presentation of Coenzyme-A Synthase Deficiency protein-associated neurodegeneration (CoPAN)
POP18 - The Experience of Peer Loss: A Dimension of Complexity in Neurometabolic Diseases
POP19 - Cognitive decline in a Gaucher patient
POP20 - Ornithine Transcarbamylase Deficiency in Females: Diverse Presentations, Shared Neurocognitive Burden
POP21 - Fairy-Tale Cells, Real Disease: Stem cells from human exfoliated deciduous teeth take on MPS IIIC

Poster session V - 20/03/2026 16h20

POP22 - Nutritional Management During Pregnancy in a Patient with Maple Syrup Urine Disease (MSUD): A Clinical Case Report
POP23 - Adult-onset Erythropoietic Protoporphyria: a case report
POP24 - When Iron-Sulphur Cluster Biogenesis Fails: Three Neonatal Cases of Lethal Multiple Mitochondiral Dysfunction Syndromes
POP25 - Reanalysis Matters: Impact of Exome Reinterpretation in a Patient with long-term suspicion of a Mitochondrial Disease
POP26 - Metachromatic leukodystrophy: silently approaches its prey like a tiger

Poster session VI - 20/03/2026 16h20

POP27 - Holocarboxylase Synthetase Deficiency and Cancer: Causality or Coincidence?
POP28 - Optimizing Access to Care in Inherited Metabolic Diseases Through Telemedicine: Clinical Outcomes, Socio-Economic Impact, and Organizational Implications from a Reference Cente
POP29 - Development of Antisense Oligonucleotide-Based Therapies for Lysososmal Storage diseases
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SELECTED E›POSTERS COMMUNICATIONS

Urinary Metabolomic Signature of Renal Involvement in Primary Mitochondrial Disease: 1-MethylNicotinamide as a Potential Biomarker

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Introduction
Primary mitochondrial disease (PMD) frequently involves the kidney, particularly the proximal tubule. Renal dysfunction may confound urinary metabolomic signatures attributed to mitochondrial dysfunction. We explored whether PMD patients with predominant renal involvement display a distinct urinary metabolomic profile compared to PMD without chronic kidney disease (CKD) and non-mitochondrial CKD.
Methods
We compared the urinary metabolome of patients with PMD and CKD (PMD+CKD) with controls, non-mitochondrial CKD, and PMD without CKD using untargeted ^{1}H NMR urinary metabolomics. Data were normalized using probabilistic quotient normalization (PQN) and analysed through multivariate analysis and exploratory univariate analysis.
Results/Case report
Final comparisons included genetically confirmed PMD without CKD (n = 13), PMD+CKD n=2), non-mitochondrial CKD (n = 28; 17 at stages 1–2 and 9 at stages 3–5), and healthy controls (n = 10). PMD+CKD patients included one with Fanconi syndrome due to a BCS1L-related disorder and one with nephrotic syndrome in mitochondrial DNA depletion syndrome.
PMD+CKD patients did not fully overlap with stage-matched CKD nor with PMD without renal involvement, suggesting a hybrid but distinguishable metabolomic profile. P15, a BCS1L-related mitochondrial tubulopathy with Fanconi syndrome, showed stable clustering across five samples, partially driven by marked glycosuria.
In exploratory analysis, urinary N-methylnicotinamide levels were reduced in PMD+CKD, similar to CKD stages 3–5, while preserved in PMD without CKD, indicating a renal-driven metabolic signal. In contrast, metabolites previously associated with mitochondrial dysfunction (e.g., Krebs cycle intermediates, tryptophan-related pathways) maintained PMD-related patterns.
Conclusion
PMD with renal involvement retains a distinguishable urinary metabolomic profile despite overlapping kidney disease. PMD+CKD exhibits a composite urinary metabolomic phenotype reflecting both mitochondrial dysfunction and renal impairment.
Reduced urinary N-methylnicotinamide emerges as a potential biomarker of kidney involvement within primary mitochondrial disease. These findings support urinary metabolomics as a functional layer capable of capturing complex phenotypes in mitochondrial disease.

References

PMD with renal involvement retains a distinguishable urinary metabolomic profile despite overlapping kidney disease. PMD+-CKD exhibits a composite urinary metabolomic phenotype reflecting both mitochondrial dysfunction and renal impairment. Reduced urinary N-methylnicotinamide emerges as a potential biomarker of kidney involvement within primary mitochondrial disease. These findings support urinary metabolomics as a functional layer capable of capturing complex phenotypes in mitochondrial disease.
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Funding: This study was funded by the grant "Bolsa de Investigação e Prática Clínica Pfizer Vacinas – SPPediatria 2019".
This work was developed within the scope of the CICECO-Aveiro Institute of Materials, UIDB/50011/2020 project (doi: 10.54499/UIDB/50011/2020), UIDP/50011/2020 (doi: 10.54499/UIDP/50011/2020) and LA/P/0006/2020 (doi:10.54499/LA/P/0006/2020), financed by national funds through the FCT/MCTES (PIDDAC). We also acknowledge funds from the Foundation for Science and Technology through the BetterBone project (2022.04286.PTDC, doi:10.54499/2022.04286.PTDC), the Portuguese National NMR Network (RNRMN), supported by Infrastructure Project N° 022161.

Palavras-chave: Primary mitochondrial disorders, Metabolomics, 1H NMR, Chronic Kidney Disease, Biomarkers

Inflammatory Biomarkers in Patients With Propionic and Methylmalonic Acidemias Under L-Carnitine Treatment

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Introduction

Propionic acidemia and methylmalonic acidemia (PA and MMA) are metabolic disorders caused by genetic defects in enzymes involved in propionate metabolism. Both disorders present similar clinical manifestations, including gastrointestinal symptoms, renal impairment, and severe neurological damage. Early treatment with protein restriction and L-carnitine (LC) is recommended and aims to minimize metabolic decompensations (1-2). In the present study, we evaluated inflammatory biomarkers in the plasma of patients with PA and MMA under treatment for up to 2 years and for more than 2 years.

Methods

Patients were recruited from REDE EIM Brasil at the Serviço de Genética Médica/HCPA. Plasma samples were obtained from 13 healthy children, 12 patients at diagnosis, and two groups of treated patients: 10 patients under treatment for up to 2 years and 9 patients under treatment for more than 2 years. Approved by the Ethics Committee (No. 2023-0157).

Results/Case report

We evaluated the levels of cathepsin D, C-reactive protein (CRP), pro-inflammatory cytokines (IL-1β, IL-2, IL-6, IL-8, IFN-γ, and TNF-α), and anti-inflammatory cytokines (IL-4 and IL-10). There were no statistically significant differences in IL-1β, IL-2 and IL-4 levels. However, IFN-γ levels tended to be higher in the diagnostic group and lower in the treated groups. A significant increase in inflammatory biomarkers (cathepsin D, CRP, IL-6, IL-8, TNF-α, and IL-10) was observed in the diagnostic group compared with healthy controls. Notably, cathepsin D, CRP, TNF-α, and IL-10 levels were significantly reduced in patients under treatment with LC for more than two years, indicating a attenuation of the inflammatory response.

Conclusion

Our findings reinforce the involvement of inflammation in patients with PA and MMA. The results demonstrate the benefit of long-term supplementation with LC in preventing the damage, suggesting that LC may be fundamental in improving the prognosis of patients with MMAcidemia and PAcidemia.

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Acknowledgements

This work was supported by Fundo de Incentivo à Pesquisa e Eventos (FIPE/HCPA) and Conselho Nacional de Desenvolvimento Científico (CNPq). The authors would like to also thank the staff from REDE-EIM Brasil and SGM-HCPA, as well as patients and their families.

Palavras-chave: Methylmalonic acidemia, Propionic acidemia, Inflammation, L-carnitine

Is 3D Printing a Promising Tool for Improving Metabolic Control in IEM?

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Introduction

Inborn Errors of Metabolism (IEM) are individualy rare disorders presenting from birth to late adulthood. Adherence to a personalized treatment is essential to prevent acute decompensation,often more severe in children (1). Disorders like Maple Syrup Urine Disease (MSUD), Methylmalonic Aciduria, Multiple acyl-CoA Dehydrogenase Deficiency or Carnitine Palmitoyl transferase I deficiency, among others, require personalized treatment. Reliable biomarkers are crucial for diagnosis, monitoring and correlate with dose adjustment(2). As many IEM lack pediatric formulations, compounding and 3D printing provide accurate, palatable, personalized treatments that enhance adherence (1).

Methods

An analysis was performed based on published literature addressing therapeutic challenges in IEM disorders that may benefit from technical capabilities of pharmaceutical 3D printing. Clinical needs were systematically matched with potential formulation solutions enabled by this technology.

Results/Case report

This analysis highlights the therapeutic potential of 3D-printed medicines in several IEMs:

• Precise, adjustable dosing: In rare metabolic disorders, e.g. MSUD or Fabry Disease, 3D printing enables individualized dose adjustments based on fluctuations in disease-specific biomarkers (2).

• Improved metabolic control: 3D-printed medicines achieved non-inferior, and in some cases, superior metabolic control vs conventional therapy, maintaining target amino acid levels (e.g., citrulline and isoleucine) with reduced variability (1).

• Polypills and regimen simplification: 3D printing technology allows the combination of multiple active substances into a single dose, simplifying complex regimens and reducing treatment burden (3).

Palatability and adherence: Personalized flavors, shapes, and textures (chewable printlets) significantly improved acceptability and adherence in pediatric patients (1).

Conclusion

Pharmaceutical 3D printing offers a clinically relevant strategy to address unmet needs in inherited metabolic disorders, characterized by heterogeneity and dynamic biochemical profiles. By integrating laboratory biomarker monitoring into therapeutic decision-making, it enables patient-specific dose titration and adaptable pharmacotherapy. Customizable dosage forms (dose, shape, texture and flavor) are particularly beneficial for pediatric patients. The use of 3D printing in conjunction with biomarker-guided therapy is a promising tool in advancing personalized medicine in these disorders.

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Palavras-chave: Inborn Errors of Metabolism, personalized medicines, 3D printing

Evidence of Altered Translational Activity in Leber's Hereditary Optic Neuropathy

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Introduction

Leber's Hereditary Optic Neuropathy (LHON) is a mitochondrial disease causing severe visual loss, affecting mainly males, and caused by three main pathogenic mitochondrial DNA alterations. Nutritional and toxic Optic Neuropathies (ON) have been linked to decreased protein synthesis (1). In LHON, this link has been hypothesized in connection to failures in mt-tRNA metabolism due to secondary variants (2) and through proteins shown to be S-Glutathionylated (3)

Methods

This study was conducted in fibroblasts from patients (n=4) and healthy controls (n=8), obtained at ULS Coimbra (with ethical approval #190/CES and obrained IC) or Coriell Biobank. To assess protein synthesis, Click-iT™ HPG and Click-iT™ Plus OPP Assays were used. Fluorescence was read in the Incucyte® System. Statistics were done in GraphPad v8.

Results/Case report

Results show a decrease in fluorescence in both HPG and OPP assays, in Normal condition (DMEM with 10% FBS) and in Stress condition (OXPHOS media), in patients' cells. However, statistical significance between groups was found only in OPP assay (Controls VS LHON, p=0,0006) in a Mixed-effects model (REML). Next, Sidak's test showed significance between Healthy Controls and LHON Patients for Normal media (p= 0,0106) and for OXPHOS media (p=0,0042). Thus, there is evidence of a decrease in protein synthesis in LHON patients in basal and stress conditions, being more pronounced in stress. Even if statistical significance was found only in OPP, HPG is also decreased, indicating a connection of protein pathways in pathology. Plus, the HPG assay relies on methionine starvation, and a larger metabolic impact of this incubation period may have led to confounding results.

Conclusion

In conclusion, this preliminary data brings novelty to the field and shows a possible decrease in protein synthesis in LHON, observed even without stress being applied to cells, in line with current hypotheses in literature. These results point to the involvement of different pathways associated with protein synthesis, demonstrating the complex inter-organellar communication that is affected and under-explored in this pathology. Studies with larger sample numbers are needed, as well the quantification of other metabolic aspects connected to protein synthesis and methionine metabolism in LHON

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Acknowledgements

This work was also financed by the European Regional Development Fund (ERDF), through the COMPETE 2020—Operational Programme for Competitiveness and Internationalisation and Por-tuguese national funds via FCT—Fundação para a Ciência e a Tecnologia, under pro-jects 2022.10296.BD, UID/04539/2020, LA/P/0058/2020 [DOI: 10.54499/LA/P/0058/2020], UID/04539/2025, UID/PRR/4539/2025.

Palavras-chave: LHON, Protein synthesis, Inter organellar communication

Tracking the Thiol Cascade: Methodological Advances for Accurate Plasma Glutathione Assessment

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Introduction

Plasma thiol redox status is a recognized biomarker of cellular oxidative stress with growing relevance in metabolic and cardiovascular diseases. However, its accurate evaluation is challenging due to auto-oxidation of the reduced fractions along sample processing. To prevent this, thiol-blocking agents were added at blood collection: N-ethylmaleimide (NEM) to trap free thiols and 7-fluorobenzofurazna-4-sulfonic acid (SBD-F) to derivatize them. We evaluated the ability of this strategy to stabilize thiol reduced (r) and oxidized (o) fractions with immediate and delayed plasma separation and deproteinization.

Methods

Thiols were analyzed in children (n=12; 1.5–10 years) and adults (n=6; 27-73 years) as SBD-F derivatives using a HPLC-fluorescence method. Blood was collected in EDTA tubes containing either NEM or SBD-F. Pediatric samples were processed 1h after collection while the adult cohort was immediately processed.

Results/Case report

Comparison between children and adults yielded the following mean±SD values: r-GSH (29.6±16.9 vs 1.5±0.8 µM), o-GSH (2.9±1.3 vs 0.6±0.1 µM), r-CysGly (13.9±7.3 vs 1.6±0.9 µM), o-CysGly (7.7±2.2 vs 5.8±1.8 µM), r-Cys (10.0±5.4 vs 15±4 µM), o-Cys (46.6±7.4 vs 46±14 µM), r-HCy (0.02±0.01 vs 0.12±0.05 µM) and o-HCy (0.66±0.19 vs 0.72±0.35 µM).
In pediatric samples, processed after a 1-hour delay, ex vivo redox reactions and additive-induced hemolysis significantly affected GSH and CysGly quantification.
In adults, individual r-GSH levels do not correlate with reduced downstream thiols while o-GSH positively correlates with o-CysGly and o-Cys. Moreover, oxidized forms significantly increased with age across all thiols while reduced fractions remained stable.
This suggests that increasing age is associated with a shift toward a more oxidized profile that propagates along the thiol cascade.

Conclusion

This study proved that even a short delay between collection and sample processing disturbs GSH equilibrium, likely due to ongoing RBC export. Immediate plasma treatment is therefore essential for its accurate assessment, while other thiols are less affected.
While GSH predominantly circulates in its reduced form, the age-related accumulation of oxidized species reveals a progressive shift toward a more oxidized systemic redox state. This highlights the importance of strict pre-analytical control and supports thiol redox profiling as a sensitive tool for detecting subtle oxidative imbalance.

Palavras-chave: Thiols, Glutathione, Oxidative stress, Aging

Deciphering the Molecular Basis of Multiple Acyl-CoA Dehydrogenase Deficiency Through Protein Analysis

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Introduction

Multiple Acyl-CoA Dehydrogenase Deficiency (MADD) is an inborn error of metabolism caused by mutations on the electron transfer flavoprotein (ETF) or ETF:ubiquinone oxidoreductase. These are crucial to transfer electrons from dehydrogenases to the mitochondrial respiratory chain, thus, mutations on their genes lead to impaired energy production. (1) MADD can be presented as a severe neonatal-onset form, which is fatal, and a mild later-onset form, characterised by a wide spectrum of symptoms and age of onset, which molecular mechanisms remain poorly understood, therefore complicating prognosis. (2)

Methods

For this work we performed spectroscopy analysis (UV-visible absorption, circular dichroism (CD), and fluorescence) to evaluate protein folding and conformational stability, as well as enzymatic assays using Medium-Chain Acyl-CoA Dehydrogenase (MCAD), an enzyme ETF partner.

Results/Case report

To improve the understanding of the genotype-phenotype relationship and the disease mechanisms of this metabolic disorder, we are assessing the structural and functional impact that mild disease variants, which map on different structural features of ETF, have on the protein. So far, the data collected shows that ETFα:p.L95V and ETF α:p.R122K are wild-type like, maintaining stability and having a slight decrease in activity. However, the ETF α:p.G255V, located near the FAD binding site, which is essential for the function of the protein, presents changes in ETF conformation and stability, cofactor binding, as about only 40% of total protein is able to bind the cofactor, and function. This will be compared with previous results made by computational studies which predict the ETF α:p.L95V and ETFα:p.R122K variants to be wild-type like, and the ETFα:p.G255V to be stable but inactive.

Conclusion

Comparing the in vitro data with the prediction studies, ETFα:p.L95V and ETFα:p.R122K are in agreement, both approaches suggesting the variants to behave similarly to the wild-type. However, predictions foresee ETF α:p.G255V to be stable but inactive and, until now, experimental data suggest that, although a significant percentage of the total amount of the variant is not able to bind FAD, the one who does is able to perform its function. With that being said, more studies need to be performed, and the results should be combined with clinical literature to improve knowledge on these variants.

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Acknowledgements

Fundação para a Ciência e Tecnologia (FCT/MCTES, Portugal) through grants 2023.15441.2023.15441.TENURE.007/-CP00003/CT00012 to BJH, and the strategic project UID/04046 2025 to Biosystems and Integrative Sciences Institute Centre. Sociedade Portuguesa de Doenças Metabólicas through the research grant Dr. Aguinaldo Cabral 2021 to BJH. This research was partially funded by the European Union (TWIN2PIPSA, GA 101079147). Views and opinions expressed are however those of the author(s) only and do not necessarily reflect those of the European Union or European Research Executive Agency (REA). Neither the European Union nor the granting authority can be held responsible for them.

Palavras-chave: Protein Folding, Biophysical Methods, FAD, Metabolism, Metabolic Disorder

Unlocking the Potential of Lipidomics: a Powerful Approach for Biochemical Validation of GM2A Variants

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Introduction

Adult-onset lysosomal disorders often present without specific clinical features, thereby delaying diagnosis. GM2 gangliosidosis AB variant is particularly challenging, as β-hexosaminidases activities remain normal, despite impaired GM2 degradation. The late onset form is exceedingly rare, with only a few cases reported worldwide with a clinical phenotype overlapping with other diseases. The authors report two adult siblings in whom integrated lipidomic and genomic evaluation clarified a clinical suspicion GM2AB-related disorder.

Methods

Two siblings with progressive motor impairment underwent extensive investigation: electromyography (EMG), muscle magnetic resonance imaging (MRI), muscle biopsy, β-hexosaminidases activity in plasma and leukocytes, Mendeliome sequencing and finally plasma LC-MS/MS lysoGM2 quantification

Results/Case report

Two brothers (57, 53 years) developed slowly progressive proximal lower limb weakness beginning in early adulthood, with gait instability, pelvic elevation and positive Gowers sign. EMG showed chronic motor neuronopathy. Muscle MRI revealed selective quadriceps and gluteal atrophy. Muscle biopsy supported a neurogenic process. Initial Neurogenetic NGS panel was negative. Hexosaminidases activities were normal. Mendeliome analysis identified compound heterozygosity in GM2A c.428G>A (p.(Gly143Glu)) and GM2A c.496G>A (p.(Gly166Arg)), initially classified as variant of uncertain significance (VUS); family segregation confirmed only in the maternal allele, as the father was already deceased. Lyso-GM2 quantification revealed increased total GM2 (71,3; 62,3 – R.R.37,4+13,8n-mol/L) and elevated GM2/GM3 ratio compared to controls, approaching values seen in confirmed GM2A cases, supporting impaired GM2 degradation.

Conclusion

These cases unequivocally prove that normal β-hexosaminidases activities cannot be relied upon to exclude the diagnosis of GM2 gangliosidosis, especially in adult-onset phenotypes. LysoGM2 plasma quantification may play a decisive role in the GM2A variant of VUS interpretation. Clinical, genomics and lipidomic data integration supports variant severity reclassification and emphasizes the value of biochemical biomarkers in late-onset lysosomal disorders.

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Palavras-chave: GM2 gangliosidosis AB variant, Lipidomic

Long-Term Follow-Up of a Patient with LCHAD Deficiency Submitted to Heart Transplantation due to Severe Cardiomyopathy

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Introduction

Long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency can lead to severe cardiomyopathy. Although there have been improvements in medical management, particularly with triheptanoin, patients may still progress to severe, refractory heart failure. Cardiac transplantation has been infrequently reported in individuals with fatty acid oxidation disorders.

Methods

We report a 32-year-old man with LCHAD deficiency diagnosed at age 4, presenting multisystem disease (pigmentary retinopathy, peripheral neuropathy, recurrent metabolic crises, dilated cardiomyopathy). Despite optimal therapy and triheptanoin, cardiac function declined. At 28, refractory cardiogenic shock required heart transplantation.

Results/Case report

Following transplant, the patient restarted his dietary protocol, triheptanoin, and immunosuppression with prednisolone, tacrolimus, and mycophenolate mofetil. He experienced several intercurrences, including acute renal failure requiring temporary dialysis, pericardial effusion, arterial access site complication, and severe critical illness myopathy. The patient was discharged two months post-transplantation and underwent prolonged intensive rehabilitation. His visual acuity deteriorated in the immediate post-transplant period, but it has remained stable since. He successfully completed orientation and mobility training and regained full independence in activities of daily living. Throughout the four-year follow-up, he had no significant episodes of metabolic decompensation or cardiac complications, including graft dysfunction. He remains clinically stable with good quality of life.

Conclusion

Cardiac transplantation was successful in our patient, with no significant cardiac or systemic complications at 4-year follow-up. This outcome suggests that transplantation may be a viable treatment option for patients with LCHAD deficiency and severe refractory cardiomyopathy.

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Palavras-chave: Long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency, Refractory cardiogenic shock, Heart transplantation

Critical Role of Determining Trans Configuration in Myopathic CPTII Deficiency for Accurate Genetic Counseling and Follow-Up

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Introduction

Carnitine Palmitoyltransferase II (CPTII) deficiency is a metabolic disorder of long-chain fatty acid oxidation. While the classic myopathic form is typically a biallelic condition, the specific p.Ser113Leu allelic variant is associated with exercise-induced myopathy even in the heterozygous state. Distinguishing between a simple carrier state and true compound heterozygosity is crucial, as variants´ phasing dictates the severity of the expected phenotype, risk of metabolic crises, necessity of lifelong clinical follow-up and genetic counseling for both the proband and at-risk relatives.

Methods

This case report was based on a review of the medical records of a patient and his first-degree relatives. Additional clinical data provided by the family included a medical report from a close relative not followed up at our institution. Informed consent was obtained.

Results/Case report

We present an 18-year-old male with recurrent exercise-induced myalgia, myoglobinuria and elevated serum creatine kinase, whose father had similar complaints. Gene panel identified two deleterious CPT2 heterozygous allelic variants (p.Ser113Leu and p.Arg296Gln). Initial parental segregation analysis was inconclusive, as the father carried both variants that were identified in the proband, while the mother carried only p.Ser113Leu. Only through a genetic report from a paternal aunt - who carried p.Arg296Gln in isolation - could we confirm that the father's variants were in trans configuration. This confirmed our proband's compound heterozygosity and was essential for establishing a definitive diagnosis and a tailored follow-up plan for the family.

Conclusion

This case highlights that identifying two variants in CPT2 is insufficient to diagnose a biallelic disorder without determining their phase; establishing trans configuration was the key to understand the patient's phenotype. It underscores the necessity of extended family segregation when parental studies are inconclusive to distinguish compound heterozygotes from complex heterozygotes. Given the clinical relevance, clarifying the genetic phase is vital for predicting disease progression and providing accurate genetic counseling.

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Acknowledgements

The authors thank the patient and his family for their collaboration and for granting permission to present this case report.

Palavras-chave: Carnitine Palmitoyltransferase II deficiency, CPT2, disorders of long-chain fatty acid oxidation, exercise-induced myopathy, genetic counseling

TANGO2 Deficiency: a Rare and Challenging Metabolic Disorder Presenting with Neurological Manifestations

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Introduction

Transport and Golgi Organization 2 (TANGO2) deficiency is a rare autosomal recessive metabolic disorder caused by pathogenic variants in the TANGO2 gene. (1) It is characterized by developmental delay, neurological impairment, and recurrent paroxysmal neurologic episodes (TANGO2 spells). (2) Patients are at risk of life-threatening metabolic decompensation, including rhabdomyolysis, hypoglycemia, and cardiac arrhythmias. No curative therapy exists; management is supportive, and B-complex vitamin supplementation may reduce the frequency or severity of metabolic crises. (2,3)

Methods

The patient underwent longitudinal multidisciplinary follow-up, including serial clinical, biochemical, genetic, neuroimaging, and neurodevelopmental assessments.

Results/Case report

We report a 3-year-old girl born at term after an uneventful pregnancy, with normal newborn screening and no relevant family history. Marked hypotonia was noted from 4 months of age. At 10 months, she presented with an afebrile generalized tonic–clonic seizure; cerebrospinal fluid studies and electroencephalogram were normal, and brain magnetic resonance imaging showed grade I periventricular hemorrhage. By 17 months, global developmental delay became evident, with axial hypotonia, hyperreflexia, motor impairment, stereotypies, and communication deficits. Extensive metabolic workup was unremarkable. Trio whole-exome sequencing identified biallelic pathogenic TANGO2 variants, establishing the diagnosis. At 3 years, she remained non-ambulatory, with unilateral exotropia and very frequent TANGO2 spells, occurring daily, mainly in the morning, characterized by clumsiness, falls, and fatigue, initially attributed to antiepileptic therapy. B-complex vitamin supplementation was started. No metabolic crises have occurred.

Conclusion

This case illustrates the diagnostic challenge of TANGO2 deficiency in the absence of overt metabolic crises and highlights how nonspecific neurological manifestations can mimic early-onset epilepsy or other neurological disorders. Early genetic diagnosis is crucial to enable cardiac surveillance, structured metabolic emergency planning, prevention of life-threatening arrhythmias, and regular thyroid function monitoring due to the risk of hypothyroidism. Timely diagnosis also supports genetic counseling, reproductive planning, and anticipatory multidisciplinary management.

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Palavras-chave: TANGO2 deficiency; inborn error of metabolism; lipid metabolism and transport; neurodevelopmental disorder

The Effect of FAD Supplementation on the Activity and Thermal Stability of the most common variant of medium-chain acyl-CoA Dehydrogenase

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Introduction

In the first step of mitochondrial fatty acid β-oxidation (mFAO), medium-chain acyl-CoA dehydrogenase (MCAD) converts medium-chain acyl-CoAs into trans-Δ2-enoyl-CoA, accepting electrons via its flavin adenine dinucleotide (FAD) cofactor. Functional MCAD assembled as FAD-containing homotetramers is reoxidized by the electron--transferring flavoprotein (ETF), linking mFAO to the respiratory chain.
MCAD deficiency (MCADD) is described as a conformational disorder. Impaired FAD incorporation observed in MCAD variants, including the prevalent p.K304E, is an underlying basis for MCADD's pathogenicity.

Methods

The effect of FAD supplementation on the structural and functional integrity of recombinant wild-type (WT) and p.K304E MCAD was studied by analyzing thermal stability, aggregation and activity (with artificial or natural electron acceptors), using different incubation times and temperatures.

Results/Case report

The p.K304E FAD content was 55 % of WT, confirming impaired cofactor incorporation during tetramer assembly. After 60 min incubation at 42 °C, MCAD p.K304E lost 45 % of the incorporated FAD (WT ≈ 28 %).
MCAD p.K304E thermal denaturation curves exhibit two transitions (Tm; 43.1 °C and 54.8 °C). FAD addition to the assay causes a concentration-dependent shift in the contribution of each transition, and Tm2 reaches WT-like values (~60 °C). The same was observed for the aggregation profile. Isothermal denaturation kinetics assays showed that FAD protects p.K304E from denaturation. FAD supplementation (25 μM) improved p.K304E's thermal stability and aggregation at 37 °C and 42 °C (more than 3 °C).
The p.K304E presented 65 % relative activity compared to WT (0.57 μmol DCPIP/min/mg). FAD supplementation did not restore enzyme activity to WT levels, but it reduced the loss of activity at 37 °C and 42 °C after 120 minutes of incubation (from ~25 % to 75 %).

Conclusion

Our results show that tetrameric p.K304E variant loses FAD at 42 °C but responds to cofactor supplementation. With 25 μM FAD, the stability parameters reach WT levels, and its activity loss over time is reduced at both 37 °C and 42 °C.
We postulate that MCADD phenotype variability can be related to FAD availability in the mitochondrial matrix. MCADD patients rely only on dietary control to avoid acute metabolic decompensation episodes. The use of riboflavin (FAD precursor) supplementation to increase FAD availability and complement the current MCADD treatment must be further investigated.
References (Limit number of references is 3. References must be identified by numbers between bracke

Acknowledgements
This work was supported by FEDER and Fundação para a Ciência e a Tecnologia, I. P., through iMED.ULisboa (Project UID/04138/2025; https://doi.org/10.54499/UID/04138/2025), research project 16047 (LISBOA2030-FEDER-00719600) and grant 2023.03088.BD (to Madeira C, https://doi.org/10.54499/2023.03088.BD)

Palavras-chave: Medium-chain fatty acids, mitochondrial β-oxidation, FAD status, medium-chain acyl-CoA dehydrogenase

How Effective Can One Carbon Be? – A Clinical Case

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Introduction

Background: Long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency (LCHADD) is a fatty acid oxidation disorder presenting with hypoketotic hypoglycemia, hepatopathy, cardiomyopathy, neuropathy, retinopathy and rhabdomyolysis triggered by fasting or illness. Management traditionally relies on fat restriction/limitation, high-carbohydrate intake, and medium-chain triglyceride (C6) supplementation. Triheptanoin (C7), an odd-chain triglyceride, offers an alternative energy source with anaplerotic benefits beyond conventional MCT therapy. We report clinical improvement following its use in an infant with LCHADD.

Methods

Case-Presentation: A 4-month-old female diagnosed by newborn screening (genotype) had failure to thrive, with frequent vomiting, axial hypotonia, and recurrent rhabdomyolysis with need of hospitalizations despite dietary therapy.

Results/Case report

Outcomes: Laboratory findings showed hypoketotic hypoglycemia, elevated transaminases(ALT 114U/L, AST 147U/L), and mild cardiomyopathy. Triheptanoin (35% of caloric intake) was initiated at 14 months with close follow-up.

After triheptanoin initiation, acute crisis and related hospitalizations decreased from three in three months to two per month, then one and finally none over six months. CK normalized, weight gain and activity improved, and cardiac function recovered. Mild gastrointestinal symptoms resolved within two weeks.

Conclusion

Triheptanoin bypasses defective long-chain fatty acid oxidation by providing acetyl-CoA and propionyl-CoA, supporting energy production and TCA cycle replenishment. In this patient, its supplementation led to marked clinical stabilization and improved quality of life, consistent with emerging evidence. Although long-term neurodevelopmental outcomes remain uncertain, early use of triheptanoin may reduce metabolic crises and disease burden in severe LCHAD phenotypes.

Overall, this case emphasizes the importance of early diagnosis, strict nutritional management, and timely introduction of novel therapies such as triheptanoin. A multidisciplinary approach remains crucial for optimizing outcomes and quality of life in LCHADD patients.

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Palavras-chave: LCHADD, triheptanoin, fatty acid oxidation disorder, inborn errors of metabolism
Intermediary metabolism: nutrients | Clinical trial

Treatment of Glucose Transporter 1 Deficiency With a Ketogenic Diet: from Concept to Practice 1-Faculdade de Medicina da Universidade De Coimbra, Portugal

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Introduction

Glucose transporter type 1 deficiency syndrome (GLUT1-DS) is a rare neurometabolic disorder (OMIM #606777) primarily caused by autosomal dominant pathogenic variants in the SLC2A1 gene. Patients exhibit a variety of neurological symptoms, including epilepsy, neurodevelopmental delay, movement disorders, and microcephaly. The current diagnostic approach primarily relies on clinical suspicion and genetic testing. The ketogenic diet (KD), which overcomes brain energy deficiency is the first-line treatment. Patients and families should receive support from a specialized interdisciplinary team.

Methods

We performed a retrospective review of the clinical manifestations, treatment implementation, adherence to diet, and evolution of five unrelated paediatric patients with GLUT1-DS who were followed at our centre.

Results/Case report

The patients presented with developmental delay (n=4), movement disorders (4), and seizures (2). The age at onset/diagnosis ranged from four to 14 months and from 22 to 54 months, respectively. The mean diagnostic delay was 24 months. Brain MRIs were normal in all patients. Genetic studies confirmed the diagnosis and revealed de novo pathogenic variants in three out of five. Hypoglycorrhachia was observed in the two patients who underwent lumbar puncture. All patients were prescribed the classic KD, which varies from 1,65-2,5:1. KD therapy required dietary preparation, introduction of new foods/ supplements and control, including home capillary ketonemia testing. This approach led to clinical improvement in four patients who adhered to the diet, although ketonemia frequently remained below 2 mmol/L. No significant secondary effects were observed (KD therapy duration two to 17 years).

Conclusion

As the clinical presentation is nonspecific, raising awareness of GLUT1-DS among healthcare professionals and the public is crucial for a timely diagnosis. KD therapy should be started as soon as possible, even pre-symptomatically. Adhering to a restrict diet for life is difficult. It requires significant dedication from family and disrupts their routine. By the time of diagnosis, most children have established feeding habits and neurodevelopmental issues, which reduces adherence. Success requires strong commitment from both the family and the multidisciplinary team.

Palavras-chave: Glucose Transporter Type 1 Deficiency Syndrome, Epilepsy, Ketogenic Diet, Movement Disorders

Betaine as an option for the Treatment of Aspartylglucosaminuria: A Case Report

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Introduction

Aspartylglucosaminuria (AGU) is a neurodegenerative lysosomal storage disorder caused by a deficiency of aspartylglucosaminidase (AGA).(1) It is characterized by slowly progressive developmental delay (DD), leading to severe intellectual disability in early adulthood. No curative therapies are currently available. Betaine (trimethylglycine) acts as a pharmacological chaperone and has been shown to increase AGA activity in fibroblasts harboring certain pathogenic missense variants.(2) We report a pediatric AGU patient treated with betaine for three years.

Methods

The patient underwent serial clinical, biochemical and neuropsychological assessments at baseline and during therapy. Plasma methionine levels were monitored throughout the treatment.

Results/Case report

A 3-year-old boy presented with DD, hearing loss, and coarse facial features. The full clinical picture included recurrent otitis media, diarrhea, gingival hypertrophy, macroglossia, and umbilical hernia. Whole-exome sequencing identified two heterozygous variants in AGA gene: c.280G>C (p.Gly94Arg), classified as uncertain, and c.503G>A (p.Trp168*), classified as pathogenic. Segregation analysis confirmed the variants were in trans. AGA activity was markedly reduced in fibroblasts and undetectable in serum. The overexpressed p.Gly94Arg variant showed no AGA activity in HEK293T AGA-knockout cells in vitro. Thus, it was possible to reclassify p.Gly94Arg into likely pathogenic, confirming the diagnosis of AGU.
At 5 years of age, betaine was initiated at 100 mg/kg/day and titrated to 200 mg/kg/day. After 3 years of therapy, developmental gains were observed without relevant adverse effects.

Conclusion

This case supports the pathogenicity of the c.280G>C (p.Gly94Arg) variant.
Betaine has been shown to be safe and well tolerated in a phase 1b/2 clinical trial in AGU patients homozygous for the AGUFin-major missense variant, increasing serum AGA activity.(3) It was linked to an improvement in some domains of the Wechsler's Intelligence Scale for Children IV.(3) Our patient seemed to improve after starting betaine; however, longer follow-up is required to better define therapeutic efficacy.

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Palavras-chave: Aspartylglucosaminuria, Betaine, Lysosomal storage disorders

POP15

Imaging Patterns in Cholesterol Metabolism Disorders With Neurological Involvement: The Examples Of SPG5 and CTX

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Introduction

Hereditary spastic paraplegia type 5 (SPG5A) and cerebrotendinous xanthomatosis (CTX) are two cholesterol metabolism disorders with significant neurological involvement, usually with spastic paraparesis and/or ataxia. Although the imaging pattern in CTX is known, mainly with posterior cerebral and cerebellar dentate nuclei hyperintensities [1], there is scarce description about specific brain imaging in SPG5A, probably owing to the rarity of the disease [2].

Methods

Clinical and brain MRI imaging description of our SPG5A and CTX cohorts and brief literature review of imaging findings in these disorders.

Results/Case report

SPG5A patients (2F, 46 and 56-years-old), presenting with early-onset spastic paraparesis, had white matter periventricular T2 hyperintensities, mostly posterior. The five CTX patients (3F/2M, ages between 44 and 62 years), all in whom symptoms included spastic paraplegia, had varying degrees of white matter disease. 4 had mostly posterior periventricular T2 hyperintensities (some reaching into the optic radiations) and 3 had cerebellar dentate nuclei T2 hyperintensities. Although CYP46A1 is the most important brain cholesterol hydrolyser [3], it is followed by CYP7B1 (implicated in SPG5A) and CYP27A1 (implicated in CTX) [4]. CYP27A1 has been found to be relatively more expressed in the cerebellum and occipital lobes [5], versus CYP46A1, and its products need further oxidizing by CYP7B1 [6].

Conclusion

Cerebral white matter disease in CTX and SPG5A may localize preferably to the posterior compartment (besides the already known cerebellum involvement in the case of CTX). Differential expressions of CYP27A1 across the central nervous system and a shared metabolic pathway may explain this similar imaging pattern in both diseases.

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Palavras-chave: SPG5A, Cerebrotendinous xanthomatosis, Cholesterol, Imaging

Early Diagnosis and Clinical Outcomes in Tyrosinemia Type I

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Introduction

Tyrosinemia type I (HT1) is a rare autosomal recessive disorder caused by fumarylacetoacetate hydrolase deficiency, leading to accumulation of toxic metabolites and progressive liver and renal damage. The disease is associated with an increased risk of hepatocellular carcinoma. Early diagnosis and prompt initiation of nitisinone have markedly improved prognosis.

Methods

We conducted a retrospective review of four pediatric patients diagnosed with HT1 at our center between 2000 and 2025. Clinical presentation, biochemical findings, genetic data, treatment strategies, and outcomes were analyzed.

Results/Case report

Currently aged 16–25 years, four patients (2 males) were diagnosed at a median age of 43 days (range 28–75). Two were identified due to high tyrosine in newborn screening with asymptomatic liver dysfunction, while the remaining presented with acute liver dysfunction. All patients had elevated plasma tyrosine and detectable succinylacetone at diagnosis. Pathogenic variants in the FAH gene were confirmed. Nitisinone therapy and a tyrosine and phenylalanine restricted diet were initiated promptly after diagnosis. The oldest patient developed progressive liver failure requiring liver transplantation. All patients have a successful academic trajectory, although one presents a lower intellectual level.

Conclusion

This series underscores the impact of early diagnosis on the clinical course of HT1. Patients identified at younger ages had milder presentations, whereas delayed diagnosis was associated with liver failure and need for transplantation. As HT1 is included in the panel of diseases screened in Portugal within the National Neonatal Screening Program, early detection allows timely initiation of nitisinone and dietary treatment, improving clinical prognosis.

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Acknowledgements

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Sapropterine Loading Test Responsiveness – Experience of a Reference Centre

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Introduction

In responsive patients, sapropterin dihydrochloride, a synthetic form of the phenylalanine hydroxylase cofactor tetrahydrobiopterin, reduces blood phenylalanine (Phe) levels and increases natural protein dietary tolerance in phenylketonuria (PKU) patients.

Between 2015 and 2016, seventy-nine patients followed at a Portuguese Reference Centre and aged >4 years, completed a 48-hour sapropterin loading test (S-LT) to assess synthetic cofactor responsiveness. A positive response was defined as a ≥30% reduction in blood Phe from baseline. Clinical response was review at the end of 2018.

Methods

Retrospective review of clinical and laboratory data extracted from medical and nutritional records of PKU patients, with a positive S-LT and treated with sapropterin, between 2015 and 2018. Disease severity was classified by blood Phe levels at newborn screening, according to Portuguese guidelines.

Results/Case report

Among the 79 patients who completed the S-LT, 36 demonstrated a positive response (30–74% Phe reduction), and 33 initiated sapropterin at 20 mg/kg/day. Two patients did not start treatment due to pregnancy and one had adherence compromised by comorbidities.

Over time, only 17 patients (82% female; 13 mild PKU, 4 classical PKU; median age 17 years, range 8–34) were confirmed as true clinical responders and continued long-term treatment.

In this patients, mean natural protein intake increased significantly from 0.61 ± 0.25 to 0.96 ± 0.24 g/kg/day ($p < 0.001$), mean phenylalanine intake increased from 1271 ± 565 to 2426 ± 884 mg/day ($p < 0.001$), and mean protein substitute intake decreased from 1.11 ± 0.34 to 0.69 ± 0.36 g/kg/day ($p < 0.001$). Median annual blood Phe levels decreased from 6.9 (5.9–8.1) mg/dl to 5.8 (4.8–6.3) mg/dl ($p = 0.002$). Blood Phe remained within target range 89% of the time.

True responders remained on sapropterin therapy at a median dose of 15 mg/kg/day (range 11–20 mg/kg/day).

Conclusion

Following a positive 48-hour S-LT, long-term responsiveness should be confirm by demonstrating an increase in natural protein intake while maintaining blood Phe level within the therapeutic range.

Of the initial potential responders, 52% were confirmed as true responders, predominantly patients with mild phenotypes, although some had classical PKU. Sapropterin therapy increased dietary Phe tolerance, allowing for a more liberalized diet; however, most patients continued to require some degree of dietary restriction. Overall, blood Phe concentrations remained within the recommended target ranges.

Acknowledgements

We thank Doutor Júlio César Rocha for his work and collaboration in the evaluation of sapropterin responsiveness among PKU patients followed at the Reference Center of Inherited Metabolic Diseases - ULS Santo António, between 2015 and 2017.

Neonatal Cardiac Presentation of Coenzyme-A Synthase Deficiency Protein-Associated Neurodegeneration (CoPAN)

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Introduction

Coenzyme-A Synthase (COASY) protein-associated neurodegeneration (CoPAN) is a rare autosomal recessive disorder of Coenzyme A (CoA) biosynthesis. It is caused by biallelic pathogenic variants in the COASY gene. CoA deficiency impairs multiple metabolic pathways, including fatty acid oxidation, mitochondrial energy production, and phospholipid metabolism. While described as a childhood-onset neurodegeneration with brain iron accumulation (NBIA), neonatal presentations of CoPAN are poorly characterized and cardiac involvement has not yet been reported.

Methods

We present the case of a newborn who was referred from the Neonatal Screening Programme due to suspicion of Carnitine-Palmitoyl Transferase1(CPT1) deficiency, while she was in the ICU due to cardiac problems. The final diagnosis of CoPAN enabled early phenotype characterization.

Results/Case report

A term female presented on day 6 with bradycardia, ST-T abnormalities and pericardial hyperechogenicity. Septic workup was negative. Newborn screening showed an acylcarnitine profile suggestive of CPT1 deficiency. Symptomatic treatment and specific diet led to clinical improvement. At 4 months, limb hypertonia was noted. Brain MRI showed symmetric T2/FLAIR hyperintensity and marked diffusion restriction in putamina, caudate nuclei, thalami, and diffuse cortical swelling. Genetic study identified compound heterozygous COASY variants, c.1403_1404dup p.(Ile469*) and c.1495C>A p.(Arg499Ser), confirming CoPAN. At 3 years she presents global developmental delay, lower limb spasticity and epilepsy. She is on normal diet, riboflavin and pantothenic acid. Subsequent MRI showed persistent basal ganglia abnormalities and new T2* hypointensities in globus pallidus, indicating evolving iron deposition.

Conclusion

This case expands CoPAN phenotype to cardiac involvement. The transient cardiac manifestations, resolved with symptomatic treatment and long-chain fatty acid restriction, might be caused by energy failure due to CoA deficiency. This accounts for the abnormal carnitine profile, previously described in CoPAN, and led to diagnosis before significant neurological symptoms occurred, deciphering the early neuroimaging signature of this progressive disorder. Early presentation and the carnitine profile were crucial for genetic diagnosis and counselling and for optimizing multidisciplinary management.

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Acknowledgements
The authors thank the patient's family for their cooperation and the multidisciplinary team involved in her care.
Palavras-chave COASY, Coenzyme A, Leukoencephalopathy, Brain MRI, Pericardial hyperechogenicity

The Experience of Peer Loss: a Dimension of Complexity in Neurometabolic Diseases

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Introduction

Neurometabolic diseases are rare conditions with a chronic course, often disabling and progressive. Despite therapeutic advances, clinical and care-related complexity remains significant. Decoding this complexity requires recognizing psychosocial and relational dimensions of care2. In prolonged therapeutic contexts, interpersonal bonds between peers may acquire direct clinical relevance, potentially influencing the experience of the disease itself. Relational loss constitutes an event with potential emotional and functional impact on the lived experience of disease and within the care setting1.

Methods

Descriptive qualitative study based on case reports of patients with progressive neurometabolic diseases. Thematic analysis of narratives on peer loss in therapeutic settings, complemented by a narrative review of the literature on care complexity and humanization.

Results/Case report

In neurometabolic diseases, peer loss is rarely studied, yet it significantly affects the care experience.
1. FD, 27 years old, with MPS IV, developed a close relational bond with JA, 50 years old, with MPS VI. They shared frequent interactions in the therapeutic setting, described as meaningful "we had coffee together at lunchtime"; "we talked about many topics". JA's sudden death triggered acute psychological distress and altered FD's experience of treatment.
2. FC, 29 years old, and her 58-year-old caregiver, followed since childhood due to FC's Pompe disease, maintained a bond with JV, 25 years old, with MPS I, and his caregivers during therapeutic encounters. Following JV's progressive decline and death, FC and her caregiver experienced significant emotional impact, marked by profound sadness.
The literature suggests that peer loss among individuals with similar clinical experiences may precipitate profound grief, compromise psychological well-being, and increase support needs, underscoring its relevance as a major source of suffering[1]

Conclusion

The cases highlight the relevance of interpersonal relationships within therapeutic settings and the need for early recognition of the impact of relational loss. In progressive neurometabolic diseases, such loss represents a critical dimension of clinical complexity[2]. Decoding this complexity enables innovation in care by integrating multi-disciplinary support, humanizing assistance, and preserving the dignity, quality of life, and emotional wellbeing of patients and caregivers, even in the face of the disease's inevitable progression[3].
True innovation in care integrates scientific rigor, humanization, and insight into the psychosocial impact inherent to the care process.

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Acknowledgements
To the multidisciplinary team of the Reference Centre for Inherited Metabolic Diseases (CR DHM) at ULS Coimbra, for their commitment to integrated models of care.
To the patients and caregivers, for their trust and for authorizing the scientific sharing that inspired this work.

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Palavras-chave: Neurometabolic diseases, Humanization, Relational loss, Innovation

Cognitive Decline in a Gaucher Patient

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Introduction
The aging of adults with hereditary metabolic disorders presents multiple clinical challenges. Cognitive decline in this population may be directly or indirectly related to the underlying metabolic condition, particularly when there is central nervous system involvement. Therefore, a systematic and comprehensive evaluation of all possible aetiologies is essential. Important clinical insights can be gained through a thorough and multidisciplinary approach.

Methods
51 years old patient with a Gaucher disease type 1 (OMIM#230800; ORPHA 77259). He presents with well controlled diabetes mellitus type 2, arterial hypertension and important co-morbidities related with Gaucher and included a severe bone disorder (short stature, kyphosis), chronic hepatic disorder with partial portal thrombosis, and MGUS.

Results/Case report
A cognitive decline was observed by the family with an impact in daily life tasks. an extensive and comprehensive study was performed until the final diagnosis.

Laboratory investigations excluded common and potentially reversible causes of cognitive decline. Brain MRI revealed a multiple T2/FLAIR hyperintensities, multifocal, confluent and dispersed within the white matter of both cerebral hemispheres, without diffusion restriction, attributable to chronic microangiopathic ischemic changes. Focal lacunar ischemic lesions found also in striato-capsular, bilateral thalamic regions, pons and cerebellum. Multiple hypointense foci on T2/SWI, distributed across the cerebral hemispheres and bilateral cerebellum, are indicative of previous small haemorrhages.

CSF evaluation excluded infectious/inflammatory, autoimmune and amyloid causes. Cerebral angiography was normal. PET scan showed no amyloid deposition.
A NGS for small vessel disease was performed and a pathologic mutation was found in NOTCH3 was found.

Conclusion
The presentation of cognitive decline associated with diffuse microangiopathy, cerebral microbleeds, and brain atrophy in this patient represented a challenging diagnostic puzzle. After excluding comorbidity-related causes and Gaucher disease as potential contributors, a rational and systematic evaluation led to the diagnosis of CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy). A therapeutic trial with rivastigmine resulted in improvement in daily functional performance. This case highlights the coexistence of two rare genetic disorders in the same patient, each requiring distinct and targeted medical management.

Palavras-chave: Gaucher, dementia

Ornithine Transcarbamylase Deficiency In Females: Diverse Presentations, Shared Neurocognitive Burden

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Introduction

Ornithine transcarbamylase deficiency (OTCD) is the most common urea cycle disorder, with X-linked inheritance. In females, random X-chromosome inactivation produces a highly variable phenotype, ranging from asymptomatic carriers to life-threatening hyperammonemic encephalopathy. We report four females with OTCD presenting distinct clinical phenotypes, highlighting the span of expression and the shared neurocognitive burden of this condition.

Methods

Retrospective study of clinical, biochemical, brain magnetic resonance imaging (MRI) and neuropsychological data from a cohort of four females, ages 10-51 years old (yo), with OTCD followed at a Reference Centre for Inherited Metabolic Diseases.

Results/Case report

Case 1, 10yo, diagnosed at 18months (m), hemiparetic metabolic stroke-like, ammonia 276µmol/L, bilateral cortico-subcortical fronto-temporo-parietal T2/FLAIR hyperintensities on MRI; treated with protein restriction, L-citrulline, sodium benzoate, phenylbutyrate; refractory epilepsy, intellectual disability, deficits in visuospatial organisation and verbal memory. Case 2, 24yo, diagnosed at 19m, Reye-like syndrome, ammonia 79µmol/L, normal MRI; treated with protein restriction and sodium benzoate, chronic mild intellectual disability, executive dysfunction, emotional lability. Case 3, 29yo, diagnosed at 29yo after affected son; lifelong protein aversion and postprandial nausea; ammonia 51µmol/L; self-reported working memory deficits. Case 4, 51yo, diagnosed at 32yo after affected son; lifelong protein aversion, ammonia 49µmol/L, white matter lesions on MRI; poor dietary adherence; chronic executive dysfunction, depression, anxiety.

Conclusion

OTCD in females encompasses a broad phenotypic spectrum, from subtle protein aversion to devastating metabolic encephalopathy. Across all cases, neurocognitive impairment emerged as a persistent and functionally significant sequela, independent of initial presentation severity. These cases underscore the need for structured long-term follow-up of females with OTCD, familiarity with the full phenotypic spectrum, and a low threshold for diagnostic suspicion and initiation of treatment, even in the absence of overt hyperammonemic crises.

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Palavras-chave: Ornithine transcarbamylase deficiency, Neurocognitive impairment, Phenotypic variability, Heterozygous females, Urea cycle disorders

Fairy-Tale Cells, Real Disease: Stem Cells from Human Exfoliated Deciduous Teeth Take on MPS IIIC

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Introduction

Mucopolysaccharidosis type III (MPSIII) is a life-threatening, neurodegenerative lysosomal storage disorder with no treatment available. A major obstacle to therapeutic development is the lack of models that accurately recapitulate the neurological phenotype. Stem cells from human exfoliated deciduous teeth (SHEDs), due to their neural crest origin (1), are a promising in vitro model with the potential to mimic these disease-relevant features. Here, we report the characterization of an MPS IIIC SHED cell line, the most recent line generated within "The 2020s Tooth Fairy Project".

Methods

Stemness was assessed by qRT-PCR and 3 germ layer differentiation. Genetic variants were analysed by Sanger Sequencing at both gDNA and cDNA levels. HSGNAT activity was measured fluorometrically, and heparan sulfate levels assessed by immunoflorescence, western blot and LC-MS/MS. Lysosomal distribution was evaluated by LAMP1 staining.

Results/Case report

The MPS IIIC SHED cell line met all International Society for Cell and Gene Therapy (2) criteria for Mesenchymal stem cell (MSC), expressing CD73, CD90, and CD105, showing low or absent CD34 and HLA-DR. Pluripotency markers SOX2, OCT4, and NANOG were also expressed. At the molecular level, two heterozygous variants were identified: c.372-2A>G, producing the expected abnormal transcript, and the novel c.837_838delCC, generating a shorter transcript lacking exons 9 and 10. Consistent with the MPS IIIC phenotype, the SHED cell line exhibited significantly reduced HGSNAT activity and increased heparan sulfate levels, accompanied by elevated LAMP-1 signal intensity.

Conclusion

Overall, these findings support the modeling potential of our MPS IIIC SHED cells, confirming their MSC identity and key phenotypic features. Now, we want to explore their therapeutic potential, in light of the benefits historically seen with hematopoietic stem cell transplantation in MPSs. Given the value of central nervous system-derived cells for ex vivo gene therapy in neurodegenerative diseases (3), we aim to use this cell line for ex vivo gene editing using prime editing. With this in mind, we are currently generating an induced pluripotent stem cell line as an isogenic control.

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Acknowledgements

This work was financed by national funds through FCT – Fundação para a Ciência e a Tecnologia, I.P., within the scope of two independent projects: EXPL/BTM SAL/0659/2021 (http://doi.org/10.54499/EXPL/BTM-SAL/0659/2021) and ASOS2cureMPSIII--2022.04667.PTDC (https://doi.org/10.54499/2022.04667.PTDC). The authors would also like to thank the Center for the Study of Animal Science and Associate Laboratory for Animal and Veterinary Sciences, as well as National Institute of Health Doutor Ricardo Jorge (INSA). MBA acknowledges FCT – Fundação para a Ciência e a Tecnologia, I.P. for the PhD fellowship (2025.07188.BDANA).

Palavras-chave: Mucopolysaccharidosis type III (MPSIII), Stem cells from human exfoliated deciduous teeth (SHEDs), Disease modelling, Ex vivo gene therapy

Nutritional Management During Pregnancy in a Patient With Maple Syrup Urine Disease (MSUD): A Clinical Case Report

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Introduction

Maple Syrup Urine Disease (MSUD) is a rare autosomal recessive inborn error of metabolism caused by deficiency of the branched-chain α-ketoacid dehydrogenase complex, leading to accumulation of leucine, isoleucine and valine and risk of metabolic crises. Management is based on lifelong natural protein restriction and supplementation with a BCAA-free formula, with regular biochemical monitoring. Estimated incidence is 1:185,000 live births. Pregnancy requires strict metabolic control to prevent maternal decompensation and adverse fetal outcomes.1-4 This study reports a clinical case.

Methods

Plasma amino acids were monitored weekly, focusing on leucine. Diet was adjusted to biochemical and clinical evolution, with controlled natural protein and BCAA-free formula, ensuring adequate gestational energy. Emergency parenteral nutrition and a hypoproteic vegan diet were used when indicated.3

Results/Case report

A 28-year-old woman with classical MSUD, anxiety and mild cognitive impairment was on a hypoproteic diet with BCAA-free formula. Preconception leucine was within the therapeutic range despite irregular adherence to diet. Plasma amino acids were monitored weekly. In the first trimester, leucine transiently exceeded targets but later stabilized after dietary adjustments. Fetal growth was regularly monitored to ensure proper development. Gestational weight gain was appropriate. The nutritional plan was adjusted with increased meal frequency, reinforcing carbohydrates and increasing BCAA-free formula dosing to compensate their nutritional needs. At 38 weeks, during labor induction, parenteral nutrition was started to prevent catabolic stress. Oral feeding resumed 12h postpartum and parenteral nutrition was stopped after 48h due to metabolic stability and good adherence to the diet.

Conclusion

Intensive metabolic monitoring and dynamic adjustment of nutritional therapy enabled prevention of metabolic decompensation, ensured recommended gestational weight gain, and supported healthy fetal growth. Pregnancy in a woman with classical MSUD is exceptionally rare, and this case underscores the essential role of a multidisciplinar team, individualized protocols, specialized nutritional follow-up, meticulous peripartum planning, and continuous monitoring to optimize maternal and fetal outcomes, contribute to evidence-based practice, and guide future management of such high-risk pregnancies.

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Palavras-chave: MSUD, pregnancy, nutrition therapy, parental nutrition, maple syrup urine disease, classical MSUD, BCAA-free formula

Adult-Onset Erythropoietic Protoporphyria: A Case Report

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Introduction

Erythropoietic protoporphyria (EPP) is an autosomal recessive disorder predominantly resulting from pathogenic variants in the FECH gene, which encodes the mitochondrial enzyme ferrochelatase. Deficiency of this enzyme impairs the final step of heme biosynthesis, leading to the accumulation of protoporphyrin IX within erythrocytes, hepatocytes, and other tissues. Clinically, EPP is characterized by acute cutaneous photosensitivity, typically manifesting in early childhood. This case reports a male with the inaugural diagnosis of erythopoietic protoporhyria at 50-year-old.

Results/Case report

A 50-year-old male presented with arthralgia and recurrent cutaneous lesions predominantly affecting the trunk and upper limbs, accompanied by fever. He was admitted to the hospital with a presumptive diagnosis of sepsis secondary to atypical mycobacterial infection, which was subsequently confirmed. During his hospital stay, it was observed that the cutaneous lesions were confined to areas of the body exposed to light. Given the clinical suspicion of porphyria, genetic testing was performed, identifiyng heterozygous variants c.68-23C>T and c.315-48T>C in the FECH gene, consistent with functional polymorphisms associated with EPP. Laboratory test demonstrated increased levels of free protoporphyrin IX and heightened peak fluorescence emission, corroborating the diagnosis. The patient underwent treatment with ursodeoxycholic acid, resulting in normalization of the values.

Conclusion

Adult-onset EPP is rare and can mimic acquired forms related to hematologic disorders, in which clones of cells with mutated ferrochelatase expand in the setting of the myelodysplastic or myeloproliferative syndrome. This case underscores the need to consider EPP in adults with compatible symptoms, even without myelodysplastic syndrome. Early recognition and targeted genetic and biochemical testing are crucial for accurate diagnosis and management, enabling timely intervention and improved patient outcomes.

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When Iron–Sulphur Cluster Biogenesis Fails: Three Neonatal Cases of Lethal Multiple Mitochondiral Dysfunction Syndromes

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Introduction

Neonatal encephalopathy with respiratory failure and leukodystrophy presents a diagnostic race against time. Multiple mitochondrial dysfunction syndromes (MMDS) are ultra-rare disorders of iron–sulphur cluster assembly, described only since 2011, with fewer than 150 cases worldwide. We report three neonates whose parallel clinical deterioration revealed distinct MMDS subtypes, illustrating how early genomic diagnosis reshapes prognosis, care planning and family counselling in catastrophic mitochondrial disease.

Methods

All infants underwent metabolic screening, serial neuroimaging, mitochondrial vitamin supplementation trials and rapid trio whole-genome sequencing. Multidisciplinary management involved metabolic medicine, neurology, cardiology, intensive care, genetics and palliative care services.

Results/Case report

Patient 1, a 4-month-old infant, presented with apnoea, pulmonary hypertension and neuroregression. MRI showed diffuse leukodystrophy with symmetric diffusion restriction. Genome sequencing identified a homozygous pathogenic NFU1 variant, confirming MMDS1. Pulmonary hypertension was refractory and care was redirected.

Patient 2, a term neonate, developed encephalopathy and ventilator-dependent apnoea. MRI demonstrated progressive symmetric corticospinal and brainstem involvement. Genetic testing revealed a likely pathogenic IBA57 variant, consistent with MMDS3.

Patient 3, a 6-week-old infant with parental consanguinity presented with apnoea, metabolic acidosis and hyperlactataemia. MRI showed corticospinal tract and brainstem involvement with lactate and glycine peaks on spectroscopy. A homozygous pathogenic ISCA2 variant confirmed MMDS4. All infants died in early despite maximal supportive care.

Conclusion

These cases demonstrate how MMDS transforms an initially opaque neonatal crisis into a molecularly defined diagnosis with profound prognostic implications. Early genomic identification enables realistic counselling, avoids futile escalation, and supports ethically grounded redirection of care. Recognising MMDS is therefore essential to precision medicine, compassionate practice and responsible decision-making in neonatal mitochondrial disease.

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We thank the patients' families for their courage and trust, and the multidisciplinary metabolic, neurology, intensive care, cardiology, genetics and palliative care teams involved in their management.

Palavras-chave: Multiple mitochondrial dysfunction syndromes, Iron–sulphur cluster biogenesis, Mitochondrial disease, Neonatal encephalopathy, Whole-genome sequencing, Pulmonary hypertension, Leukodystrophy, NFU1, IBA57, ISCA2

Reanalysis Matters: Impact of Exome Reinterpretation in a Patient with Long-Term Suspicion of a Mitochondrial Disease

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Introduction

Primary mitochondrial diseases are clinically heterogeneous disorders caused by genetic pathogenic variants affecting oxidative phosphorylation. Isolated complex I deficiency is the most common respiratory chain defect and is typically associated with early-onset neurological impairment and Leigh spectrum features. The FOXRED1 encodes a complex I assembly factor and pathogenic variants in this gene are a rare cause of autosomal recessive isolated complex I deficiency. Molecular confirmation may be challenging despite suggestive biochemical findings.

Methods

Clinical, metabolic, neuroimaging, enzymatic and genetic data were retrospectively reviewed. Investigations included metabolic profiling, brain MRI/H1MRS, muscle respiratory chain enzymology and extensive genetic testing, including blood and muscle mtDNA and whole exome sequencing with reanalysis.

Results/Case report

A 17-year-old female presented, at 7 months, with strabismus, hypotonia, failure to thrive and developmental delay. At 12 months she had protracted vomiting. Investigation showed persistent moderate hyperlactatemia, elevated lactate/pyruvate ratio and intermittent mild organic aciduria. Given suspicion of mitochondrial disease, a muscle biopsy was performed at 4 years of age, revealing isolated complex I deficiency. Brain MRIs at 9 and 14 years old were normal; H1MRS showed lactate peaks at 9 years of age. She subsequently developed progressive gait imbalance, generalized chorea, axial dystonia, epilepsy and persistent vomiting. Extensive genetic testing, including WES (2021) was negative. Reanalysis in 2025, taking into account the updated databases, allowed identification of the compound heterozygous variants in FOXRED1 (c.612_615dup p.(Ala206Glufs*15) and c.920G>A p.(Gly307Glu)), confirming the diagnosis of isolated complex I deficiency (OMIM#618241; ORPHA:2609).

Conclusion

This case illustrates the diagnostic odyssey to which patients with mitochondrial disease or other rare, complex disorders are prone, as well as the progressive neurological phenotype associated with FOXRED1-related complex I deficiency. It highlights the diagnostic value of multidisciplinary teams, integrating clinical, biochemical, enzymatic and genetic approaches, and underscores the pivotal role of genetic reanalysis in unresolved cases. Such systematic reanalysis can transform unsolved metabolic disorders into genetically defined conditions, refining prognosis, recurrence risk (25%) and family counselling.

Acknowledgements

The authors thank the patient's family for their cooperation and the multidisciplinary team involved in clinical care. We also gratefully acknowledge Luísa Diogo, MD, PhD, for critical revision of the manuscript and valuable contributions to this work.

Metachromatic Leukodystrophy: Silently Approaches its Prey Like a Tiger

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Introduction

Metachromatic leukodystrophy (MLD, OMIM #250100) is a rare lysosomal storage disorder. It is suspected when a patient exhibits motor and cognitive decline alongside characteristic brain MRI findings, such as the "tigroid" pattern. Biochemically, MLD is characterized by decreased activity of the enzyme arylsulfatase A, and genetically, it results from pathogenic variants in the ARSA gene. With the recent approval of new treatments, early identification of pre symptomatic individuals has become increasingly important to increase the awareness for this devastating disorder.

Methods

The authors will present the casuistic of ULSSA Inborn Errors of Metabolism Reference Center between 2008 and 2025.

The work will include clinical (age, gender, and detailed medical history, clinical manifestations); biochemical, genetic data and symptoms management.

Results/Case report

This cohort descrive nine patients: six are male; only two patients are alive (one infantile form, recently diagnosed and the adult form). Five patients had late infantile form and three patients had juvenile form and one adult form. Those 5 patients were diagnosed during the second year of life presenting walking deterioration, followed by a general regression, especially difficulty in feeding. By the final of second year were severely handicap, with difficult pain management and death occurred before 5 years of age. The 3 juvenile MLD patients presented motor, cognitive, and behavioral symptoms and death occurred before 15 years of age. The adult MLD (4 decade of life) initial presentation included cognitive decline along with psychiatric and mood changes. Palliative care was essential in all cases to ease the burden of the rapid neuro-regression.

Conclusion

MLD is now a possible treatable neurometabolic disease in pre symptomatic patients. This opens a new possibility of including this disorder in the newborn screening. This is especially important, as clinical evolution of patients diagnosed symptomatically is catastrophic, leading to severe disease burden in families and professionals.

Palavras-chave: Metachromatic leukodystrophy

Holocarboxylase Synthetase Deficiency and Cancer: Causality Or Coincidence?

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Introduction

Holocarboxylase synthetase (HCS) deficiency is a rare autosomal recessive disorder of the biotin cycle leading to multiple carboxylase deficiency. Impaired biotin attachment reduces the activity of biotin-dependent carboxylases, disrupting fatty acid metabolism, gluconeogenesis, and amino acid catabolism. Clinical presentation is heterogeneous, with onset from the neonatal period to school age. We present a case identified through newborn screening responsive to biotin.

Methods

Results/Case report

A 1-month-old asymptomatic boy was referred after elevated 3-hydroxyisovalerylcarnitine on newborn screening (1.2 µM; reference <0.57 µM). Biotin (10 mg/day) was initiated with good biochemical response. Genetic testing confirmed HCS deficiency. He remained on biotin (10–20 mg/day) and carnitine. Neurodevelopment was normal until age 2, when speech delay was noted. At 11 years, he was diagnosed with attention-deficit/hyperactivity disorder and specific learning disorder. At 17 years, he developed a unilateral testicular tumor and underwent radical orchiectomy followed by chemotherapy. No metabolic decompensation occurred. He is currently 18 years old, cancer-free and metabolically stable.

Conclusion

Early detection and continuous biotin supplementation were associated with sustained metabolic control and favorable long-term outcome, even under significant catabolic stress such as chemotherapy. The diagnosis of testicular cancer raises questions regarding possible metabolic or therapeutic interactions; however, current evidence does not support a causal association, suggesting a coincidental finding.

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Palavras-chave: Holocarboxylase Synthetase Deficiency, Cancer, Biotin

Optimizing Access to Care in Inherited Metabolic Diseases Through Telemedicine: Clinical Outcomes, Socio-Economic Impact, and Organizational Implications From a Reference Center

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Introduction

Telemedicine is defined as the delivery of healthcare services through remote electronic interfaces, either synchronously or asynchronously (1). It represents a strategic tool for chronic and rare diseases such as inherited metabolic diseases (IMDs), which require highly specialized, multidisciplinary management typically concentrated in tertiary urban centers. When appropriately implemented, teleconsultation (TC) allows faster disease management, reducing length of hospitalization and caregivers' anxiety and improving patients' global quality of life (2,3).

Methods

We conducted a retrospective study of all TCs performed by pediatricians, internists and nutritionists of the ReferenceCenter of IMD at Unidade Local de Saúde de São José in 2025, collecting demographic data, diagnoses, reason for contact, clinical outcomes and biochemical disease markers.

Results/Case report

This audit revealed 583 medical and 23 nutritional TCs, accounting for 51% and 7% of all consultations, respectively. Among medical TCs, 14% were synchronous, by phone or video call (51% clinical status update, 23% test results communication ± treatment adjustment, 22% pre-hospital emergency, 4% hospital consult), and 86% were asynchronous, by e-mail (75% test results communication, 20% chronic prescription renewal, 5% medical reports or other). A group of 113 patients had TC, including 80 with confirmed IMDs (34% amino acid disorders, 15% lysosomal storage diseases, 11% mitochondrial diseases, 8% fatty acid oxidation defects, 7% intracellular cobalamin defects, 5% organic acidurias and others). Out of the studied group, 49 patients (43%) had physical and/or intellectual disabilities. Mean residence distance was 98 km (range 0–1540) and families saved 10,424 km and 129 working days/year in total. Hospitalization was avoided in 77% cases of pre-hospital emergency calls. Good metabolic control was maintained in 77% of PKU children.

Conclusion

Telemedicine constitutes a safe and effective adjunct to standard care in IMDs, improving accessibility, reducing unnecessary hospitalizations and socio-economic burden, and supporting metabolic stability. It is particularly advantageous for patients with disabilities and those living at significant distance from referral centers. Integration into routine care pathways should account for the substantial organizational and professional workload associated with telemedicine activities.

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Palavras-chave: Telemedicine, Inherited metabolic diseases, Clinical outcomes, Socio-economic impact

Development of Antisense Oligonucleotide–Based Therapies for Lysososmal Storage Diseases

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Introduction

Mucopolysaccharidoses type III (MPS III), also known as Sanfilippo syndrome, is an ultra-rare lysosomal disorder caused by impaired heparan sulfate (HS) degradation, leading to progressive central nervous system (CNS) accumulation and neurodegeneration. No effective CNS-directed therapies exist. We propose a substrate reduction strategy using gapmer antisense oligonucleotides (ASOs) that block translation of enzymes that participate in the HS biosynthetic pathway, aiming to reduce HS production and provide a broadly applicable therapeutic platform across MPS III subtypes (1-2).

Methods

2'-MOE-PS gapmer ASOs targeting B3GALT6 and B4GALT7 were designed in silico and transfected into control (HDFa) and MPS IIIC patients fibroblasts. mRNA knockdown was measured by RT-qPCR and HS by LC-MS/MS. iPSC-derived brain organoids and CRISPR zebrafish KO will be developed in future PhD work to evaluate molecular and functional ASO effects.

Results/Case report

Preliminary results demonstrate that ASO treatment induces downregulation of B3GALT6 and B4GALT7 mRNA in both HDFa and MPS IIIC patient fibroblasts, as measured by RT-qPCR. These findings confirm effective target engagement and validate the capacity of the designed gapmers to modulate early HS biosynthesis genes.
Previous work from our group targeting XYLT1, another gene involved in HS biosynthesis, demonstrated robust mRNA and protein reduction accompanied by decreased intracellular HS levels, supporting the rationale for RNA--based substrate reduction (3). Building on this approach, we are currently quantifying the effects of B3GALT6 and B4GALT7 inhibition on HS accumulation to assess their impact on substrate storage and associated cellular phenotypes.

Conclusion

These preliminary findings support the feasibility of targeting HS biosynthesis through gapmer ASOs as a substrate reduction strategy for MPS IIIC. Early mRNA knockdown confirms molecular efficacy, while previous proof-of-concept data on XYLT1 validates the approach and supports translational potential. Future studies in iPSC-derived brain organoids and CRISPR-KO zebrafish models will further evaluate the impact on HS accumulation and functional disease features, ultimately aiming to develop a broadly applicable RNA-based therapeutic platform for all MPS III subtypes.

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Acknowledgements

HORIZON-MSCA-2023-DN — EFFecT — No.101168372

Palavras-chave: Mucopolysaccharidosis II type C (MPS IIIC), Lysosomal storage diseases (LSDs); heparan sulfate (HS); antisense oligonucleotides (ASOs); substrate reduction therapy

Impact of Sibling-Target Screening on the Prognosis of Inherited Metabolic Diseases

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Introduction

Inherited metabolic diseases (IMDs) often present in childhood and may remain asymptomatic until irreversible damage occurs. Early diagnosis enables timely treatment and improves outcomes. We describe five families with four different IMDs in which identification of an index case prompted targeted testing of siblings, allowing presymptomatic diagnosis and effective intervention.

Methods

Retrospective study of clinical information of five families (F 1-5) with four different IMDs (cblC; MSUD; MADD; X-ALD) followed in our Reference Center. For each patient, targeted biochemical and genetic screening was extended to siblings. Clinical course, laboratory findings and response to treatment were analyzed.

Results/Case report

F1 cblC, index presented at 3 years old with global developmental delay and ataxia. Treatment with hydroxocobalamin and betaine led to marked improvement. Quick neonatal diagnosis of the sibling prompted therapy initiation on day 6 of life with normal development.
F2 MSUD, index had severe neonatal encephalopathy requiring hemofiltration; sibling, diagnosed prenatally, started nutritional intervention at birth and no severe metabolic decompensations were observed in the neonatal period.
F3 MADD, index had a subacute myopathic episode at 5 years old. Treatment with riboflavin and coenzyme Q10 led to complete recovery, the younger asymptomatic sibling was tested and currently has no symptoms or signs of myopathy.
F4–5 X-linked ALD, index cases presented with adrenal failure and progressive neurological decline, exceeded timely treatment; pre-symptomatic siblings carrying the ABCD1 variant are receiving regular clinical and MRI monitoring for HSCT indication and all have hydrocortisone stress dosing due to adrenal insufficiency.

Conclusion

Across four IMDs, sibling screening enabled early treatment and /or close surveillance, preventing severe complications and improving prognosis. These cases highlight the critical role of systematic familial investigation in IMDs, allowing timely intervention, reducing morbidity, and supporting personalized care.

Palavras-chave: screening, Intracellular Cobalamin Metabolism Type cblC deficiency, maple syrup disease, X-linked adrenoleukodystrophy

Investigation of Carrier State of Recessive Diseases for Early Diagnosis of Treatable Inherited Metabolic Diseases: A Case Study of Classic Galactosemia

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Introduction

Carrier screening for recessive diseases is usually performed after an index case has been identified within a family. It is also used as a genetic counselling tool for couples at risk who have not previously received a diagnosis.
Classic galactosemia (OMIM #230400, CG) is a rare, autosomal recessive disorder of galactose catabolism, due to galactose-1-phosphate uridyltransferase deficiency (GALT enzyme), leading to multisystem, acute neonatal manifestations and long-term complications. Early treatment with galactose restriction is lifesaving in the neonatal period.

Methods

We present a family in which a previous child died of unknown cause at 4 months of age. Carrier screening for recessive diseases using an expanded gene panel based in whole exome sequencing was performed in parents. Clinical, metabolic, enzymatic and genetic evaluation of their child is analyzed.

Results/Case report

This healthy, non-consanguineous couple of African descent previously had a child who experienced prolonged vomiting, weight loss and lethargy. The child died at four months of age without a diagnosis. The remaining family history was unremarkable. During the couple's second pregnancy, carrier screening was performed in the context of family counselling and disclosed a pathogenic variant in the GALT gene in both parents.
Due to the 25% risk of CG and the parents' decision not to undergo invasive prenatal diagnosis, the child was started on a rice-based formula at birth. The diagnosis of CG was confirmed by undetectable GALT enzyme activity and by the presence of the familial pathogenic variant in homozygosity. She had transient neonatal jaundice (phototherapy for one day) and currently, at 16 months of age, she is asymptomatic, with normal growth and neurodevelopment.

Conclusion

CG is a rare, genetic, multisystem disorder caused by an inability to convert maternal milk/formula's galactose into glucose. Symptoms appear within the first few days of life and include vomiting, postprandial hypoglycemia, weight loss, hepatic and renal symptoms and pseudotumor cerebri.
All clinicians should be aware of this disorder because a galactose-free diet can prevent life-threatening symptoms. CG was most likely the cause of death of this couple's first child. Genetic counselling and the use of new diagnostic methodologies were crucial for the early treatment of their second child.

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Acknowledgements

The authors thank the patient's family for their cooperation and the multidisciplinary team involved in clinical care.

Palavras-chave: Galactosemia, GALT deficiency, Genetic Carrier Screening

POSTERS _

P001

From Information to Empowerment: A Multidisciplinary Health Literacy Model For Individuals With Lysosomal Storage Diseases

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Introduction

Lysosomal storage diseases (LSD) are rare inherited metabolic disorders characterized by progressive multisystem involvement, chronic disability and psychosocial impact (Saudubray et al., 2025). Even when disease-specific therapies exist, outcomes depend on early diagnosis, timely treatment and sustained patient engagement. Health literacy enables patients and caregivers to understand information, adhere to therapy and participate in shared decision-making (Almeida, 2019). However, important gaps remain. In this context, the development of this project aims to strengthen health literacy and improve self-management in LSD.

Methods

Structured intervention: individualized education in day-hospital/clinic; monthly 60-min online multidisciplinary sessions; plain-language resources; and a hybrid World LSD Day event. A questionnaire was developed to identify needs. A satisfaction evaluation questionnaire will be administered at the end of each session.

Results/Case report

Needs assessment of patients, caregivers and clinicians highlighted gaps in symptom monitoring, treatment adherence, mental health, caregiver stress, travel/holidays planning and navigation of the National Health Service. In response, we created the program "Understanding Lysosomal Storage Diseases: more information for better decision-making". Core topics include: clinical manifestations and diagnostic delay; available therapies and their benefits/limitations; nutrition; rights and duties of patients/caregivers; rehabilitation; palliative care; and psychological wellbeing. Sessions are delivered by a multidisciplinary team and include patient-association participation. Educational materials are produced following health-literacy best practices (clear language, actionable messages). Evaluation metrics include attendance per session/event and satisfaction rates.

Conclusion

A targeted health-literacy and therapeutic-education strategy may empower LSD patients and caregivers, support shared decision-making and strengthen self-management. By addressing practical needs and psychosocial burden, this model is expected to improve understanding and adherence, help prevent complications and promote quality of life, while encouraging appropriate use of healthcare resources. The approach is scalable to other rare inherited metabolic diseases. Digital delivery increases reach and equity, fostering a coordinated care network.

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Palavras-chave: Lysosomal Diseases, Health Literacy, Therapeutic Education, Self-Management, Patient Empowerment, Rare Diseases, Multidisciplinary Team

PO02

Use of Human Milk in a Ketogenic Diet in an Asymptomatic Patient With Glut-1 Deficiency Syndrome

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Introduction
Glucose transporter type 1 deficiency syndrome (GLUT1DS) is a rare neurometabolic disorder caused by haploinsufficiency of the SLC2A1 gene, leading to impaired cerebral glucose transport and chronic neuroglycopenia (1-4). The condition typically manifests with early-onset epilepsy, developmental delay, acquired microcephaly, and movement disorders (3, 6, 7). Diagnosis relies on hypoglycorrhachia and confirmation of a pathogenic SLC2A1 variant (6). Ketogenic diet therapy (KDT) is the first-line treatment, providing ketone bodies as an alternative cerebral energy substrate and significantly improving neurological outcomes (1, 4, 6, 7).

Methods
Although breastfeeding is often limited during KDT, emerging evidence suggest that human milk may be safely incorporated under specialized supervision (8-10).

Results/Case report
We report a female preterm infant born at 32+3 weeks with suspected non-immune hydrops fetalis and severe neonatal anemia (Hb 2.5 g/dL). Array-CGH identified two clinically significant copy number variants: a heterozygous deletion involving the β-globin gene cluster (11p15.4) explaining hydrops, and a heterozygous deletion at 1p34.2 encompassing the entire SLC2A1 gene, confirming GLUT1.
At diagnosis, the infant was neurologically asymptomatic, with normal tone and head growth and no seizures. Given evidence supporting improved neurological outcomes with early treatment, a multidisciplinary team initiated early KD.
The ketogenic ratio was gradually increased from 1.5:1 to 3.5:1, achieving blood ketone between 2 to 4 mmol/L, with stable glycemia (>70 mg/dL). Human milk was maintained throughout the diet regiment.
Over the first two months, the infant demonstrated appropriate growth with a mean weight gain of 22 g/day and no metabolic or neurological complications.

Conclusion
This case supports the feasibility of combining breastfeeding with KDT in early infancy, including prematurity. Early initiation of KDT in an asymptomatic genetically confirmed patient may potentially prevent neurological manifestations of GLUT1DS. Individualized dietary planning by an experienced multidisciplinary team is essential to achieve therapeutic ketosis while preserving the benefits of human milk.
Human milk can be safely incorporated into KDT in infants with GLUT1. Further research and clinical experience are needed to refine this approach and develop comprehensive guidelines for its application in similar cases.

Palavras-chave: Glucose transporter type 1 deficiency syndrome, Ketogenic Diet, Breastfeeding, Metabolic disorders

P003

Phenotypic Spectrum Of TANGO2-Related Metabolic Encephalopathy And Arrhythmias: Acute Decompensation Across Two Distinct Clinical Phenotypes

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Introduction
TANGO2 deficiency is an ultra-rare autosomal recessive neurometabolic disease. Its main features are developmental delays/regression, hypothyroidism, epilepsy and cardiac changes.
Physical stress due to overexertion, dehydration, fasting, or infections may trigger acute decompensation. This can present as an acute metabolic crisis (rhabdomyolysis, hypoglycemia, cardiac crisis and impaired consciousness) or as neurologic episodes known as "TANGO2 spells", non-life-threatening paroxysmal worsening of baseline symptoms. Case reports are scarce and genotype-phenotype correlation remains unclear.

Methods
We present two cases of female patients with TANGO2 deficiency that reflect the dual presentations of acute decompensation, the first (C1) a 19-year-old with a clear disease phenotype and suggestive findings in a targeted metabolic diseases NGS panel and the second (C2) a 21-year-old with molecular confirmation through whole exome sequencing (WES).

Results/Case report
C1: Presented at age 10 with episodes of hypoglycemia, acute motor deficits and cardiac arrhythmias, with cognitive and functional regression leading to dependence at 16. She had dysarthria, ophthalmoparesis and spastic tetraparesis. NGS panel revealed a biallelic VUS with a negative WES for alternative causes and segregation studies confirming both parents as carriers.
C2: Presented with early developmental delay and epilepsy and at age 10 acute episodes of dystonia, focal motor deficits, ataxia, lethargy and dysarthria, often triggered by infection and recovering with rest. At that time she also showed severe cognitive regression, with loss of autonomy. She had spastic tetraparesis, lower extremities hypotonia and hand dystonia. WES evealed compound heterozygosity for a pathogenic variant and a 23,8Kb deletion (exons 3-9).

Conclusion
TANGO2 deficiency appears to have a clear phenotype, which facilitates diagnosis. Regression hinders disease management; therefore, a physician's awareness is essential to avoid triggers and manage acute crises more effectively. While TANGO2 spells are generally non-life threatening, early recognition and treatment of acute metabolic crisis are critical to prevent potentially fatal cardiac complications.

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Palavras-chave: TANGO2 deficiency, neurometabolic disease, metabolic encephalopathy, TANGO2 spells

P004

Spinocerebellar Ataxia Type 25: A Rare Cause of Ataxia Due to Mitochondrial Dysfunction

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Introduction
Spinocerebellar ataxia type 25 (SCA25) is an ultra-rare cerebellar ataxia with less than 20 cases described worldwide. It is caused by heterozygous pathogenic variants in the PNPT1 gene, an important component of the mitochondrial degradosome. There is significant clinical heterogeneity among the described cases, with incomplete penetrance and phenotypes ranging from childhood-onset of slowly progressive cerebellar ataxia to milder later-onset polyneuropathy.

Methods
We describe the case of a patient presenting with adult-onset ataxia due to a heterozygous nonsense PNPT1 variant.

Results/Case report
A 67-year-old male, with vertigo and bilateral deafness at 22, type 2 diabetes at 23, and motor symptoms at 28 with progressive gait impairment, lower limb weakness and atrophy, as well as distal hypoesthesia. Mild-rate heart failure secondary to dilated cardiomyopathy was also present. Family history revealed a sister and niece with similar symptoms and a brother with early-onset diabetes. Examination showed paraparesis, generalized hyporeflexia, bilateral lower limb 'high stocking' hypoesthesia, hypopallesthesia and ataxia, with an ataxic–paretic gait. Blood and CSF studies were unremarkable; EMG showed an axonal sensory-motor polyneuropathy and brain MRI revealed generalized cortico-subcortical atrophy with cerebellar vermis predominance. Whole-exome sequencing identified a heterozygous PNPT1 nonsense variant, classified as probably pathogenic [PNPT1:c.451C>T(p.Gln151*)].

Conclusion
This case further expands the knowledge regarding SCA25/PNPT1-related disorders. It also highlights the need for careful neurological and multisystemic assessment in cases of ataxia, that can provide helpful clues in the differential diagnosis. The presence of early onset diabetes and deafness may point to a possible dysfunction in mitochondrial proteins, similarly with what happens in Friedreich's ataxia.

P005

Carnitine Uptake Deficiency – A Treatable Metabolic Disorder Causing Hypoketotic Hypoglycaemia

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Introduction

Carnitine uptake deficiency (CUD) is an easily treatable inborn error of metabolism included in several newborn screening programs throughout Europe, including Portugal.

CUD is a disease caused by a defect in the active cellular uptake of carnitine by its specific transporter (OCTN2), leading to renal carnitine wasting and causing low plasma and intracellular C0 levels.

It may cause severe cardiomyopathy, arrhythmia, and hypoketotic hypoglycaemic crises in children, but also sudden death in children and adults by arrhythmia, mainly in periods of high metabolic demands, like infections.

Results/Case report

We present a clinical report of a 16-month-old boy, admitted for hypoglycaemia with altered conscience level in context of febrile urinary infection.

In the admission day he was difficult to awake after overnight fast and had blood glucose 44mg/dl on arrival to the emergency department. Blood chemistry was otherwise normal and urinalysis was remarkable for low level ketonuria. Acylcarnitines showed low C0 level 8,42µmol/L.

He had had a normal newborn screening, including normal C0 levels of 10,5 µM (normal between 9,13-68.45 µM). His diet included appropriate for age ingestion of meat and fish.

He repeated metabolic evaluation that maintained low C0 7,4 µmol/L, and all acylcarnitines, and low free (15 µmol/L) and total (19 µmol/L) carnitine in plasma. He had normal cardiac and hepatic evaluations.

SLC22A5 gene sequencing found two likely pathogenic variants (c.453G>A and c.679C>A) in compound heterozygosity, confirming the CUD diagnosis.

Conclusion

CUD has a wide spectrum of severity, from asymptomatic patients to a potential life-threatening disease. Hypoketotic hypoglycaemia should always raise the concern of a possible inborn error of metabolism involving carnitine cycle or β oxidation disorders, despite normal results of normal newborn screening.

As an example of this variable spectrum, our patient had a C0 screening value that was in the low normal range. This leads to the discussion of negative predictive and cut-off value of the test, and the possible need of second tier testing in low normal C0 values this pathology.

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Palavras-chave: Carnitine, Carnitine Uptake Deficiency, Newborn Screening, Hypoketotic Hypoglycaemia

P006

Mitochondrial Disease beyond mtDNA: Nuclear-Encoded Complex I Deficiency Due To NDUFAF6

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Introduction

Primary mitochondrial OXPHOS disorders must be considered in children with chronic multisystem disease of unknown aetiology. Respiratory chain defects often present with nonspecific clinical features and persistent metabolic abnormalities, making diagnosis challenging. Accurate identification requires integration of clinical findings, biochemical markers, functional studies, and molecular analysis. Therefore, genetic confirmation is essential to establish a definitive diagnosis, define inheritance, guide management with prognostic stratification and provide appropriate genetic counseling.

Methods

Metabolic evaluation included plasma amino acids, lactate, organic acids and, liver and muscle respiratory chain activity. Genetic testing in liver, muscle and blood included mitochondrial gene panels, CNV analysis and whole exome sequencing (WES). Parental segregation studies are ongoing.

Results/Case report

A 15-year-old boy presented from 10 months of age with recurrent vomiting, failure to thrive, persistent high plasma lactate, alanine, AST and ALT with normal CK, metabolic acidosis with normal/high anion gap, and organic aciduria and lactate peaks in H1MRS, raising suspicion of primary mitochondrial disease. He developed fasting-induced hypoglycaemia with severe lactic acidosis corrected with oral bicarbonate. Progressive neurocognitive decline, short stature, proximal tubulopathy and chronic kidney disease followed, without hepatic or cardiac involvement. Liver respiratory chain analysis revealed partial complex I deficiency (35% of the reference mean). Prior genetic testing including mtDNA sequencing was non-diagnostic. WES identified biallelic pathogenic variants in NDUFAF6, consistent with autosomal recessive Fanconi renotubular syndrome type 5 (MIM:618913; ORPHA:3337).

Conclusion

This report highlights the 14 years long diagnosis odyssey of an "old" OXPHOS disease case integrating clinical, biochemical, and molecular data. Although complex I deficiency supported mitochondrial dysfunction, definitive diagnosis was only achieved after identification of biallelic pathogenic variants in NDUFAF6, establishing a nuclear-encoded, autosomal recessive disorder. Comprehensive genetic testing is essential in children with unexplained metabolic, complex, multisystem involvement and is currently one of the primary diagnosis approaches.

Acknowledgements

The authors thank the patient's family for their cooperation and the multidisciplinary team involved in clinical care. We also gratefully acknowledge Luísa Diogo, MD, PhD, for her insightful critical review and important contributions to this work.

Palavras-chave: Mitochondrial Diseases, Respiratory Chain Complex I Deficiency, NDUFAF6, Fanconi Syndrome, Whole Exome Sequencing

P007

A Late Diagnosis of Glutaric Aciduria Type 1

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Introduction

Glutaric aciduria type I (OMIM #231670; ORPHA: 25) is an autosomal recessive neurometabolic disorder caused by mutations in gene of glutaryl-CoA dehydrogenase GCDH and is typically diagnosed in childhood. GCDH is involved in degradation of L-lysine, L-hydroxylysine, and L-tryptophan, converting the glutaryl-CoA to crotonyl-CoA in the mitochondrial matrix.
Adult presentation is rare and may manifest as cognitive decline, gait disturbance or extrapyramidal features. Late-onset cases represent a diagnostic challenge, but sub-ependymal nodules in neuroimaging are a key radiological clue.

Methods

We present a 59-year-old woman with epilepsy in childhood and learning difficulties. A progressive cognitive decline, gait instability and anxiety were observed over the last two years. No acute encephalopathic crisis were ever reported. No consanguinity or relevant family history. Neurological examination was normal.

Results/Case report

MRI revealed exuberant bilateral temporal polar and opercular arachnoid cysts, causing mass effect on the adjacent brain parenchyma and global cortical atrophy with microangiopathic leukoencephalopathy. EEG showed mild diffuse slowing activity without epileptic activity. Glutaric acid (3394 µmol/mol creatinine) and 3-hydroxyglutaric acid were markedly elevated in urine, with increased glutarylcarnitine and low free carnitine in blood, consistent with a high-excretory phenotype. Molecular study (NGS) identified a homozygous pathogenic GCDH variant (c.1204C>T; p.Arg402Trp).

Conclusion

Treatment with L-carnitine and diet (low lysine) were initiated, with a low compliance on the last. The gait instability persisted with no recent falls. Donepezil was introduced recently with minor improvements. Urinary glutaric acid persisted elevated with a reduction in 30%.
Adult diagnosis of glutaric aciduria type I is rare. Diagnosis could be suspected in neuroimage and urinary biomarkers (not usually requested). Impact of treatment I these late presentations appears to be beneficial but limited.

Palavras-chave: Glutaric aciduria type 1

P008

Two Pediatric Patients with TK2 Deficiency with Strikingly Different Clinical Evolution

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Introduction

TK2 deficiency is a mitochondrial maintenance disorder affecting predominantly the muscle. It is caused by biallelic TK2 variants, the nuclear gene encoding mitochondrial thymidine kinase, an enzyme involved in the phosphorylation of deoxycytidine and deoxythymidine nucleosides. Depending on the age of onset, it can be defined as infantile-onset (≤1 year), childhood-onset (1–12 years) and late-onset (≥12 years). Earlier presentations usually correlate with increased clinical severity, more rapidly progressive weakness and shorter survival. A recent treatment option with nucleoside supplementation can change the natural history of this severe disease.

Methods

We present two cases of early-onset TK2 deficiency, with markedly different clinical courses.

Results/Case report

The first case was a boy who presented at 15 months with progressive weakness, loss of independent ambulation, later evolving to feeding difficulties. Muscle biopsy revealed myopathic changes, increased COX-negative fibers, and severe mtDNA depletion. Genetic testing identified two pathogenic TK2 variants (p.Lys50Ilefs*99 and p.Thr108Met). While awaiting initiation of nucleoside supplementation, he died at 23 months following an aspiration event that resulted in severe hypoxic-ischemic brain injury. The second case was a Brazilian girl who developed progressive motor impairment at 2.5 years of age. Later she required ICU admission for mechanical ventilation due to pneumonia. Two TK2 variants (p.Thr108Met and p.Gly91Asp) were identified. She was subsequently enrolled in a nucleoside supplementation clinical trial (NCT03845712), with a favorable clinical response. At nine years of age, she has normal muscle function while remaining on therapy.

Conclusion

The markedly different outcomes observed in these two cases highlight the importance of early disease recognition and prompt therapeutic intervention in modifying disease progression. Timely molecular diagnosis is also crucial for the inclusion of TK2 patients in ongoing clinical trials.

Palavras-chave: TK2 myopathy, Mitochondrial

P009

Phosphatidylserine Decarboxylase Deficiency – A New Case of Liberfarb Syndrome With The Founder Portuguese Variant

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Introduction

The PISD gene encodes for phosphatidylserine decarboxylase (PISD), which converts phosphatidylserine to phosphatidylethanolamine – a phospholipid in the inner mitochondrial membrane. Biallelic pathogenic PISD variants cause a wide phenotypic spectrum, from the multisystem disorder Liberfarb syndrome, characterized by short stature, epiphyseal dysplasia, joint dislocation, kyphoscoliosis, microcephaly, intellectual disability, retinal degeneration and sensorineural hearing loss, to a pure skeletal phenotype with spondyloepimetaphyseal dysplasia and large epiphyses.

Methods

We report a new patient with Liberfarb syndrome and the Portuguese founder variant. DNA from peripheral blood was analysed using a skeletal dysplasia NGS panel with 733 genes (Illumina NovaSeq6000), achieving 354× mean coverage (99.12% >20×) with bioinformatic evaluation of coding and exon–intron boundaries.

Results/Case report

The patient is a 19-month-old female, born to non-consanguineous parents. She presented with a congenital bilateral hip dislocation and femoral head dysplasia. This was managed with a Denis-Browne bar at six months of age, which corrected the dislocation on the right side. Progressive short stature raised the suspicion of skeletal dysplasia syndrome, prompting a gene panel which revealed the homozygous pathogenic variant NM_014338.4:c.904-12_904-3del in intron 8 of PISD. Developmental evaluation at 17 months (Griffiths) revealed a global DQ of 73, indicating a global developmental delay most significantly impacting the locomotor area (DQ 62). At 18 months, the uncorrected visual acuity was 20/310 in both eyes with bilateral myopic astigmatism and healthy fundi. Hearing screening showed an OAE pass/fail result (AD/AS) with Type A tympanometry. Auditory brainstem response test is pending.

Conclusion

The underlying cause of mitochondrial dysfunction in PISD deficiency appears to be impaired mitochondrial protein homeostasis.
In our patient, the genetic panel revealed the homozygous 10 bp deletion in the last PISD intron, which was present in five other patients with Liberfarb syndrome. A timely diagnosis enables better planning of surgery due to risk of joint dislocation relapse, and facilitates a multisystem evaluation for skeletal dysplasia, retinal degeneration, hearing loss and developmental delay. It also enables appropriate genetic counselling.

Palavras-chave: Phosphatidylserine decarboxylase deficiency, PISD, Liberfarb syndrome, Skeletal dysplasia, Intellectual disability, Retinal degeneration, Sensorineural hearing loss

PO10

Valproate in Inherited Metabolic Disorders: Ally or Aggravating Factor in Seizures Management?

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Introduction

Inherited Metabolic Disorders (IMD) often present with epileptic seizures, making long-term anticonvulsant treatment essential for neurological prognosis. Valproate is widely used in generalized and symptomatic epilepsies, including in patients with IMD, but specific metabolic concerns arise in this population regarding the safety profile of this drug. Epileptic seizures should be controlled without destabilizing fragile metabolic pathways, leading to the question of whether valproate acts primarily as an ally or as an aggravating factor in IMD.

Methods

Structured research was conducted in regulatory documents from the European Medicines Agency (EMA), including European Public Assessment Reports (EPARs), supported by a PubMed literature search, to identify data relating valproate exposure to changes in biochemical biomarkers.

Results/Case report

Valproate is consistently associated with characteristic biochemical changes that are particularly relevant in patients with inherited metabolic disorders. It is linked to disruption of urea-cycle homeostasis, with reductions in free carnitine and hypocarnitinaemia accompanied by altered acylcarnitine profiles and consequent accumulation of ammonia that is not efficiently converted into urea, resulting in hyperammonaemia. At the hepatic level, abnormalities range from mild, reversible elevations of aminotransferases (AST and ALT) to clinically significant hepatotoxicity. Proposed mechanisms include inhibition of mitochondrial β-oxidation and formation of immunogenic/cytotoxic metabolites resulting from extensive CYP450-mediated metabolism of this drug.

Conclusion

Valproate remains a valuable option for difficult to treat epilepsies in IMD, yet its impact on carnitine homeostasis, urea-cycle function and hepatic mitochondria makes these patients particularly vulnerable to adverse metabolic effects. Systematic monitoring of ammonia, carnitines and liver enzymes, combined with high clinical vigilance, is crucial to distinguish therapeutic benefit from metabolic harm. An individualized, biomarker-guided approach may help clarify, for each patient with IMD, whether valproate is predominantly an ally in seizure control or a driver of metabolic deterioration.

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Palavras-chave: Valproic Acid, Metabolism, Inborn Errors, Epilepsy, Seizures, Hyperammonemia, Carnitine, Acylcarnitines, Urea Cycle Disorders, Liver Diseases, Drug-Induced, Hepatotoxicity, Mitochondria, beta-Oxidation

PO11

A Late Diagnose of Cerebrotendinous Xantomatosis

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Introduction

Cerebrotendinous xantomatosis (CTX) (OMIM#213700; ORPHA 909) is a rare autosomal recessive disorder caused by pathogenic variants in the CYP27A1 gene. The compromised synthesis of bile acid salts and accumulation of cholestanol, manifests as a progressive neurologic dysfunction with neuropsychiatric symptoms, xanthomas and cataract. An early diagnosis and treatment with chenodeoxycholic acid is important for improve prognosis of these patients.

Methods

45 years old male with a late diagnosis of CTX with a long history of psychiatric symptoms. A bipolar disorder was diagnosed since adolescence, with several hospitalizations in the last decade. Xanthomata were noted also since adolescence with need of removal surgery in Aquiles tendon. No consanguinity or other cases in family history were suspected.

Results/Case report

A neurologic decline was noted with progressive ataxia, bradykinetic-rigid syndrome and loss of autonomous gait. In neurological examination an axial and hand dystonic posture, generalized rigidity and rest and action tremor. A slow parkinsonian and instable gait was noted.
Brain MRI multifocal hyperintensities on T2- and T2-weighted FLAIR in frontal and parietal white matter, with more diffuse involvement of the posterior periventricular substance bilaterally, associated with a slight asymmetry of the insula signal, with hypersignal on the right T2-weighted sequences; also a hypersignal on T2/FLAIR sequences in the dentate nuclei of the cerebellum and, very incipiently, in the cerebral peduncles, and a thin linear hypersignal in the posterior arm of both internal capsules.
Cholestanol was elevated 2,6 times the upper normal level (UNL). The genetic study showed a homozygous mutation on gene CYP (2741 c.1016c>T p (thr33Met), confirming the diagnosis of CTX.
Treatment was started with chenodeoxycholic acid and levodopa.

Conclusion

We observed a slight improvement of the akinetic rigid syndrome and of ataxia. The levels of cholestanol was decreased 24%, remaining elevaded (~2 times ULN). The prognosis persists poor because the late recognition, neurologic manifestations and MRI alterations like dentate nucleus involvement. Increased awareness of this treatable neurometabolic disorder is essential to enable earlier recognition and timely initiation of disease-modifying therapy, potentially altering the natural history of the condition.

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Palavras-chave: cerebrotendinous xantomatosis

PO12

Low Arylsulfatase a Activity is Not Always Metachromatic Leukodystrophy: A Case Highlighting The Role Of Arsa Pseudodeficiency Alleles

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Introduction

Metachromatic leukodystrophy (MLD) is a rare autosomal recessive lysosomal disorder caused by deleterious variants in the ARSA gene, leading to arylsulfatase A (ASA) deficiency and progressive demyelination. In addition to pathogenic variants, ARSA harbors pseudodeficiency alleles (PD-ARSA) that significantly reduce in vitro ASA activity without clinical consequences. Distinguishing true MLD from pseudodeficiency remains a diagnostic challenge, particularly when enzymatic activity is markedly reduced, emphasizing the relevance of evaluating sulfatide levels whenever possible.

Methods

Clinical revision of patient clinical data, ASA activity determination and ARSA gene sequencing to review known pseudodeficiency alleles. Informed consent signed by parents.

Results/Case report

We report a 15-year-old female with cerebral palsy (perinatal anoxia) presenting with progressive neurological decline and worsening dystonia. A commercial dystonia gene panel identified a heterozygous pathogenic variant in the ARSA gene. To clarify its clinical significance, biochemical analysis revealed markedly reduced leukocyte ASA activity. Urinary sulfatide analysis was not possible due to incontinence. Subsequent in-house ARSA characterization via Sanger sequencing confirmed the initial heterozygous variant alongside two alleles associated with PD-ARSA. In-house comparative analysis demonstrated that the patient's enzymatic activity levels are consistent with those of asymptomatic carriers or individuals with pseudodeficiency, effectively ruling out MLD as the primary cause of her current neurological worsening.

Conclusion

This case highlights the critical importance of comprehensive allele characterization in the interpretation of reduced ASA activity. Awareness of PD-ARSA alleles and their biochemical impact is essential to avoid misdiagnosis of MLD. An integrated diagnostic approach combining clinical assessment, enzymatic analysis, and detailed molecular characterization is crucial to ensure accurate diagnosis and to prevent unnecessary psychological burden and inappropriate counseling.

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Palavras-chave: ARSA gene, Pseudodeficiency alleles, Genotype–phenotype correlation, Variant interpretation, Enzyme assay interpretation, Metachromatic leukodystrophy, Inherited metabolic disorders, Diagnostic challenge

PO13

Access to Therapeutic Innovation in Rare Diseases

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Introduction

Advances in therapeutic technology have allowed many new diseases to be diagnosed and potentially treated. The field of precision medicine, in both diagnosis and treatment, has provided a new opportunity to treat diseases that we were unable to treat in the past, more specifically in the area of rare diseases.

Methods

According to a study by the Orphanet database, 72% of rare diseases are of genetic origin, making them very attractive candidates for precision medicine.
But why isn't this innovation reaching rare disease patients?

Results/Case report

Because it is necessary to change the paradigm of drug development and evaluation, more specifically, the concept of what effectively constitutes the benefit of drugs and the legislation surrounding it.
For diseases with small populations, slower progression, complex variability, and progressive irreversibility, the standard rule of regulators can be extraordinarily difficult to apply, if not impossible. If the goal is to treat many rare and complex neurogenetic diseases, whose symptoms are complex, variable, and in most cases, irreversible, the approach must be innovative.
In Portugal, according to the National Action Plan for Rare Diseases, one of the priority actions is: "Equitable access to therapeutics".

Conclusion

It was within this framework that RD-Portugal (a non-profit organization, in the form of a Federation) organized an event on the theme: Access to Therapeutic Innovation in Rare Diseases.

References

The aim was to bring together various experts (patients, clinicians, researchers, decision-makers, consultants) invited to contribute their relevant insights in the areas of Health and/or Rare Diseases, to identify the current barriers preventing innovative therapies from reaching patients. The event featured structured key questions that led participants to identify problems and propose solutions. Through collaborative work, RD-Portugal was able to lead a process that fostered constructive discussion, developing a report that will be shared with strategic public national and international regulatory agencies and government.

PO14

Natural Protein-Restricted Diets and Nutrition Status of Patients With Protein Inherited Metabolic Disorders

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Introduction

Protein inherited metabolic disorders treatment involves a diet restricted in natural proteins and supplemented with a protein substitute without amino acid(s) whose metabolism is affected. Anthropometric parameters (weight, height, and BMI) are important in patients diagnosed with Protein inherited metabolic disorders. Their therapeutic management includes restriction of natural protein intake and the prescribed degree of protein restriction varies according to the specific disorder and individual protein tolerance.

Methods

We included pediatric patients monitored at the Hereditary Metabolic Disorders Reference Center of ULS São João and anthropometric parameters (weight, height, and BMI) were evaluated for 15 of these patients.

Results/Case report

The sample consisted of 15 patients, 8 males and 7 females. Nine patients were under 10 years of age, and the remaining six were older, with a mean age of 10 ± 4 months. The average BMI Zscore of the total sample was 0.08. When stratified by sex, males presented an average BMI Zscore of –0.64, whereas females presented +0.91. In the subgroup of females 3 presented overweight/obesity. Although the male subgroup showed a lower average BMI Zscore, both sexes exhibited average values consistent with eutrophic nutritional status (BMI Zscore between –1 and +2).

Conclusion

The findings demonstrate that dietary natural protein-restriction in children with Protein inherited metabolic disorders does not appear to confer a risk of undernutrition. All patients receive supplementation with amino acid mixtures free of the disease specific harmful amino acid. These results support the effectiveness of current dietary management strategies in promoting normal growth in this population.

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Palavras-chave: Protein-Restricted Diets, Nutritional Status

PO15

Acrodermatitis Enteropathica: Lifelong Zinc Malabsorption in a Consanguineous Family

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Introduction

Acrodermatitis enteropathica (AE; OMIM 201100; ORPHA 37) is a rare autosomal recessive disorder of zinc metabolism caused by biallelic pathogenic variants in SLC39A4, which encodes the intestinal zinc transporter ZIP4 (1). Pathogenic SLC39A4 variants are predominantly loss-of-function (LoF) and impair zinc absorption in enterocytes. AE classically presents in infancy with periorificial and acral dermatitis, diarrhea and growth failure (2,3). We report a consanguineous family with lifelong zinc deficiency due to AE, highlighting its metabolic and hereditary implications.

Methods

Clinical, biochemical, and nutritional data were collected during longitudinal follow-up. Whole-exome sequencing (WES) was performed to identify the causal genetic variant in the patient, and segregation analysis is ongoing.

Results/Case report

A 31-year-old woman, born to first-cousin parents, presented lifelong erythematous-desquamative dermatitis involving perioral, periocular and intertriginous areas, beginning at one year of age. Zinc deficiency was documented in infancy, prompting supplementation. Long-term zinc sulfate therapy maintained remission, with worsening during treatment interruptions. Gastrointestinal intolerance was reported when zinc was taken without gastric protection. Her 23-year-old brother exhibited similar manifestations, also beginning in infancy. At age 31, with 43kg and 1.55m (BMI 17kg/m^2), her serum zinc was 0.16mg/L (ref. 0.70–1.20), for which she resumed zinc supplementation at 2mg/kg/day. After evaluation at our medical genetics clinic, WES identified a homozygous pathogenic c.599C>T p.(Pro200Leu) variant in SLC39A4 (NM_130849.3), providing molecular confirmation of acrodermatitis enteropathica.

Conclusion

This case illustrates the lifelong clinical consequences of impaired zinc absorption and the need for continuous replacement therapy. We identified a homozygous missense variant in SLC39A4 resulting in a proline-to-leucine substitution at codon 200. Proline residues are critical for structural constraints; their substitution may disrupt local folding, helix stability, or membrane topology, impairing ZIP4 function and intestinal zinc uptake. Genetic confirmation reinforces the importance of early diagnosis, adequate zinc supplementation and family genetic counseling.

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Palavras-chave: SLC39A4, zinc deficiency, supplementation, genetic counseling

PO16

Challenges In The Long-Term Management of Glutaric Aciduria Type I Despite Newborn Screening: A Pediatric Case Report

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Introduction

Background

Glutaric aciduria type I (GA-1) is a rare autosomal recessive disorder caused by glutaryl-CoA dehydrogenase deficiency, leading to accumulation of neurotoxic organic acids. It carries a high risk of acute encephalopathic crises and irreversible neurological damage, especially during catabolic stress. Early diagnosis via newborn screening and prompt dietary treatment improve outcomes; however, 10–20% of patients still experience crises, resulting in lasting neurological impairment and reduced quality of life.

Methods

Case Presentation

A female child was diagnosed by newborn screening started low-lysine diet and L-carnitine supplementation. Psychomotor development was normal until 9 months of age. At 10 months, viral infection triggered metabolic encephalopathy with axial hypotonia, global dystonia, oromandibular dyskinesia, and feeding impairment.

Results/Case report

Case Presentation (...)

She had multiple hospitalizations for intercurrent illnesses. Another crisis at 3 years of age, during gastroenteritis caused severe metabolic acidosis, dehydration resulting in seizures, worsening of the dystonic movements, and rhabdomyolysis. Throughout follow-up the child maintained severe dystonia/dyskinesia, resistant to therapy, poor feeding and malnutrition progressed due to parental refusal to gastrostomy.

Conclusion

Discussion

This case illustrates that catabolic stress remains a major risk factor even after early diagnosis. Individualized nutritional management, emergency protocols, and caregiver education are essential to prevent crises. Close collaboration between metabolic specialists, dietitians, and families plays a crucial role in long-term management.

GA-1 requires continuous monitoring and proactive nutritional intervention. Early recognition and rapid implementation of emergency management may reduce morbidity and improve long-term outcomes, preventing neurological deterioration.

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Palavras-chave: Glutaric aciduria type I, Inborn errors of metabolism, Metabolic crisis, Dietetic therapy, Newborn screening

PO17

Multiple Mitochondrial Dysfunction Syndrome Type 1 – Pulmonary Hypertension as a Possible Clue

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Introduction

Multiple Mitochondrial Dysfunction Syndromes (MMDS) are associated with defective maturation of iron-sulfur (Fe-S) proteins, resulting in dysfunction of multiple essential cellular pathways and impaired ATP synthesis. MMDS1, caused by biallelic pathogenic variants in the NFU1 gene, presents with a severe encephalopathy, lactic acidosis and frequently with pulmonary hypertension.

Results/Case report

Case description

A 6-month-old girl with prior developmental delay was admitted due to recurrent episodes of cyanosis and apnea, predominantly triggered by crying, with increased frequency and severity, eventually requiring invasive ventilation. The parents were consanguineous and of Pakistanis origin. Family history was notable for a previous fetal loss and a sibling with similar symptoms who died aged 4 months without a definitive diagnosis. Brain MRI revealed subcortical and central white matter abnormalities. Diagnostic evaluation demonstrated lactic acidosis and pulmonary arterial hypertension, which progressively worsened and become refractory to treatment with inhaled nitric oxide and sildenafil. The patient died at 7 months of age. Molecular analysis identified a homozygous pathogenic NFU1 variant (c.545+5G>A; r.?), confirming the diagnosis of MMDS1.

Conclusion

This case highlights pulmonary hypertension as a key and early clinical feature of Multiple Mitochondrial Dysfunction Syndrome type 1 (MMDS1). In infants presenting with unexplained pulmonary hypertension associated with neurological impairment, lactic acidosis, and a suggestive family history, MMDS1 should be considered in the differential diagnosis. Although no disease-specific treatment is currently available and the prognosis remains poor, early recognition is essential for appropriate genetic counseling and may contribute to a better understanding of the role of mitochondrial dysfunction in the pathophysiology of pulmonary hypertension.

Palavras-chave: Multiple Mitochondrial Dysfunction Syndrome

PO18

Variant Spectrum and Complex Allele Interpretation in Cyp21a2: A 10-Year Experience (2015–2025)

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Introduction

Congenital adrenal hyperplasia due to 21-hydroxylase deficiency results from pathogenic variants in CYP21A2, a gene with high homology to the nearby pseudogene CYP21A1P. This genomic architecture of RCCX locus leads to frequent gene conversions, duplications and complex alleles, making molecular diagnosis challenging.
In Portugal, multicentre paediatric cohorts identify a variant spectrum led by c.844G>T p.(V282L), c.293-13C>G and c.518T>A p.(I173N), mirroring Southern-European patterns.
We review 10 years of CYP21A2 testing to characterise variant distribution and identify complex cases with impact on genetic counselling.

Methods

Retrospective analysis of 242 cases (2015–2025) by sequencing and MLPA. Data included suspected patients, relatives and partners. Variant frequency, zygosity and copy-number variation were evaluated, including complex alleles and segregation inconsistencies.

Results/Case report

We analysed 242 cases: 141 from CGMJM, 58 paediatric endocrinology and 30 adult endocrinology.
Among 137 suspected, 48 were confirmed, 22 heterozygotes and 67 without confirmation. Family studies (n=75) yielded 7 affected-genotype relatives, 61 carriers (51 obligatory; 10 non-obligatory) and 7 with no-risk genotypes. Partner testing (n=30) found 10 carriers and 20 no-risk (~33%).

Conclusion

Our dataset confirms c.844G>T p.(V282L) as the dominant variant, in line with Portuguese cohorts. Variants c.293-13C>A, c.92C>T p.(P31L), and those with ≤9 alleles—including c.518T>A p.(I173N), c.1360C>T p.(P454S), c.*13G>A, c.955C>T p.(Q319*), c.332_339del p.(D111Afs*20), and c.923dupT p.(L308Ffs*6). These results align with European studies. A benign allele, c.955C>T (p.Q319*) in duplicated CYP21A2, identified in 10 individuals, highlights the need for sequencing+MLPA/CNV to avoid misclassification. The ~33% partner-carrier frequency exceeds general-population estimates (~1:50–1:70 or ~9–10%), reinforcing the clinical value of partner testing.

Palavras-chave: CAH, CYP21A2

PO19

Developmental Delay as an Early Clue to an Inborn Error of Metabolism: A Case Report of Infantile GM1 Gangliosidosis

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Introduction
Lysosomal storage disorders (LSD) are a group of inborn errors of metabolism that, in paediatric patients, often present as progressive multisystemic syndromes with developmental delay/regression. GM1 gangliosidosis (OMIM#230500) is a rare neurodegenerative LSD caused by variants in GLB1 gene, resulting in β-galactosidase deficiency. The infantile form of GM1 gangliosidosis is the most severe phenotype. Early diagnosis is challenging due to non-specific initial manifestations. Recognition of clinical red flags is key to timely diagnosis, management and genetic counselling.

Methods
Clinical evaluation, including ophthalmological assessment, and laboratory testing were performed. Enzymatic assays were conducted at a specialized metabolic genetics centre to confirm the suspected diagnosis. Genetic test is ongoing.

Results/Case report
A 9-month-old female, first child of consanguineous parents, born after a pregnancy complicated by foetal growth restriction, was admitted for global developmental delay and failure to thrive. Physical examination revealed relative macrocephaly, coarse facial features, gingival hypertrophy, hepatosplenomegaly, marked hypotonia, absent visual fixation and tracking, and an absent suck reflex. Laboratory tests showed elevated plasma aspartate aminotransferase, alanine aminotransferase and alkaline phosphatase. Fundoscopic examination identified a characteristic macular cherry-red spot. Lysosomal studies revealed low beta-galactosidase activity in leukocytes and plasma, confirming the diagnosis of Infantile GM1 Gangliosidosis, consistent with the clinical findings. The patient was referred for multidisciplinary management, including metabolic specialists, genetic counselling and palliative support.

Conclusion
This case highlights the importance of recognizing key clinical features, such as neurodevelopmental delay, hepatosplenomegaly and cherry-red spot, in the diagnosis of GM1 Gangliosidosis. Consanguinity remains a significant risk factor for autosomal recessive metabolic disorders. Early identification enabled definitive diagnosis, informed prognosis and timely initiation of multidisciplinary and palliative care, emphasizing the value of specialized metabolic evaluation in complex paediatric cases.

PO20

Introduction of Extended-Release Modified Cornstarch in Child with Glycogen Storage Disease Type Ib: Impact on Metabolic Stability and Quality of Life

Joana Maria Palhotas[1]; Inês Agostinho[1]; Daniela Dos Santos Dias[1]; Anabela Belo[1]; Patrícia Almeida Nunes[1]; Rita Jotta[2]; Patrícia Lipari Pinto[2]; Patrícia Janeiro[2]; Ana Gaspar[2]

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Introduction

Background

Glycogen Storage Disease type Ib (GSD Ib) is a rare inherited metabolic disorder characterized by impaired glucose homeostasis, leading to fasting hypoglycemia, lactic acidosis, hyperuricemia, hypertriglyceridemia, and neutropenia. Nutritional therapy is central to management. An extended-release modified cornstarch, may prolong fasting tolerance and reduce nocturnal feeding burden.

Methods

Case Presentation

A 5-year-old female with genetically confirmed GSD Ib, gastrostomy-dependent since infancy, with previous need for nocturnal enteral feeding to prevent hypoglycemia, treated with empagliflozine since 2 years old.

Results/Case report

Case Presentation (...)

In August 2025, she was electively admitted for the structured introduction of extended-release modified cornstarch and gradual discontinuation of overnight enteral nutrition. A personalized dosing protocol was implemented with close monitoring of capillary glucose, biochemical parameters, and clinical tolerance. Dietary adjustments were performed In subsequent outpatient follow-up between August and November 2025.

Outcomes

After initiating of the extended-release modified cornstarch, glycaemic stability improved with rare mild hypoglycemia easily corrected. Gastrointestinal intolerance was an issue at the beginning, with need of dose adjustments. Lactate, liver function and acid-base status remained normal and triglycerides improved. The patient was able to discontinue continuous nocturnal feeding, maintaining nutrition predominantly orally, with gastrectomy use limited to selected meals.

Overall, it enhanced daily functioning, school activities participation, and quality of life.

Conclusion

Discussion

This case illustrates that an extended-release modified cornstarch can be a valuable therapeutic tool in children with GSD Ib, allowing safer fasting intervals, reduced treatment burden, and improved family routines. However, individualized titration and individualized nutritional planning remain essential to avoid hypoglycemia and optimize metabolic outcomes.

This case supports the role of extended-release cornstarch as an effective component of long-term management in GSD Ib when carefully individualized, treated with empagliflozine.

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Palavras-chave: Glycogen Storage Disease type Ib, Extended-release cornstarch, Hypoglycemia prevention, Metabolic disorders

PO21

Emergency Oral and Enteral Nutritional Support in Inherited Metabolic Disorders: A Comparative Analysis of Commercial Protein-Free Formulations Available in Portugal

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Introduction

Some inborn errors of amino acid metabolism, urea cycle disorders and organic acidurias predispose patients to metabolic decompensation, particularly during catabolic stress. Emergency treatment aims rapidly reverse catabolism and reduce the accumulation of toxic metabolites, preferably using the enteral route. Management protocols generally use carbohydrate-rich formulas, with or without lipids, to increase energy intake and decrease protein breakdown. Since commercial formulas vary in composition, a detailed evaluation is essential to provide safe and effective emergency nutritional support.

Methods

Nutritional composition data of protein/amino acid-free commercial formulas available in Portugal (General Directorate of Health list) were obtained from official Vademecums and manufacturers' websites. A descriptive analysis of ingredients and nutrient content per 100g of formula was performed.

Results/Case report

Two carbohydrate-based formulas with similar energy content are available: Fantomalt® containing maltodextrin, maltose and glucose; and Dextrinomaltosa NM® composed of dextrins and maltodextrin without simple sugars. Three carbohydrate-and lipid-based formulas are also available: PFD1® designed up to 3y, shows the highest energy and lipid density with elevated levels of saturated and polyunsaturated fatty acids including essential fatty acids and a higher overall vitamin supply; PFD2® from 3y onwards, presents high carbohydrate and sugar content, low lipid levels, absence of essential fatty acids and a vitamin profile focused on the B complex; Energivit®, formulated for all age groups, shows a more balanced nutritional profile with moderate lipids, lower sugar levels, presence of essential fatty acids, and relative emphasis on vitamins E and K.

Conclusion

The presence of mono and disaccharides in available protein/amino acid-free formulas may influence sweetness and absorption kinetics, while differences in lipid profiles and micronutrient composition have relevant patient's health implications, highlighting the need for an individualized supplementation. Optimizing dietary management in emergency regimens for IMD patients requires systematic biochemical monitoring, adequate hospital supply logistics, trained teams and close collaboration between nutritionists from reference/treatment centres, promoting the development of national protocols.

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