21ST

INTERNATIONAL SYMPOSIUM OF THE PORTUGUESE SOCIETY FOR METABOLIC DISORDERS

RAISING AWARENESS ON INHERITED METABOLIC DISORDERS

spdm
SOCIEDADE PORTUGUESA DE DOENÇAS METABÓLICAS

26th–29th March

SANA METROPOLITAN HOTEL, LISBON

WELCOME ADDRESS _

Dear Colleagues and Friends,

On behalf of the Organizing Committee, it is with great pleasure that I welcome you to the 21st International Symposium of the Portuguese Society for Metabolic Disorders (SPDM).

This year´s programme will focus on "Raising awareness on Inherited Metabolic Disorders", with the scope to explore and review the main advances 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 international worldwide experts who will bring you the most recent scientific advances in the IMD field, including challenges in newborn screening, innovation in diagnostic techniques and new approaches to IMD treatment.

We will also have a special focus on neurometabolic disorders. We hope that participants can get together in person, so important for exchange of ideas in an informal environment.

The Sana Metropolitan Hotel offers ideal conference conditions in a modern and pleasant atmosphere.

This meeting has been made possible by the support of the sponsors, which we acknowledge. We are delighted to be hosting the 2025 SPDM Annual Symposium, hoping that it will be a success, and very much look forward to welcome all of you in Lisbon.

Daniel Gomes
Symposium Chairperson

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National Reference Centre for Hereditary Diseases of Metabolism
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Patrícia Janeiro – SPDM Vice-President
National Reference Centre for Hereditary Diseases of Metabolism
Unidade Local de Saúde Santa Maria, Lisbon, PT

PROGRAMME

SOCIEDADE PORTUGUESA
DE DOENÇAS METABÓLICAS

SCIENTIFIC PROGRAMME

WEDNESDAY, 26TH MARCH

17:00	**SPDM Working Groups Meeting**
18:00	**SPDM Nutrition Group Meeting**

THURSDAY, 27TH MARCH

09:00	**Symposium Opening – Welcome Address on behalf of the SPDM** *Symposium Chairperson - Daniel Costa Gomes*
09:15	**Session I – Innovation in diagnostic methods for classic Inherited Metabolic Disorders (IMD)** *Chairperson - Célia Nogueira, Porto, PT | Margarida F. B. Silva, Lisbon, PT*
09:15	**Metabolomics to screen for classic IMD** *George Ruijter, Rotterdam, NL*
09:40	**Advances on integrative omics approaches to IMD diagnosis** *Holger Prokisch, Munich, DE*
10:05	**Quantitative proteomics in mitochondrial disease - where are we now?** *Marco Moedas, Stockholm, SE*
10:30	**Lipidomics in IMD for biomarker discovery** *Frédéric Vaz, Amsterdam, NL*
10:55	Coffee Break
11:30	**Session II – Rethinking Newborn Screening (NBS)** *Chairperson - Esmeralda Martins, Porto, PT | Laura Vilarinho, Porto, PT*
11:30	**New challenges in NBS** *Hugo Rocha, Porto, PT*
11:55	**Challenges of using whole genome sequencing in population NBS** *Robin Lachmann, London, UK*
12:20	**Lessons from adult metabolic medicine** *Fanny Mochel, Paris, FR*
12:45	Lunch Symposium **Cipaglucosidase alfa + miglustat: Now you can do more (+) for your Pompe patients (AMICUS)** *Arlindo Guimas, Porto, PT*
14:15	**Session III – Raising awareness on neurometabolic diseases** *Chairperson - Patrícia Janeiro, Lisbon, PT | João Durães, Coimbra, PT*
14:15	**Metabolic epilepsies - clinical and biochemical footprints of IMD** *Ángeles García-Cazorla, Barcelona, ES*
14:40	**Update on leukodystrophies and developing trials** *Karen Gunanayagam, London, UK*
15:05	**Movement disorder increases with age in argininosuccinic aciduria** *Julien Baruteau, London, UK*
15:30	Coffee Break
16:00	**Session IV – Oral Communications** *Chairperson - Teresa Campos, Porto, PT | Isaura Rodrigues, Porto, PT*
17:00	**Session V – E-posters guided walk**
19:30	Departure to Dinner

FRIDAY, 28TH MARCH

09:00	**Session VI – Development and challenges for new therapies in IMD** *Chairperson - Arlindo Guimas, Porto, PT | Margarida Coelho, Porto, PT*
09:00	**The basis for mRNA-based therapies in IMD** *Fátima Ventura, Lisbon, PT*
09:25	**mRNA therapy for lysosomal disorders** *Sandra Alves, Porto, PT*
09:50	**Mitochondrial disorders - hope for the future?** *Shamima Rahman, London, UK*
10:15	**New treatment approaches for CDG** *Dulce Quelhas, Porto, PT*
10:40	Coffee Break
11:15	**Session VII – Revisiting nutritional approaches in IMD** *Chairperson - Júlio César Rocha, Lisbon, PT | Vânia Magalhães, Porto, PT*
11:15	**Exploring asymptomatic childhood methionine cycle disorders** *Patrícia Lipari Pinto, Lisbon, PT*
11:40	**Supplementation for performance and health in patients with phenylketonuria** *Domingo Gonzalez-Lamuño, Santander, ES*
12:05	**Personalised parenteral nutrition for acute IMD decompensations** *Marjorie Dixon, London, UK*
12:30	Lunch Symposium **Unmet Needs of ARG1-D Patients: New Perspectives (IMMEDICA)** *Elisa Leão Teles, Porto, PT*
14:00	**Session VIII – Selected E-posters Communications** *Chairperson - Ana Cristina Ferreira, Lisbon, PT | Hugo Rocha, Porto, PT*
15:00	**Session IX – Moving from research and clinical practice to digital health and decision making in IMD** *Chairperson - Bárbara J. Henriques, Lisbon, PT | Daniel Costa Gomes, Lisbon, PT*
15:00	**The European Health Data Space: impact for disease management at the individual and population level** *Cátia Sousa Pinto, Lisbon, PT*
15:25	**Using data science for better healthcare and opportunities in IMD** *João Guimarães, Lisbon, PT*
15:50	**Sustainability in the development of the treatments for IMD** *Rui Santos Ivo, Lisbon, PT*
16:15	Coffee Break
16:45	**Session X – SPDM grants communications** *Chairperson - Dulce Quelhas, Porto, PT | Isabel Tavares de Almeida, Lisbon, PT*
16:45	**Can enzyme replacement therapy revert *iNKT* cell dysfunction in acid sphingomyelinase deficiency patients?** *Fátima Macedo, Porto, PT*
17:05	**Functional and structural impact of 10 *ACADM* missense mutations on human medium chain acyl-CoA dehydrogenase** *Ana Paula Leandro, Lisbon, PT*
17:30	**Awards and Closing Remarks**
17:30	**End of the Symposium**
18:00	**SPDM General Assembly**

SATURDAY, 29TH MARCH

Raising awareness in innovative therapies in IMD

SPEAKERS

ANA PAULA LEANDRO
PORTUGAL

Ana Paula Leandro, PhD

Is an Associate Professor at Faculty of Pharmacy, University of Lisboa.
She obtained her PhD in Biochemistry in 2001 and the Habilitation degree in Biochemistry in 2020.
Currently Paula Leandro is the coordinator of the research group "Metabolism, Genetics and Proteins in Health and Disease" from the Research Institute for Medicines (iMed.ULisboa).
Her research focuses on the study of misfolded variant proteins responsible for Inborn Metabolic Disorders (IMD), with a focus on Phenylketonuria, Classical Homocystinuria and Medium-chain Acyl-CoA Dehydrogenase Deficiency. She has been using biochemical and biophysical tools to characterise IMD variant proteins, to study the effect of small molecules on the rescue of protein conformation and to identify the mechanisms of protein stabilisation aiming to develop novel pharmacological therapies for IMD.
She has been involved in national and international research projects, both as Principal Investigator (PI) and Co-PI, and in the supervision of several Master and PhD students mainly in the field of IMD.

ÁNGELES GARCÍA-CAZORLA
SPAIN

Ángeles García-Cazorla, MD, PhD

Is a neuropaediatrician and researcher at the Hospital Sant Joan de Déu (Barcelona) where she directs the Neurometabolic Diseases Unit. She is also director of the International Master's Degree in Neurometabolism and Cell Biology for clinicians at the University of Barcelona.
Her main focuses of interest are defects in neurotransmission and the development of personalised therapies in various neurometabolic pathologies.
Coordinates the neurotransmitter working group of the European MetabERN network and is a member of the scientific committee of the SSIEM (European Society for Inborn Errors of Metabolism).
She has published more than 260 articles and is co-editor of the reference book 'Inborn Errors of Metabolism: Diagnosis and Treatment', Springer, 2022.

CÁTIA SOUSA PINTO
PORTUGAL

Cátia Sousa Pinto, MD

Head for Global Digital Health & Public Health Specialist (Portugal).
Is a medical doctor and public health specialist with extensive expertise in digital health transformation, public health surveillance, and international collaboration. She currently serves as Head of the Global Digital Health and International Affairs Unit at SPMS, EPE, where she coordinates Portugal's participation in 17 EU-funded digital health projects and leads the implementation of MyHealth@EU services.
Previously, Dr. Sousa Pinto coordinated the modernization of Portugal's national health surveillance systems as Head of the Epidemiology and Surveillance Division at the Directorate-General of Health (2012–2018). She has been a national representative for Portugal to the ECDC, WHO, and European Commission, contributing to critical discussions on infectious diseases, mortality data systems, and health data standards.
An advocate for data-driven innovation, Dr. Sousa Pinto has led strategic initiatives in health information ecosystems and secondary data use within Portugal's National Health Service. She is also the Deputy Vice-Chair for the Global Digital Health Partnership (2024–2025) and a national nominated expert on the European Health Data Space Regulation for the EU Council.
Dr. Sousa Pinto holds degrees from the University of Lisbon and the National School of Public Health and has pursued advanced studies at Harvard University, Università Cattolica del Sacro Cuore, and the University of Edinburgh.

DOMINGO LAMUÑO
SPAIN

Domingo González-Lamuño, MD, PhD

Education & Qualifications: Specialist in Pediatrics with specific training in "Pediatric Nephrology" and "Inborn Errors of Metabolism." PhD in Medicine and Surgery with a doctoral thesis in Genetics.
Training: Post-residency Fellowship, FISS Research Training Grant, Municipal Institute of Medical Research, Barcelona (IMIM). Research stays in leading international centers for rare metabolic hereditary diseases at the Department of Neurology, Johns Hopkins Hospital, Baltimore, USA (Aug 2005- Mar 2006), and the Metabolic-Hereditary Diseases Service, at Necker Hospital, Paris, France (July-Aug 2012).
Current Position: Full Professor of Pediatrics, University of Cantabria. Director, Department of Medical and Surgical Sciences, University of Cantabria. Consultant and Attending Physician in Pediatrics at the Marqués de Valdecilla University Hospital, Santander, Cantabria. President of the Spanish Association for the Study of Inborn Errors of Metabolism (AECOM). Full Member, Royal Academy of Medicine of Cantabria (since Nov 2019).

DULCE QUELHAS
PORTUGAL

Dulce Quelhas, PharmaD, PhD

Obtained her degree in Pharmaceutical Sciences – Clinical Analysis from the University of Porto in 1986, a Master's in Human Genetics from the Faculty of Sciences, and a PhD in Biomedical Sciences from the Abel Salazar Institute of Biomedical Sciences, also at the same university.
She completed her specialist training in Human Genetics at the Jacinto de Magalhães Medical Genetics Center in Porto, which is now part of the Santo António Local Health Unit (ULSSA).
She has extensive laboratory experience in the diagnosis and monitoring of hereditary metabolic diseases and specialized in biochemical and molecular diagnostics of Congenital Disorders of Glycosylation at the Department of Metabolism and Genetics at Gasthuisberg University Hospital in Leuven, Belgium, working with Professors Jaak Jaeken and Gert Matthijs.
Currently, she is responsible for the Genetic Biochemistry Laboratory at the Laboratory Genetics Service of the ULSSA Clinical Genetics and Pathology Department. Since 2015, she has been certified by the European Board of Medical Genetics.
She is a researcher at the Multidisciplinary Unit of Biomedical Research (UMIB) at the Abel Salazar Institute of Biomedical Sciences – University of Porto and has published over 60 scientific articles in internationally indexed journals.
She was a Council Member of the Society for the Study of Inborn Errors of Metabolism from 2017 to 2024. She is currently a member of the National Commission for Pharmaceutical Residency and President of the Portuguese Society of Metabolic Diseases.

FANNY MOCHEL
FRANCE

Fanny Mochel, MD, PhD

Is a professor of genetics at Sorbonne University. She received her MD in Genetics in 2005 at the University Paris Descartes, her PhD in Neuroscience in 2010 at Sorbonne University and is board certified in inherited metabolic disorders. Prof. Mochel leads a national reference center for neurometabolic diseases in adults as well as a national reference center for leukodystrophies in adults. She is also the co-team leader of the MIND team ("Metabolism, Immunity and NeuroDegeneration") at the Paris Brain Institute of La Pitié-Salpêtrière University Hospital in Paris. From 2018 to 2024, she served as chair of the Adult Metabolic Physicians group of the Society for the Study of Inborn Errors of Metabolism (SSIEM) and she is co-chair of the French society for inborn of errors of metabolism in adults since 2014. Her research has focused on the characterization and treatment of brain energy deficiencies in neurometabolic and neurodegenerative diseases. Her major areas of expertise are the identification of neurometabolic biomarkers in vitro (metabolomics) and in vivo (metabolic imaging) as well as therapeutic approaches targeting the Krebs cycle. Recently, she has developed a new area of research, together with Ángeles García-Cazorla, on the connections between physics and metabolism in brain functions and diseases.

FÁTIMA MACEDO
PORTUGAL

Fátima Macedo, PhD

Has a PhD in Biomedical Sciences (2006), a Master's degree in Immunology (1999) and a first degree in Biology (1996) all conferred by the University of Porto.
Throughout her doctoral and master's studies, she was a visiting student at Harvard University in Boston and Loyola University in Chicago, USA.
Currently, she is a professor at the Faculty of Medicine and Biomedical Sciences of University of Algarve and a researcher at the Algarve Biomedical Center Research Institute (ABC-Ri) from the same University.
Previously she served as Invited Professor at University of Aveiro and worked as a researcher at Institute for Research and Innovation in Health (i3S) and Institute for Cellular and Molecular Biology (IBMC), University of Porto.
Fátima Macedo research focuses on Lipid Immunology, particularly the role of sphingolipids in modulating CD1-restricted T lymphocytes. She investigates how this modulation impacts various Lysosomal Storage Diseases, including sphingolipidoses such as Acid Sphingomyelinase Deficiency, Gaucher disease, and Fabry disease.
She has pioneering work published on the Molecular Genetic and Metabolism Journal, the official journal of the Society for Inherited Metabolic Disorders, as well as in The European Journal of Immunology and Nature Immunology.
Fatima Macedo work has received several awards including The Gaucher Generation Award and awards from the Portuguese Society of Metabolic Diseases.

FÁTIMA VENTURA
PORTUGAL

Fátima Ventura, PhD

Pharmacist, PhD in Biochemistry, Assistant Professor and member of the Metabolism, Genetics and Proteins in Health & Disease Group from iMed, Research Institute of Medicines, both at the Faculty of Pharmacy of the University of Lisbon.
Since 2007 is under service commission at INFARMED - National Authority of Medicines and Health Products, I.P., where is the current Head of the Scientific Evaluation Unit of the Medicines from the Medicines Evaluation Department. Since 2010 is a member of the Medicines Evaluation Committee from INFARMED.
From 2016 until 2024 was the alternate member for Portugal at the Committee for Medicinal Products for Human Use (CHMP) from the European Medicines Unit (EMA). Is currently the member representing Portugal in this committee. Since 2016 is also the member representing the CHMP in the Healthcare Professionals Working Party (HCPWP) and the alternate member in the Patients and Consumers Working Party.
Since 2020 is the member representing INFARMED in the Technical Commission for the Vaccines against COVID-19 (CTVC) currently renamed Technical Commission for the Seasonal Vaccines (CTVS) from the Health General Directorate.
Has a scientific interest for Inborn Errors of Metabolism, in particular related with fatty acids metabolism and their underlying pathogenic mechanisms such as metabolites toxicity and protein misfolding and the search for new therapeutic strategies.

FRÉDÉRIC M. VAZ
THE NETHERLANDS

Frédéric M. Vaz, MS, PhD

Clinical Biochemist in Inborn Errors of Metabolism and Head of the Core Facility Metabolomics, Amsterdam UMC.
Frédéric Maxime Vaz obtained his Master's degree in Chemistry, specializing in biochemistry, at the University of Utrecht in 1997. He conducted his PhD research at the Laboratory Genetic Metabolic Diseases in Amsterdam, focusing on carnitine biosynthesis.
During his postdoctoral studies, he expanded his research on carnitine biosynthesis and began investigating Barth syndrome, which sparked his interest in lipid metabolism, particularly cardiolipin. During this period, he also trained as a clinical biochemist specializing in inborn errors of metabolism and became an NVKC-certified instructor in 2012.
Currently, Dr. Vaz is part of the management team of the Laboratory Genetic Metabolic Diseases at Amsterdam UMC, where he oversees metabolite diagnostics for inborn errors of metabolism. As the head of the Core Facility Metabolomics, he leads the development of advanced lipidomics and metabolomics platforms, including the necessary bioinformatics.
His work focuses on discovering novel biomarkers for inborn errors of metabolism and applying these platforms for both diagnostic and research purposes, with the goal of advancing the understanding and management of metabolic diseases.

GEORGE J.G. RUIJTER
THE NETHERLANDS

George J.G. Ruijter, PhD

Has a PhD in chemistry and is a registered Laboratory Specialist Clinical Genetics at the department of Clinical Genetics, Erasmus Medical Centre, Rotterdam, The Netherlands, since 2006.

He is the head of the laboratory for diagnostics of Inborn Metabolic Disorders, which performs screening new patients as well as metabolite analysis in known IMD patients for therapy monitoring using state-of-the-art methods, such as mass spectrometry. In addition, he is responsible for training of biochemical geneticists in the Erasmus MC.

He has been involved in External Quality Assurance since 2009 as the Scientific Advisor of the ERNDIM Diagnostic Proficiency scheme.

As of 2016 he is member of the ERNDIM Executive Committee and currently chair of the Scientific Advisory Board. His main professional interests are diagnostic test development, novel applications of mass spectrometry such as metabolomics, and biochemistry and treatment of lysosomal storage disorders. He supervises development of metabolomics as a diagnostic tool as well as metabolomics research projects to understand pathology of metabolic diseases and discovery of novel biomarkers. He has published more than 100 papers in peer reviewed international journals and books.

HOLGER PROKISCH
GERMANY

Holger Prokisch, PhD

Is the head of the research group "Genetics of Mitochondrial Diseases" at the Institute of Human Genetics, School of Medicine, TUM Klinikum, and the Institute of Neurogenomics, Department of Computational Health, Helmholtz Munich, Germany.

Holger Prokisch explores genetic variation in both rare and common diseases with a functional focus on mitochondria-related disease mechanisms.

His group was successful in integrating genomic approaches with detailed functional biochemical investigations.

Holger Prokisch contributed to the discovery of more than 80 novel disease genes, by applying whole exome and genome sequencing. He extended the diagnostic toolbox by establishing RNA-sequencing and proteomics pipelines for the diagnosis of Mendelian diseases. Much of his work is focused on advanced diagnostics by multi-omics integration. He coordinates the German and Eurasian network for mitochondrial disorders mitoNET and GENOMIT (EJP RD).

In 2024 Holger Prokisch was awarded with the GfH most prestigious award, the GfH Medal of Honor. The GfH Medal of Honor recognizes human geneticists who have made significant scientific contributions, advanced the field of human genetics, and demonstrated exemplary character in Germany.

HUGO ROCHA
PORTUGAL

Hugo Rocha, PhD

Has a PhD in Biochemistry, a Master in Applied Human Genetics, and a degree in Biology. He is a Clinical Laboratory Geneticist at Newborn Screening, Metabolism and Genetics Unit of the Genetics Department from the National Institute of Health Doutor Ricardo Jorge at Porto, and Invited Professor at School of Health of Polytechnic Institute of Porto.

The main areas of interest are Newborn Screening and Inherited Metabolic Disorders, namely new screening/diagnostic approaches as well the unrevealing of the pathophysiologic basis of inborn errors of metabolism.

Has particular interest in the application of mass spectrometry to the field of inborn errors of metabolism. He is a Board Member of the SPDM – Portuguese Society for Metabolic Disorders and integrates several international working groups in the field of Newborn Screening and Metabolic Diseases.

JOÃO GUIMARÃES
PORTUGAL

João Guimarães, BSc, PhD

Has a BSc in Computer Science and Systems Engineering (2007) and a PhD in Artificial Intelligence (2013) from University of Minho, Braga, Portugal. He leads the research group in health data science and genomics at Lisbon School of Medicine, using "big data" and cutting-edge technology to develop computational models for improving human disease management.

During his PhD studies, João developed several machine learning models to predict sequence-activity relationships in the model organism E. coli. His discoveries led to a better understanding of gene expression regulation in microorganisms and how related biological processes could be harnessed to optimize the production of biochemical compounds for human benefit. For his postdoctoral studies, Joao shifted his focus to studying mammalian systems and developed a strong interest in building computational models to understand normal physiology and disease development. His work focused on integrating biological "big data" (genomics) to reveal insights into human health-related open questions in the areas of immunology, cancer, and aging.

In 2023, João was selected to be the ERA Chair Holder for the iSTARS (Informatics and Statistical Tools for the Advancement of Research Success) project at the Lisbon School of Medicine, where he is an Invited Full Professor leading a multidisciplinary team working in the biomedical and healthcare fields, combining data science, machine learning, computational biology, genomics, and systems biology. His research interests include the development of machine learning models that integrate distinct health-related data modalities to better understand normal physiology and disease development.

JULIEN BARUTEAU
UNITED KINGDOM

Julien Baruteau, MRC

Is a MRC Clinician Scientist Fellow at University College London Great Ormond Street Institute of Child Health, and Consultant in Metabolic Medicine at Great Ormond Street Hospital for Children, London.
His research focuses on studying the pathophysiology and developing novel therapies for inherited metabolic diseases.
He is developing gene therapy using both viral and non-viral vectors and has expertise in translating academic and industry-led programmes of gene therapies into first-in-human clinical trials.

KAREN GUNANAYAGAM
UNITED KINGDOM

Karen Gunanayagam, MD

Is a clinical research fellow at the UCL Queen Square Institute of Neurology in London. She works in the departments of Neuromuscular/Neurogenetics and Neuroinflammation under the supervision of Professor Henry Houlden, Professor Jeremy Chataway, and Dr David Lynch.
After graduating from Imperial College London, she completed her adult neurology specialist training in Australia, with subspecialty training in Sydney in multiple sclerosis and neuroimmunology, as well as mitochondrial disorders under Professor Carolyn Sue.
Having been clinically focused with the opportunity to work in diverse hospitals across Australia, Karen joined Queen Square to study white matter and myelin disorders and develop her academic career. In addition to clinical and trial work, she presents the UK adult inherited white matter disorder meetings and is exploring genetic research techniques and analyses for her PhD thesis, which will focus on unravelling genetically unsolved leukodystrophies.

MARCO F. MOEDAS
SWEDEN

Marco F. Moedas, MSc, PhD

Was born in Portugal in 1986 in the city of Almada, just across the river from Lisbon. Graduated from Universidade Nova de Lisboa (FCT-UNL) in Cellular and Molecular Biology in 2007 and followed by a MSc from the Universidade de Lisboa (FCUL) in Human Molecular Biology in 2009.
He joined Prof. Isabel Tavares de Almeida's lab at Faculdade de Farmácia of the Universidade de Lisboa (FFUL) in 2010 as an analytical chemist in the area of IEM. Started his Ph.D. in 2011 with Prof. Margarida F. B. Silva at FFUL and with Prof. Ronald Wanders at the Amsterdam Academical Medical Center in the Netherlands (AMC, currently UMC) on the topic of xenobiotic metabolism, focusing on the effects of sodium valproate on liver metabolism.
In 2017 he rejoined Prof. Isabel Tavares de Almeida's lab as analytical chemist until 2018 when he joined Prof. Anna Wredenberg's lab at the Karolinska Institute in Stockholm Sweden as postdoctoral researcher. There he worked on establishing cellular, mouse and fruit fly models of mitochondrial disease, developing of new mass spectrometry-based methods for quantification of mitochondrial metabolites, and analysis of proteomes in human mitochondrial disease patients.
Since 2022 he works as a clinical chemist at the national newborn screening laboratory at the Karolinska University Hospital (PKU-Lab) in Stockholm, in charge of maintenance and development of mass spectrometry-based methods and instruments related with newborn screening.

MARJORIE DIXON
UNITED KINGDOM

Marjorie Dixon, MSc

Is a Clinical Lead Dietitian for metabolic medicine, at Great Ormond Street Hospital for Children, London.
Marjorie has specialised in the dietary management of children with inherited metabolic disorders for over 35 years. She is primarily a clinical dietitian but is also actively involved in teaching, both nationally and internationally, as well as in research. She is a committee member of SSIEM-Dietitians Group and is an active member of the BIMDG-Dietitians Group, UK.
Marjorie is the dietitian member of the IMD Screening Advisory Board, NHS England. She was lead dietitian for the Dietetic management of Inherited Metabolic Disorders module for the MSc in Advanced Professional Practice in Paediatric Dietetics.
She is co-author of the Dietary Management of Inherited Metabolic Disorders section in Clinical Paediatric Dietetics, 6th edition, in press.

PATRÍCIA LIPARI PINTO
PORTUGAL

Patrícia Lipari Pinto, MD

Hereditary Metabolic Disease Reference Center, Paediatric Department, Santa Maria's Hospital - Lisbon North University Hospital Center, EPE, Lisbon, Portugal.
Responsible for metabolic diseases consultation at the out-patient clinic for diagnostic orientation and therapeutic management of hospitalised patients with metabolic diseases.
Responsible for expert support in metabolic diseases, upon request, to other pediatric units for suspected diagnosis of inborn errors of metabolism.
Member of the Neonatal Intensive Care Emergency team of the Pediatric Department, Santa Maria's Hospital.
Orientation and training of paediatric residents and medical students of the Faculty of Medicine, Lisbon University.
Member of the Portuguese Society of Metabolic Diseases (SPDM).
Member of the Working Group on Lysosomal Storage Diseases of the SPDM.
Member of the Training Unit of the Paediatrics Department of CHULN.
Specialised Training in Medical Paediatrics.
Inborn Errors of metabolism (6 months), Neuropediatric (6 months), Genetics (3 months), Paediatric Intensive Care (3 months), Neonatal Intensive Care (3 months), Paediatric Gastroenterology (3 months).
Master's in Medicine at: Lisbon Medical University, Lisbon, Portugal.
Master's Degree, with a final course average of 17 out of 20. The final master's work is titled, "Creatine Carrier Deficit - How far do we investigate the cause of a developmental delay?"
Fellowship in Paediatric Metabolic Department at Great Ormond Street Hospital for Children. London, UK.
Fellowship in Pediatric Neurology Department, in Neurometabolic Disorders at Sant Joan de Déu Hospital, with Dr. Àngels García Cazorla, Barcelona-Spain.

ROBIN LACHMANN
UNITED KINGDOM

Robin Lachmann, MD, PhD

Qualified in 1990 and trained in general internal medicine before completing a PhD on the use of Herpes Simplex Virus for gene delivery to the brain. Then combined ongoing research on gene delivery in mouse models of lysosomal storage disorders with training in metabolic medicine.
In 2005, took up his current position at the Charles Dent Metabolic Unit at University College London Hospitals. The unit provides multidisciplinary care for adults with a range of inherited metabolic disorders, caring for approximately 2000 patients.
Robin Lachmann is a former chair of the SSIEM Adult Metabolic Physician Group, Chair of the Scientific Committee of the Recordati Rare Diseases Foundation, a member of the Fetal, Maternal and Child Health Group of the UK National Screening Committee, and NHS England's National Specialist Advisor for Metabolic Disorders.

RUI SANTOS IVO
PORTUGAL

Rui Santos Ivo, PhD

Is currently President of INFARMED – National Authority of Medicines and Health Products, I.P. (since july 2019), and Guest Associate Professor at the Faculty of Pharmacy of the University of Lisbon in the area of Medicines Regulation (since 2009).
At European level, he is the Vice-President of the Management Board of the European Medicines Agency (EMA) (since October 2024), Vice-Chair of the Valletta Standing Technical Committee/Valletta Declaration (since July 2017) and also Chair of the Heads of Health Technology Assessment Agencies Group (HAG) (since September 2021).
Rui Santos Ivo graduated in Pharmaceutical Sciences from the University of Lisbon in 1987. Specialist in Hospital Pharmacy by the Ministry of Health (1992) and the Portuguese Pharmaceutical Society (2006) and in Regulatory Affairs, honorary by the Portuguese Pharmaceutical Society (1997). With postgraduate training in Health Law (Faculty of Law, University of Lisbon and National School of Public Health, 1997), Pharmaceutical Medicine (University of Basel, 1999), Regulation (London School of Economics and Political Science, 1999), Management of Health Units (Portuguese Catholic University, 2000 and AESE Business School, 2015).

SANDRA ALVES
PORTUGAL

Sandra Alves, PhD

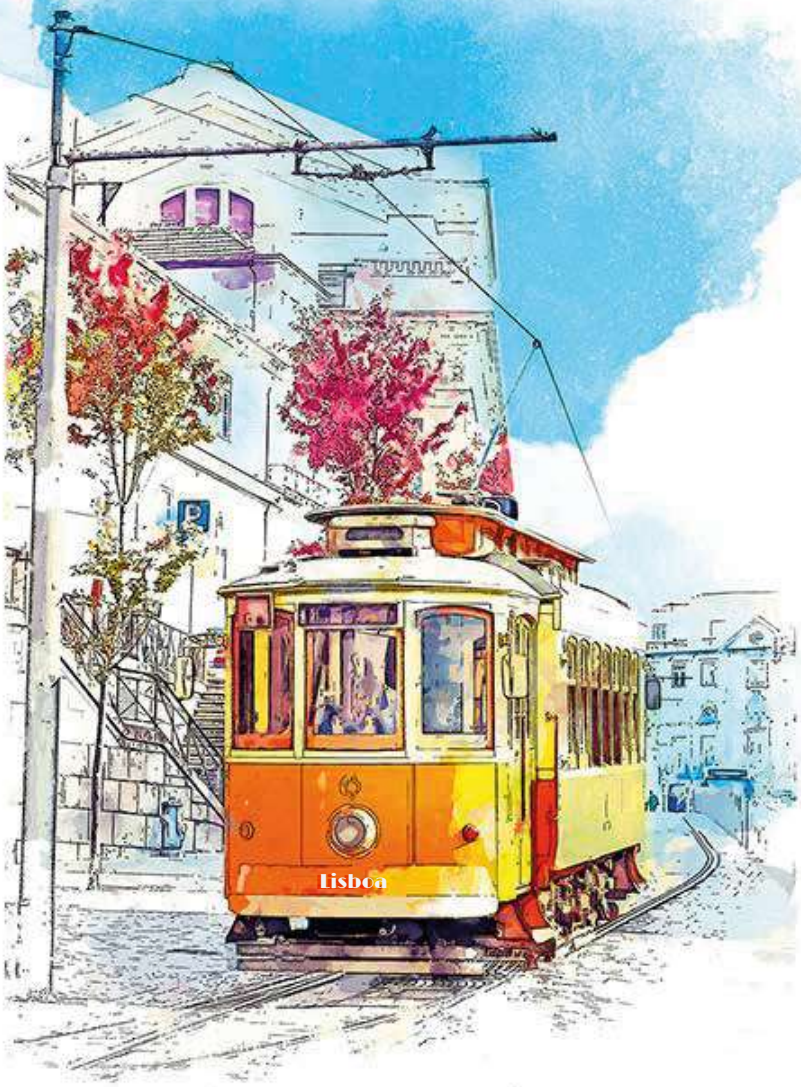
Has a degree in Biology (1995), a master in Applied Human Genetics (1997) and a PhD in Biology (2002) from the Faculty of Sciences - University of Porto.
Currently, she is Principal Investigator at the Research Unit - Department of Human Genetics, National Institute of Health Dr. Ricardo Jorge (INSA) and leader of the Lysosomal Storage Disorders Research Group. Presently her group integrates the FCT Research Unit, Center for the Study of Animal Science (CECA) - University of Porto being Sandra Alves also responsible for the thematic line - Inherited metabolic diseases in human and animals: mechanisms and therapies.
She is the INSA's representative in the Portuguese Commission for the Treatment of Lysosomal Storage Diseases and in the European Rare Diseases Research Alliance (ERDERA) and coordinator of the National Mirror Group of this Programme in Portugal.
Her research focuses on LSDs, with an emphasis on the development of innovative therapies, including RNA-based approaches. With over 50 publications and over 150 peer-reviewed presentations, she has contributed to the study of these rare diseases, as well as to the training of several specialists in the field.

SHAMIMA RAHMAN
UNITED KINGDOM

Shamima Rahman, MD, PhD

Is Professor of Paediatric Metabolic Medicine at the UCL Great Ormond Street Institute of Child Health (ICH) and honorary Consultant at Great Ormond Street Hospital for Children, London.
She established the Mitochondrial Research Group at ICH in 2000, which she continues to lead. The group focuses on enhancing outcomes for children affected by mitochondrial and other rare metabolic diseases by improving diagnostic strategies and investigating novel therapeutic approaches.
Professor Rahman is Editor in Chief of the Journal of Inherited Metabolic Disease, sits on the Medical Advisory Boards of the Lily Foundation and the Freya Foundation, is a member of the Medical Research Council Clinical Training Panel, a Director of the North American Metabolic Academy, and acts as a special adviser to the UK's Human Fertilisation and Embryology Authority.

SESSION I



INNOVATION IN DIAGNOSTIC METHODS FOR CLASSIC INHERITED METABLIC DISORDERS (IMD)

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Metabolomics to screen for classic IMD

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Untargeted metabolomics is a powerful approach to analyse metabolite profiles because of the ability to detect many metabolites using a single platform. For many years untargeted metabolomics has been used to investigate differences between defined sample sets, each including multiple samples, e.g. disease versus control. Only recently, untargeted metabolomics approaches have been applied successfully as diagnostic methods in the field of inborn metabolic diseases (IMD). Compared to a research setting a diagnostic procedure is very different: analyzing a single sample to detect metabolite abnormalities suggestive for an IMD. Generally, such approaches analyse plasma samples and include sample workup, liquid chromatography, high-resolution mass-spectrometry, raw data processing and data analysis. While an untargeted metabolomics dataset measures thousands of metabolites, a subset of several hundreds of metabolites relevant to IMD is identified with high confidence to ensure high-quality diagnostic reporting. The possibilities and limitations of untargeted metabolomics as a diagnostic screening tool will be demonstrated with results from several IMD's, such as PKU, CPT II deficiency, pyridoxin-dependent epilepsy (antiquitin deficiency) and alkaptonuria. A major advantage of metabolomics is the possibility to detect new biomarkers as well as known biomarkers that are outside the scope of traditional targeted assays, which I will show with examples such as arginase deficiency and homocystinuria (Cystathionine-beta-synthase deficiency). Integration of DNA sequencing data (WES/WGS) and metabolomics data is a key step to improve diagnostic screening for IMD. Firstly, metabolomics can be used ad hoc to clarify the pathogenicity of variants of unknown significance (VUS), just as traditional targeted assays, but using the above mentioned advantages of metabolomics. As a next step we have developed an algorithm, 'Reafect', to translate metabolomics profiles to enzyme deficiencies. Reafect calculates for each reaction (enzyme) in metabolic pathways a score indicating whether that reaction is deficient or not. Combining Reafect scores with CADD scores obtained from sequence data significantly improved the prioritization of the genes containing the disease-causing variant when compared with the two approaches individually.

Advances on integrative omics approaches to IMD diagnosis

Holger Prokisch

School of Medicine, Institute of Human Genetics, Technical University of Munich, Munich, Germany and Institute of Neurogenomics, Computational Health Center, Helmholtz Munich, Neuherberg, DE

Quantitative Proteomics in Mitochondrial Disease – where are we now?

Marco F. Moedas

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Background: Mitochondrial diseases are a group within inborn errors of metabolism (IEM) that mainly affect cellular energy metabolism. These disorders present with a prevalence of between 1:2000 to 1:5000 births and are caused by genetic variants in around 400 genes in both mitochondrial and nuclear genomes. The clinical presentations of these diseases are diverse and manifesting at any age, affecting multiple organ systems. Mitochondrial disease diagnosis was classically performed with a combination of biochemical analysis and clinical investigations but yielded poor diagnostic rates. The inclusion of genomic data through next-generation sequencing has greatly aided these investigations, increasing the diagnostic rate to approximately 50%. The inclusion of other -omics tools such as RNA sequencing (RNA-seq) and Proteomics is expected to further increase this rate. This study aimed to investigate if the inclusion of proteomic analysis in the diagnostic pipeline can provide extra information that can assist in the diagnosis odyssey of these patients.
Methods: A label-free quantification (LFQ) mass spectrometry-based proteomics analysis was performed on cultured fibroblasts obtained from 67 mitochondrial disease patients where a genetic cause was either identified or suspected and from 17 suitable control individuals. Descriptive and inferential analysis was performed at a group or individual level using adequate statistical modelling.
Results: We identified six potential biomarkers of mitochondrial disease that were consistently up- or downregulated in all the patient groups when compared with controls. Gene set enrichment analysis (GSEA) of the obtained datasets also revealed specific changes in pathways related with the mitochondrial disease groups, namely changes to inflammatory and mitochondrial stress responses. Furthermore, we potentially solved a suspected case of mitochondrial disease where a variant of uncertain significance had been identified.
Conclusion: The application of mass spectrometry-based proteomics in fibroblasts from mitochondrial disease patients yields promising results, providing further evidence for the versatility of this tool in the mitochondrial disease diagnosis pipeline.

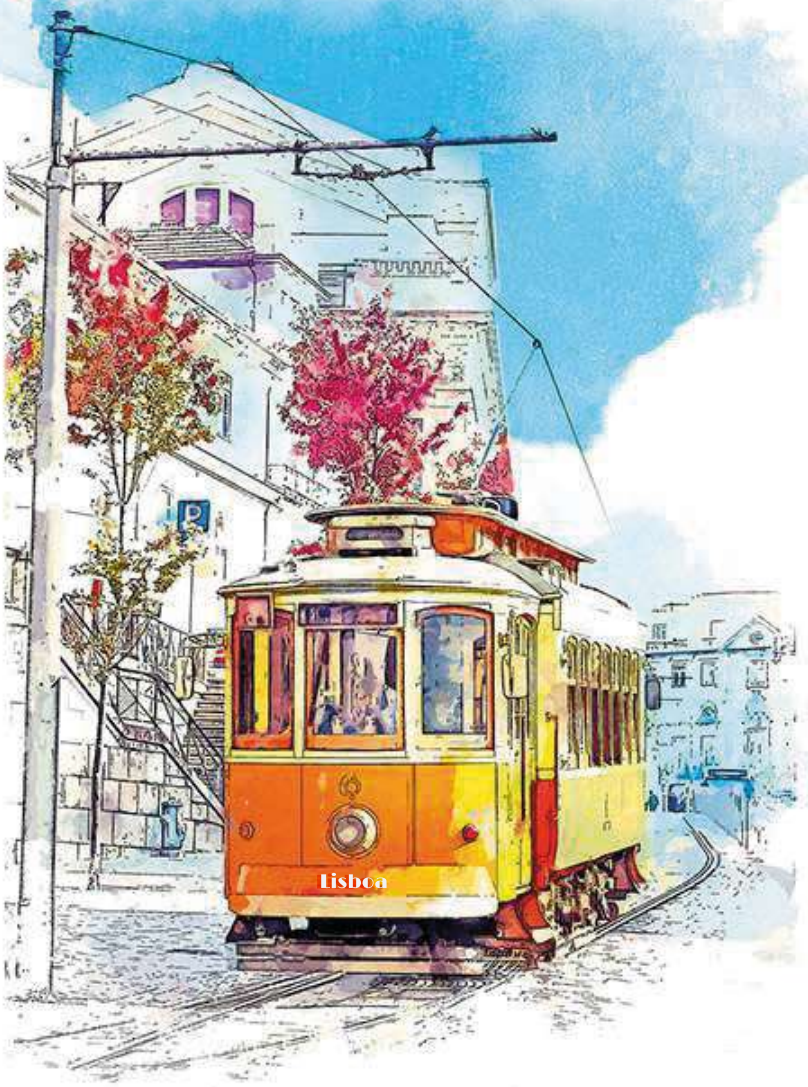
Lipidomics in IMD for biomarker discovery

Frédéric M. Vaz

Laboratory Genetic Metabolic Diseases, Department of Laboratory Medicine, Amsterdam UMC location University of Amsterdam, Amsterdam, NL

Lipidomics has become an essential tool for expanding our understanding of inherited metabolic disorders (IMDs). This presentation introduces a novel lipidomics platform that enhances the detection of IMDs in plasma, serving as a valuable addition to small molecule metabolomics. By enabling comprehensive lipid profiling, this platform provides a broader perspective on metabolic disruptions associated with IMDs.
Beyond plasma diagnostics, this technology supports biomarker discovery in various tissues. Recent findings in brain tissue have highlighted its potential to identify novel lipid biomarkers, offering critical insights into the pathophysiology of neurological metabolic disorders. These advancements underline the role of lipidomics in improving diagnostics and fostering therapeutic innovation for IMDs.

SESSION II



RETHINKING NEWBORN SCREENING (NBS)

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New Challenges in Newborn Screening

Hugo Rocha

Instituto Nacional de Saúde Dr Ricardo Jorge, Porto, PT

Newborn screening (NBS) programs are public health interventions aimed to identify newborns with severe but treatable conditions and have seen significant evolutions since their initial implementation, more than 60 years ago. Recent developments include the adoption of a broader class of laboratory screening approaches, an increasing number and type of biomarkers and of disorders included in screening panels. These developments, that are based on the combination of technological laboratory advancements along with the development of new and effective therapies, pose several challenges to NBS programs. Among these are the need to keep sensitivity and specificity (analytical and from the screening process) within acceptable values in public health; analytical and clinical validity of NBS for rare/ultra-rare disorders; definition of true patients; definition on who to treat; long-term clinical benefits; ethical and psychosocial issues, just to cite some. In addition, the possibility to screen an unprecedented number of pathologies, envisioned through the adoption of new technologies, such as genomics, significantly increases public pressure on the Programs to rapidly expand the number of screened diseases.
We are living times of unprecedent developments in NBS which fill us all with hope, but that are accompanied by increasingly growing challenges to be faced by NBS programs.

Challenges of using whole genome sequencing in population NBS

Robin Lachmann

Charles Dent Metabolic Unit, National Hospital for Neurology and Neurosurgery, London, UK

The UK has one of the most limited newborn screening programmes of any developed nation. This is mostly because the National Screening Committee, which oversees all screening programmes in the UK, requires levels of evidence which are difficult to obtain for rare diseases. Partly in order to address this issue, Genomics England, a company wholly owned and funded by the UK Government, proposed the Generations Study. The Generations Study will perform whole genome sequencing on 100,000 neonates with the aims of identifying babies with rare conditions earlier, and enabling population genomics research by linking genomic data to lifetime health records. The Generations Study is currently screening for genetic variants involved in over 220 different, treatable diseases. In this presentation I will discuss the potential problems with using genetic testing as a screening test in an unselected population and how it might compare with our current screening protocols for inherited metabolic diseases, and the ethics of collecting genomic data from newborn babies.

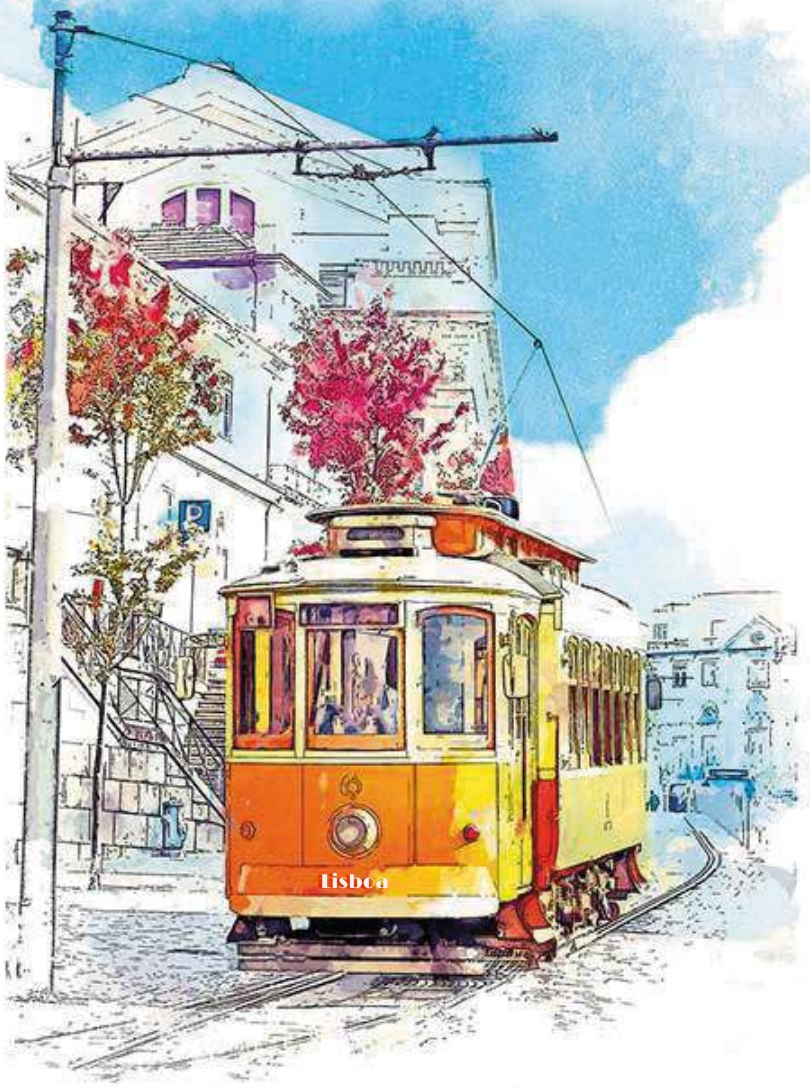
Rethinking NBS – Lessons from adult metabolic medicine

Fanny Mochel

Department of Medical Genetics Reference Centers for Adult Leukodystrophies, Paris and Brain Institute, La Pitié-Salpêtrière University Hospital, Paris, FR

It has been a few years since the adult metabolic physicians (AMP) group of the SSIEM has tried to raise awareness among the community about the need to learn from the experience of adult patients with inherited metabolic disorders (IMDs) to build NBS programs. Likewise, NBS was the main theme of our adult session at the SSIEM 2018 and again a main topic at the 2024 edition in Porto. The main consideration is to realize that NBS programs have been developed primarily to prevent severe pediatric forms of IMDs when a treatment is available.
However, most NBS programs are not able to differentiate pediatric forms from adult-onset forms of the disease, leading to long-term (and sometimes harmful) monitoring and possibly unnecessary treatments. Some conditions detected by NBS may even be 'risk factors' for metabolic decompensations under certain conditions, but not diseases per se. In a recent collaborative effort, the AMP advocates to develop NBS programs that use resources aiming at identifying newborns that benefit from early disease detection and treatment, without unnecessary burden on individuals that will develop disease in adulthood or potentially not at all. I will discuss especially implications of NBS for X-linked adrenoleukodystrophy, metachromatic leukodystrophy and cerebrotendinous xanthomatosis.

SESSION III



RAISING AWARENESS ON NEUROMETABOLIC DISEASES

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Metabolic epilepsies – clinical and biochemical footprints of IMD

Ángeles García-Cazorla

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Update on leukodystrophies and developing trials

Karen Gunanayagam

UCL Queen Square Institute of Neurology, London, UK

Leukodystrophies are a heterogenous group of genetic disorders predominantly affecting cerebral white matter and broadly subdivided into hypomyelinating leukodystrophies and demyelinating leukodystrophies. Manifesting from infancy to adulthood, they are often progressive, degenerative and lead to death within 5-10 years. Although leukodystrophies are considered individually rare, their true prevalence remains unknown. Estimates suggest a collective incidence of at least 1 in 4,733 and a recent UK analysis of CSF1R-related leukodystrophy suggested significant underdiagnosis. Diagnosis can be challenging requiring detailed clinical evaluation, neuroimaging, metabolic and molecular genetic testing, as well as exclusion of more common acquired mimics.

Despite available genetic testing, over 40% of leukodystrophies remain undiagnosed. Early diagnosis is critical when treatment options are limited. Disease-modifying treatments include chenodeoxycholic acid replacement therapy for Cerebrotendinous xanthomatosis, as well as haematopoietic stem cell transplantation for patients with selected leukodystrophies in the very early stages of disease (X-linked Adrenoleukodystrophy, Metachromatic Leukodystrophy, Krabbe Disease, and Adult-onset Leukoencephalopathy with Axonal Spheroids and Pigmented Glia). Furthermore, a diagnosis provides access to much-needed emerging clinical trials and novel genetic therapies.

This presentation outlines a diagnostic framework through a case study, explores clinical trials and emerging therapeutic options, and describes how advanced genetic techniques will be used to unravel genetically unsolved leukodystrophy cases.

Movement disorder increases with age in argininosuccinic aciduria

Julien Baruteau

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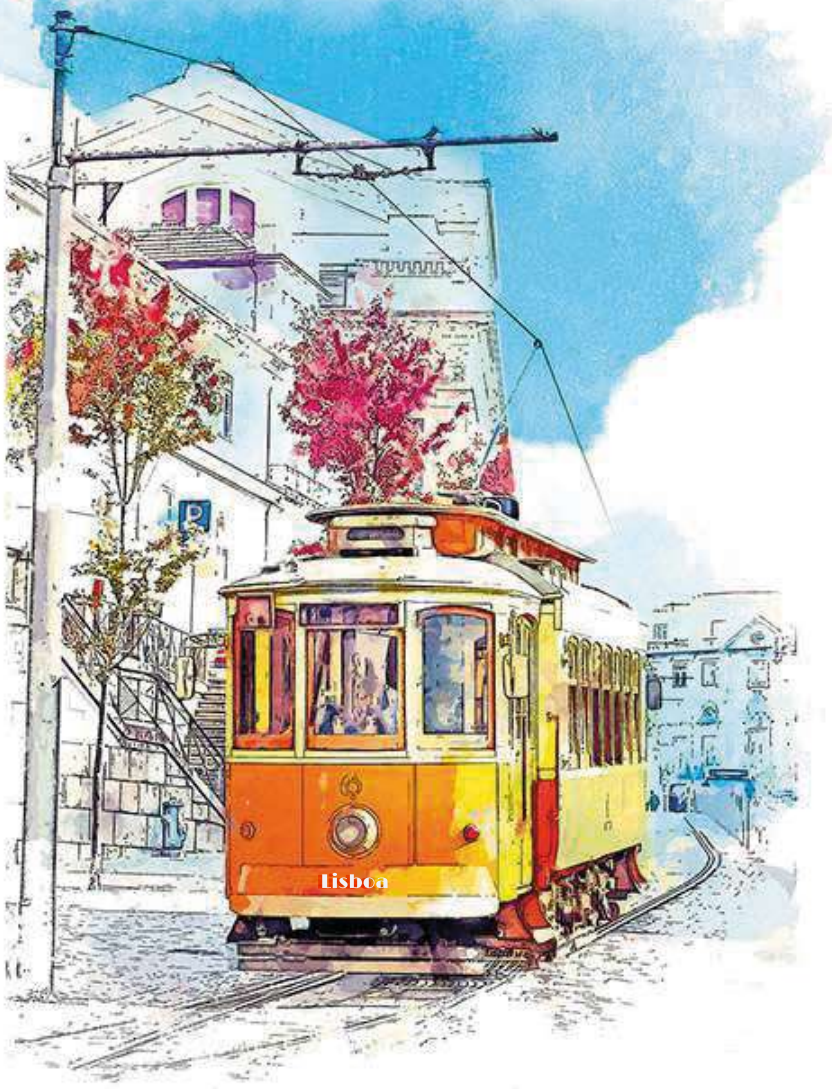
Argininosuccinic aciduria (ASA) is the second most common urea cycle defect and presents with a systemic phenotype, especially a chronic encephalopathy, in addition to the ureagenesis defect. This neurological disease entails intellectual disability, epilepsy and movement disorder, and remains refractory to standard of care. The long-term neurological phenotype is poorly described and the pathophysiology remains largely unknown.
We conducted a retrospective multicenter British study on a cohort of 60 patients, to delineate the phenotype of movement disorder. We showed that these symptoms usually start in the 2nd and 3rd decades and their frequency increase with age.
We studied brain MRI findings including diffusion tensor imaging (DTI) sequences of a juvenile patient with movement disorders and compared it to sex- and age-matched controls. Conventional sequence T1 was normal, but abnormal DTI features affected both grey and white matter, preferentially basal ganglia.
We attempted to model these abnormal neuroimaging features in ASA mice treated with systemic hASL mRNA and normalised ureagenesis.
We assessed the neurological disease with behaviour, biochemistry, oxidative stress and neuroimaging via conventional and DTI MRI alongside single photon emission computer tomography (SPECT) with dopamine analogue radionuclide 123I-ioflupane. We showed significant improvement of the neurological disease between wild-type and mRNA-treated ASA mice.
We observed expression of human ASL in the brain, confirming significant LNP-mRNA crossing of BBB to enable cerebral in situ endogenous ASL expression.
In summary, these findings support the pathophysiology of a late-onset movement disorders with functional central catecholamine dysregulation recently described. Systemically-administered hASL mRNA-LNP therapy crosses the BBB and enables in situ cerebral ASL expression. This therapy provides significant neurological benefit in ASA, which supports clinical translation.

SESSION IV



ORAL COMMUNICATIONS

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OC01

Characterization of quaternary structures of human phenylalanine hydroxylase

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Main category: Basic science study

Disease category: Intermediary metabolism: nutrients

Introduction: Biologically active human phenylalanine hydroxylase (PAH) is a homotetramer (HT; 200 kDa) assembling as a dimer of homodimers (HD; 100 kDa), existing in solution in a HT (major species) ↔ HD equilibrium. Comparing to HD, HT present higher catalytic activity, substrate (L-Phe) pre-activation and a sigmoidal L-Phe kinetics. Remarkably, when produced in different prokaryotic expression systems, an oligomeric form of 400 kDa corresponding to octamers (HO) is systematically detected.
The aim of this study was to isolate HO and characterize their functional and structural properties.

Methods: PAH was produced in E. coli, with a 6xHis tag and purified by affinity chromatography. HO and HT were then isolated using a size exclusion chromatography (SEC) and evaluated regarding enzyme activity, L-Phe activation, thermal stability, global conformation, and aggregation profile.

Results/Case report: The 6xHis-PAH SEC profile showed the presence of HT (60.4%), HO (22.4%), aggregates (10.7%) and HD (6.5%). HO (HO:1.25x; HT: 3.2x). The comparative analysis between HO and HT indicates that HO present: (i) lower catalytic activity (82.5% of HT) and a lower L-Phe activation ratio (2.56x decrease); (ii) similar intrinsic tryptophan fluorescence spectra in the absence and presence of L-Phe; (iii) lower susceptibility to proteolysis, but also responded to L-Phe (impacting the HO's global conformation); (iv) a regulatory domain (RD) less stable, with the catalytic domain (CD) presenting similar stability (in the absence of L-Phe) and a more stable domains in the presence of L-Phe with the CD maintaining a lower stability; (v) aggregates at lower temperature (less stable) and in the presence of L-Phe at higher temperatures (compared to HT).

Conclusion: HO are an enzymatically active form. The lower L-Phe activation ratio suggests that HO exist in partially activated form, or that HO are not able to respond to L-Phe activation at the same extent than HT. Thermostability studies showed that the Tm of the HO-RD (absence of L-Phe) and HT-RD (presence of L-Phe) are different, suggesting that HO do not exist in a pre-activated form. Hence, an inefficient/compromised L-Phe binding to the allosteric site localized in the RD may be responsible for the lower L-Phe activation. We postulate that HO may assemble as tetramers of tetramers impacting the RD.

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

OC02

Off target effect of the in vivo brain delivery of CYP46A1 by intravenous administration of adeno-associated virus vector has a beneficial role in NPC liver phenotype

M. Nunes [1,2]; A. Neves Carvalho [1,2]; D. Risso [2]; J. Reis [2]; I. Caria [2]; J. Mateus [3]; R. Mendes de Almeida [2]; M. Gama [1,2]; C. Pereira Rodrigues [1,2]; S. Xapelli [3]; M. Diógenes [3]; M. Castro-Caldas [2,4]; R. Castro [1,2]; F. Piguet [5]; N. Cartier [5]; E. Rodrigues [1,2]

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Main category: Translational science study

Disease category: Complex molecule and organelle metabolism

Introduction: Niemann-Pick type C disease (NPC) is a rare and fatal autosomal recessive lysosomal storage disorder, marked by the accumulation of cholesterol and other lipids in the late endosomes and lysosomes [1]. As a neurovisceral disorder, NPC is characterized by progressive neurodegeneration, leading to motor impairment, cognitive decline, and premature death. Additionally, patients exhibit a metabolic dysfunction, including hepatomegaly, hepatic inflammation, and mild fibrosis, further contributing to disease pathology.

Methods: We have shown that intravenous AAV-mediated CYP46A1 delivery to Npc1tm(I1061T) mice improves NPC disease neuronal phenotype [2]. Herein, we evaluated the consequences of CYP46A1 expression, a neuron-specific enzyme, on liver function and physiology.

Results/Case report: The systemic delivery of CYP46A1 gene therapy vector, while clinically relevant, may result in off-target expression of this neuron-specific enzyme in peripheral tissues, particularly the liver, prompting an evaluation of its broader physiological effects.
Ectopic expression of CYP46A1 in the NPC mouse liver reduced hepatomegaly, serum alanine aminotransferase levels, inflammation, and fibrosis. It partially reverted the upregulation of Cx3cr1 mRNA levels while increasing Arg1 and Hmox1, suggesting a shift in Kupffer cell polarization toward a pro-resolving phenotype, despite unchanged infiltration.
Interestingly, CYP46A1 expression partially counteracted the severe depletion in lipid droplets in the liver of NPC mice, and increased de novo lipogenesis, suggestive of greater carbon availability for fatty acid and triglyceride synthesis.

Conclusion: Our results demonstrate that ectopic expression of CYP46A1 significantly ameliorates key pathological changes in the liver of NPC mice. While the precise mechanisms by which CYP46A1 enhances liver function remain to be elucidated, our findings further validate CYP46A1 as a promising therapeutic target for NPC disease and highlight the beneficial effects of its off-target delivery to the liver.

References:
(1) Vanier, M.T. Niemann-Pick disease type C. Orphanet J Rare Dis. 2010;5, 16;
(2) Nunes MJ, et al. Cholesterol redistribution triggered by CYP46A1 gene therapy improves major hallmarks of Niemann - Pick type C disease but is not sufficient to halt neurodegeneration. Biochimica et biophysica acta - Molecular basis of disease. 2024; 1870(3): 166993.

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OC03

Decoding Mitochondrial Glutamyl-tRNA Synthetase Variants: Structural and Biochemical Approaches to Understanding Leukoencephalopathy

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Main category: Intermediary metabolism: energy

Disease category: Several disease categories

Introduction: Mitochondrial aminoacyl-tRNA synthetases (mt-aaRS) are essential for mitochondrial protein synthesis by attaching amino acids to their corresponding tRNAs. Variants in these enzymes are increasingly linked to mitochondrial disorders (MDs), including several identified in Portugal. Understanding how these variants disrupt mitochondrial function is key to advancing our knowledge of MDs. Our study focuses on mitochondrial glutamyl-tRNA synthetase (EARS2), exploring both wild-type and disease-associated variants to better understand genotype-phenotype correlations.

Methods: EARS2 proteins, including wild-type and three disease variants, were heterologously expressed in E. coli and purified through chromatographic methods. We use biochemical and biophysical methods (CD, fluorescence, DSF) to assess the proteins' conformation and stability.

Results/Case report: EARS2 disease variants exhibited lower expression yields compared to the wild-type protein. Co-expression of the EARS2-p.Glu96Lys variant with molecular chaperones GroEL/GroES facilitated its production. Both wild-type and EARS2-p.Glu96Lys proteins were purified and displayed similar folded structures with an α-helical configuration, confirmed by far-UV CD. However, the EARS2-p.Glu96Lys variant demonstrated reduced thermal stability, with a melting temperature 4°C lower than the wild-type. EARS2-E96K also showed consistently lower chemical stability, greater susceptibility to proteolysis degradation with trypsin, and increased propensity to precipitation.

Conclusion: Our work provides a crucial step toward understanding the structural and functional impacts of mt-aaRS variants in mitochondrial diseases. The refined purification protocols for EARS2 will enable further investigation into these variants and may pave the way for targeted therapeutic strategies in the future.

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OC04

Advances in the diagnosis and understanding of mitochondrial cytopathies: a retrospective study of genetic and clinical variability

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Main category: Case series

Disease category: Intermediary metabolism: energy

Introduction: Mitochondrial cytopathies (MCs) are a phenotypically heterogeneous group of inborn metabolic disorders (IMD) caused by mitochondrial respiratory chain dysfunction. Recent advances in molecular diagnostics have improved our understanding of these complex disorders. However, the extensive genetic and phenotypic heterogeneity of MCs remains only partially characterized and the correlations between specific genetic variants and clinical manifestations are just beginning to be unraveled. We hereby describe the phenotypic and genotypic variability of a cohort of 49 patients with MC.

Methods: Retrospective analysis of 102 patient records with clinical suspicion of MC, followed at a reference center for IMD in Portugal between 1967 and 2024. We analyzed data on genetic diagnosis, clinical signs, symptoms and their evolution, as well as complementary diagnostic analysis.

Results/Case report: Symptoms onset ranged from the neonatal period to the third decade of life, with a median onset at six months. Patients were followed for a median period of six and a half years, with 86% of patients revealing central nervous system involvement, followed by ophthalmological (38%), cardiac (26%), muscular (10%) and auditory (10%) symptoms. The median time from symptom onset to genetic diagnosis was two and a half years. Diagnosis work-up shifted from muscle biopsy towards molecular analysis. Mitochondria-related variants were found in 49 (48%) patients. Among these, 40 (82%) had nuclear DNA (nDNA) and 9 (18%) mitochondrial DNA (mtDNA) variants. Pathogenic and likely pathogenic variants were identified, some previously unreported. The most frequently implicated genes were SURF1, POLG, LYRM7, and ACAD9, among several other genes. During the follow-up period, 11 patients (22%) passed away.

Conclusion: This retrospective analysis underscores the extensive clinical and genetic heterogeneity of MCs. The shift from muscle biopsy to molecular analysis has improved the diagnostic yield, with nearly half of the cohort genetically confirmed—predominantly with nuclear DNA variants. Despite these advances, a median diagnostic delay of two and a half years and a notable mortality rate (22%) highlight the ongoing challenges. These findings stress the need for improved molecular diagnostic strategies and a personalized approach to managing MCs refining genotype-phenotype correlations.

OC05

Endocrine manifestations in patients with inherited metabolic diseases: experience of a reference center

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Main category: Basic science study

Disease category: Several disease categories

Introduction: Inherited metabolic disorders (IMDs) are rare genetic diseases that affect specific metabolic pathways on a cellular or sub-cellular level, affecting several systems, including endocrine system. IMDs are classified into 3 main groups according to their mechanisms: cellular intoxication, energy deficiency and defects of complex molecules. Despite the existence of consensus guidelines, endocrinological manifestations continue to be underrecognized. This study aims to describe endocrine manifestations in a cohort of patients with IMDs, followed in a Reference Center of Inherited Metabolic Disease.

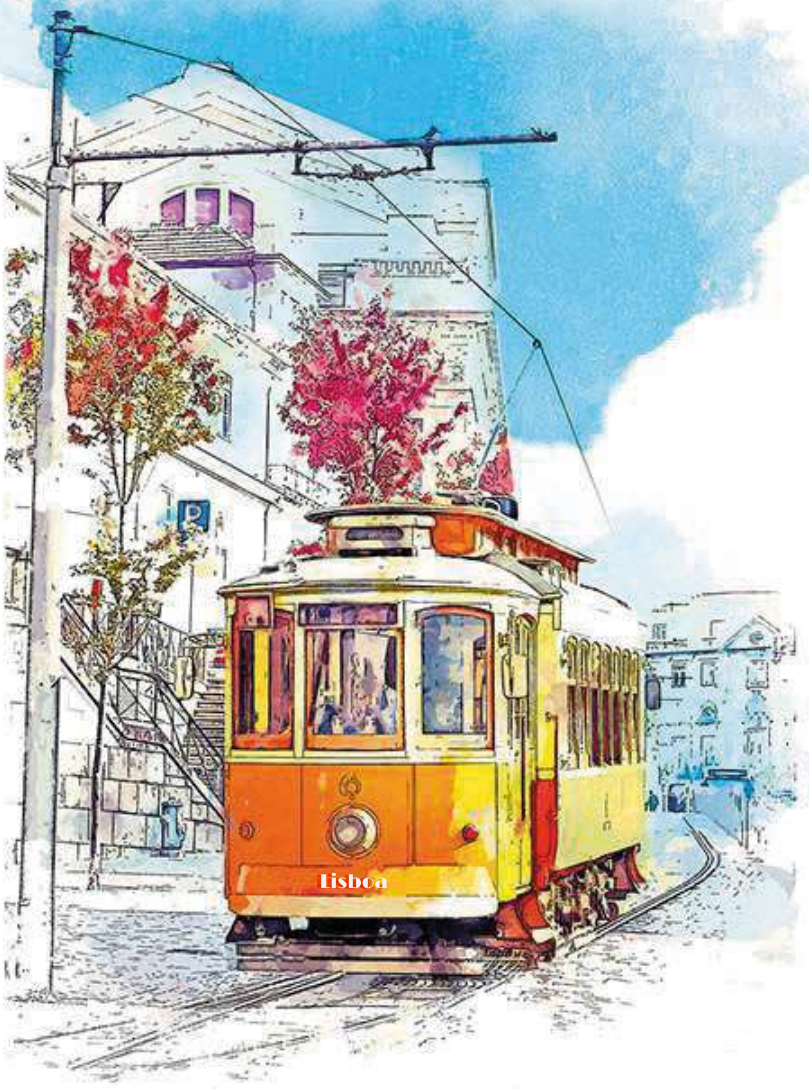
Methods: Retrospective study of demographic, clinical, and laboratory data collected from clinical records of patients with confirmed diagnosis of IMDs followed by the multidisciplinary team of the RC-IMD of ULS São José, from 2002 to 2024 (22 years).

Results/Case report: Twenty-five patients with endocrine manifestations were included: 14 (56%) from energy deficiency group (10 mitochondrial disorders, 3 MCT8 deficiency, 1 glycogenosis type I); 9 (36%) from complex molecule group (6 X-linked adrenoleukodystrophy; 3 congenital disorder of glycosylation) and 2 (8%) from intoxication group (1 galactosemia; 1 methylmalonic acidemia). Five patients (20%) had more than 1 manifestation. Fourteen (56%) were male; 5 (20%) have died; median age is 13,5 years (min 3; max 27).
In our cohort, we identified: 9 (32%) adrenal insufficiency; 7 (32%) short stature with IGF1 deficit; 6 (24%) dys/hypothyroidism; 3 (12%) premature adrenarche; 2 (8%) diabetes mellitus; 2 (8%) hypogonadism; 1 (4%) hypoparathyroidism; 1 ovarian insufficiency and 1 panhypopituitarism. Most endocrine manifestations occurred during IMDs' evolution, only 5 (20%) occurred as an initial manifestation.

Conclusion: A prospective investigation of endocrine function is included in most recent consensus guidelines since numerous asymptomatic endocrine disorders with delayed manifestations have been found. Our cohort could be underestimated, since clinical-laboratory investigation were not always carried out, in the earliest years. Each case should be individually assessed, and the greater potential for endocrine involvement of some diseases should be taken into account to ensure timely referral and intervention.

References:
(1) Heald AH, et al. Endocrine disorders in adult patients with inherited metabolic diseases: Their diagnosis and long-term management. Clin Endocrinol (Oxf), 2024;101(5):562-568;
(2) Stepien KM. Hormonal dysfunction in adult patients affected with inherited metabolic disorders. J Mother Child. 2020;24(2):21-31;
(3) Saudubray JM, et al. Proposal for a simplified classification of IMD based on a pathophysiological approach: A practical guide for clinicians. J Inherit Metab Dis. 2019;42(4):706-727.

SESSION V



E-POSTERS GUIDED WALK

P001

The Usefulness of Plasma Methylmalonic Acid and Homocysteine as Biomarkers to Assess Vitamin B12 Restriction

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Main category: Basic science study

Disease category: Cofactor and mineral metabolism

Introduction: The increasing adoption of vegan diets (VD), which lack the essential micronutrient vitamin B12, raises concerns about metabolic health. Identifying early biomarkers of B12 deficiency is critical for timely intervention, as serum B12 levels alone may be misleading and not accurately reflect true vitamin B12 status.(1,2) Chronic vitamin B12 deficiency can lead to irreversible neurological damage, emphasizing the importance of early detection and intervention.(1)
This study investigated the metabolic impact of VD-induced B12 restriction and assessed deficiency biomarkers in mice.

Methods: Female C57BL/6 mice (4 weeks old) were fed either a control diet (CD, n=7) or a B12-restricted diet mimicking a VD (n=14) for 21 weeks. Parameters evaluated: body weight, food intake, oral glucose tolerance tests (OGTT), plasma methylmalonic acid (MMA) and total homocysteine (tHcy).

Results/Case report: Body weight was monitored twice weekly, food intake was recorded from weeks 14 to 18, and OGTT were performed at baseline, week 10, and week 21. Plasma MMA and tHcy levels were measured at week 21 as biomarkers of B12 status.
No significant differences in body weight, food intake, or glucose tolerance were observed between groups. However, B12-restricted mice exhibited significantly elevated MMA (CD: 0.53 ± 0.048 μM; VD: 8.15 ± 1.62 μM, $p < 0.0001$) and tHcy (CD: 6.6 ± 1.39 μM; VD: 13.00 ± 3.83 μM, $p < 0.01$), indicating metabolic disruption.

Conclusion: Despite the absence of overt metabolic impairments, elevated levels of MMA and tHcy confirm early biochemical alterations due to vitamin B12 restriction. The marked rise in MMA suggests it is a more sensitive biomarker for detecting B12 deficiency. These findings underscore the importance of monitoring MMA before clinical symptoms manifest to identify subclinical B12 deficiency, particularly in populations with dietary restrictions or genetic defects linked to impaired B12 utilization.

References:
(1) Herrmann W., ObeidR.. Causes and early diagnosis of vitamin B12 deficiency. Dtsch Arztebl Int. 2008;105(40):680-5;
(2) Pankaj Vashi, et al. Methylmalonic Acid and Homocysteine as Indicators of Vitamin B-12 Deficiency in Cancer. PLoS One. 2016;11(1):e0147843.

PO02

Alkaptonuria – a call for action

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Main category: Case series

Disease category: Intermediary metabolism: nutrients

Introduction: Alkaptonuria (AKU), a disorder of tyrosine metabolism resulting in the production of homogentisic acid (HGA) with subsequent deposition of ochronotic pigment in the soft tissues, was one of the first IMD to be described. It is one of the rarest inherited metabolic disorders, but its prevalence is underestimated due to the late onset of symptoms. The resulting accumulation of HGA leads to a multisystemic and highly debilitating disease. Nitisinone is currently approved for the treatment of AKU and has been consistently shown to reverse disease progression and improve quality of life (1) (2).

Methods: We present a single-centre cross-sectional study of adult patients with AKU registered at a national reference centre for IMD. Clinical data were collected retrospectively by chart review.

Results/Case report: A total of 12 patients from 7 families were identified (approximately 4% of all patients registered at the centre). The median age was 57 (IQR 29) years at data collection and 50 (IQR 44) years at diagnosis. Half were male. Only 3 patients (25%) were diagnosed in childhood and 4 (33%) by clinical suspicion. The remainder were diagnosed by family screening (33%) or incidental finding of ochronotic pigment after joint surgery (33%). Most patients had articular or musculoskeletal involvement (83%) resulting in debilitating symptoms (75% had an ECOG > 0). Four patients had valvular heart disease (33%). No patients are currently being treated with nitisinone due to national regulatory issues.

Conclusion: AKU is an under-diagnosed inherited metabolic disorder with a prevalence in our adult clinic population comparable to other disorders considered more common. Our case series demonstrates that AKU causes debilitating symptoms that have a direct impact on quality of life and functionality. Further national epidemiological studies and the approval of nitisinone treatment for AKU in Portugal, following the example of other European countries, are urgently needed.

References:

(1) Ranganath LR, Psarelli EE, Arnoux JB, et al. Efficacy and safety of once-daily nitisinone for patients with alkaptonuria (SONIA 2): an international, multicentre, open-label, randomised controlled trial. Lancet Diabetes Endocrinol. 2020 Sep;8(9):762-772;
(2) Spears KR, Rossignol F, Perry MB, et al. Patient-reported outcomes and functional assessments of patients with Alkaptonuria in a 3-year Nitisinone treatment trial. Mol Genet Metab. 2024 Sep-Oct;143(1-2):108562.

PO03

Non-syndromic retinitis pigmentosa caused by COQ8B bi-allelic variants

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Main category: Case series

Disease category: Intermediary metabolism: energy

Introduction: Retinitis pigmentosa is a form of inherited retinal degeneration caused by mutations in more than 100 genes coding for proteins with different functions, namely those involved in mitochondrial function. Clinical manifestations of primary coenzyme Q10 deficiencies are most often severe and include nephrotic syndrome, encephalopathy, hypertrophic cardiomyopathy, and sensorineural hearing loss[1]. Retinal manifestations have been reported in association with: PDSS1 (COQ1), COQ2, COQ4, COQ5, COQ6 and COQ8B[1,2].

Methods: We investigated the genotypes of 415 individuals affected by an inherited retinal disease who were negative for disease-causing variants in genes previously associated with IRDs by using genome-wide and unbiased methods, such as exome sequencing (ES) or genome sequencing (GS).

Results/Case report: 4 individuals from 3 distinct families with a clinical diagnosis of retinitis pigmentosa were found to be positive for a biallelic assortment of 4 rare and potentially disease-causing variants in COQ8B. Segregation study confirmed these variants to be in trans. M1 ans M2 were present in 1 patient. M1 was absent from all databases and M2 was reported as ultra-rare in gnomAD. Both were predicted as deleterious by in silico tools. All other patient were compound heterozigous for M3/M4. M3 was reported as pathogenic in ClinVar [3] and M4 presented a low frequency in gnomAD with two healthy homozigous individuals reported. This could represent an hypomorphic allele. NanoBRET assay was performed simulating patient's.
Subsequent nephrological examination was performed and none of the patients displayed evidence of glomerular injury.

Conclusion: We present a case series of patients with isolated retinitis pigmentosa caused by biallelic variants in COQ8B, a gene involved in coenzyme Q10 biosynthetic pathway. These findings substantiate the association between COQ8B and retinitis pigmentosa, addressing part of the missing hereditability in IRDs since genetic diagnostic yield is at the most 80%. Furthermore, it contributes to understand the phenotypic continuum of primary CoQ10 deficiencies.

References:
(1) Mantle, D., Millichap, L., Castro-Marrero, J. & Hargreaves, I. P. Primary Coenzyme Q10 Deficiency: An Update. Antioxidants 12, 1652 (2023);
(2) Drovandi, S. et al. Variation of the clinical spectrum and genotype-phenotype associations in Coenzyme Q10 deficiency associated glomerulopathy. Kidney International 2022; 102, 592–603 (2022);
(3) AbuMaziad AS, et al. The role of novel COQ8B mutations in glomerulopathy and related kidney defects. Am J Med Genet A. 2021 Jan;185(1):60-67.

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PO04

Impact of mitochondrial DNA variants in inherited retinal disorders: a revision utilizing the Portuguese national IRD.pt registry

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Disease category: Several disease categories

Introduction: Inherited retinal disorders (IRDs) can result from nuclear or mitochondrial DNA (mtDNA) variants. While mtDNA variants are known to contribute to IRD phenotypes, their prevalence, and specific clinical features remain poorly understood (1). This study aimed to characterize genotype-phenotype correlations in IRDs associated with mtDNA variants.

Methods: We analyzed a Portuguese database of 1423 patients with confirmed or suspected IRDs registered by ophthalmologists (2). Phenotype, genotype, and heteroplasmy levels were collected.

Results/Case report: We identified 19 individuals (1.3%) from 14 families harboring mtDNA deleterious variants, four asymptomatic. Two recurring variants were the most prevalent: m.3243A>G (8 families/11 patients), m.8993-T>G (3 families/5 patients), mtDNA deletions (2 families/2 patients) and m.3271T>C (1 family/1 patient). The most common diagnosis by the family was maternally inherited diabetes and deafness (MIDD) (5/14 families).

Conclusion: MIDD was a common phenotype, but its association with a recognizable maculopathy could contribute to and enrichment of this diagnosis with ophthalmology-based registries. It would be worthwhile to evaluate registries outside of ophthalmology to provide a more comprehensive understanding of the national representation of MIDD since it is a multisystem disorder.

References:

(1) Carelli V et al. Mitochondrial Retinopathies. Progr Mol Biol Transl Sci. 2021; 170, 247-280;
(2) Marta A et al. Clinical and genetic landscape of IRD in Portugal: pooled data from the nationwide IRD-PT registry. NPG Genom Med. 2025; 10(1), 1-11.

PO05

Validation of Portuguese version of SCOFF questionnaire to assess eating disorders in adult IMD patients requiring dietary treatment

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Main category: Basic science study

Disease category: Several disease categories

Introduction: Dietary therapy is the cornerstone of treatment for some inherited metabolic disorders(IMD). Living with IMD requiring dietary treatment can negatively affect eating attitudes and behaviors, which are associated with an increased susceptibility to developing eating disorders(ED). Early screening ED is very important in IMD patients requiring dietary treatment. The Sick; Control; One Stone; Fat; Food (SCOFF) questionnaire is a tool to detect ED and has been previously validated for the Portuguese language (P-SCOFF). This project aims to statistically validate the P-SCOFF in adult IMD patients.

Methods: P-SCOFF was applied to adult IMD patients at 3 Portuguese IMD Centres. Internal consistency was measured by Cronbach's α. Spearman Rho assessed correlations between continuous variables. Construct validity was tested through P-SCOFF sensitivity with age, age of diagnosis and Body Mass Index (BMI).

Results/Case report: Cronbach's α of 0.55 (IC 95% 0.38-0.67) was obtained, which means an acceptable internal consistency for P-SCOFF. In a sample of n=65, 29.2% were males, median age of 28 years, 70.8% had PKU, 72.3% had an IMD diagnosis at newborn screening, 86.2% of patients fully adhere to nutritional therapy and 38.5% had risk of ED through P-SCOFF. Two participants were previously diagnosed with ED and for these the P-SCOFF detected risk of ED, but there was no significant relationship between P-SCOFF score and previous diagnosis of ED. IMD patients with highest BMI have a higher score in P-SCOFF. BMI <25kg/m2 was a good indicator that the IMD patient has no risk of ED. There was no significant relationship between P-SCOFF score and age or age of diagnosis, despite that, age of diagnosis <1 month was a moderate predictor that the IMD patients have no risk of ED.

Conclusion: Through the statistical analysis, this study demonstrates the validation of P-SCOFF. This important tool would be available to regularly screen for ED in adult IMD patients of all Portuguese Reference/Treatment Centers.

References:
(1) Morgan J F, Reid F, Lacey J H. The SCOFF questionnaire: assessment of a new screening tool for eating disorders BMJ 1999; 319 :1467 doi:10.1136/bmj.319.7223.1467;
(2) Treasure J, Duarte TA, Schmidt U. Eating disorders. Lancet. 2020 Mar 14;395(10227):899-911. doi: 10.1016/S0140--6736(20)30059-3. PMID: 32171414;
(3) Giovannini M, Biasucci G, Luotti D, Fiori L, Riva E. Nutrition in children affected by inherited metabolic diseases. Ann Ist Super Sanita. 1995;31(4):489-502. PMID: 8851705.

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P006

Osteogenesis Imperfecta – Experience from a Paediatric Centre

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Main category: Case series

Disease category: Cofactor and mineral metabolism

Introduction: Osteogenesis imperfecta (OI) is an inherited metabolic disorder characterized by bone fragility and osteopenia. Treatment involves a multidisciplinary approach, with medical and surgical management.

Objectives: To describe the paediatric patients with OI followed up at our centre and to evaluate the medical treatment carried out and the clinical and bone mineral density (BMD) evolution.

Methods: Observational and retrospective study of children with OI followed in our centre, born in the last 20 years. The data obtained were recorded in Excel® 2019 and processed using IBM® SPSS® Statistics 29.0. A 5% significance level was used.

Results/Case report: 21 children, 67% male were included. Median age at diagnosis was 2.2 years with 7 years of follow-up. 52% had a positive family history. Variants were found in COL1A1 (65%), COL1A2 (10%), IFITM5, FKBP10, TMEM38B and WNT1 (62% Silence type I). The median age of the first fracture was 1.2 years, 33% were in neonates and 86% <3 years. The mean number of fractures/patient/year was 0.9, 50.4% in the lower limbs. 95% were treated with calcium and vitD and 81% with IV bisphosphonates (7-pamidronate, 5-zoledronate and 5-pamidronate followed by zoledronate), with a mean of 5 cycles/patient. Fever occurred in 20% of pamidronate- and 18% of zoledronate-treated patients in the first cycle, with no other adverse events. With bisphosphonates, the mean BMD z-score at the lumbar spine improved from -3.1 to -1.7 ($p<0.001$) and the mean number of fractures/patient/year decreased from 2.5 to 0.6 ($p=0.02$).

Conclusion: OI has a wide genotypic and phenotypic variability. Several clinical trials are underway, but there is still no effective treatment. Bisphosphonates improved bone mineral density and significantly reduced the number of fractures in our patients, with few side effects, in line with the experience of other centres. We started using zoledronate at our centre in 2019, which allowed us to reduce the administration time from 3 days to 1 day/cycle, with great benefits for patients and families.

PO07

Differential Diagnosis of α-Mannosidosis in MPSs

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Main category: Case series

Disease category: Complex molecule and organelle metabolism

Introduction: Mucopolysaccharidosis (MPSs) and oligosaccharidosis, two subgroups of lysosomal storage disorders (LSDs), face diagnostic challenges due to their wide spectrum of clinical presentations and overlapping symptoms. One of the oligosaccharidose is α-mannosidosis, an extremely rare and often undiagnosed disorder. It is characterized by a deficiency in the enzymatic activity of α-mannosidase, which is responsible for cleaving mannose from N-linked oligosaccharides. This study aimed to investigate the activity of α-mannosidase in dried blood spot (DBS) samples that had undergone screening for MPSs.

Methods: Three enzymatic assays were performed in the DBS received (α-mannosidase, β-mannosidase, β-galactosidase). Results were obtained through a calibration curve of 4-methylumbelliferone and expressed in nmol\h\spot. Molecular characterization of the MAN2B1 was performed in the suspicious samples.

Results/Case report: Among the 400 samples analysed, we identified eight cases with reduced α-mannosidase. The molecular findings confirm the biochemical data. The main features observed in those patients were skeletal abnormalities, coarse facies and cognitive impairment.

Conclusion: Since there is an overlap of symptoms in these two subgroups of disorders, differential diagnosis of oligosaccharidosis in children having suggestive symptoms of MPSs is crucial. An early treatment may significantly delay or prevent the onset of the major clinical signs, substantially modifying the natural history of the disease namely in the attenuated forms. Although rare, α-mannosidase should be considered as differential diagnosis for MPSs.

PO08

Case study: methylmalonic acidemia and episodes of pancreatitis requiring parenteral nutrition

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Main category: Basic science study

Disease category: Intermediary metabolism: nutrients

Introduction: Methylmalonic acidemia (MMA) is a rare inherited metabolic disorder that requires strict dietary management to prevent metabolic decompensation. Nutritional support in these patients is particularly challenging, especially in other comorbidities such as pancreatitis, where nutritioal restrictions must be carefully balanced. While parenteral nutrition (PN) is generally avoided for fear of amino acid overload and exacerbation of biochemical derangements, it may be necessary in critical situations where enteral feeding is not feasible.

Methods: To describe the implementation of parenteral nutrition in a 4-year-old child with MMA and newly diagnosed pancreatitis aiming to optimize nutritional support.

Results/Case report: Implementation of parenteral nutrition in a 4-year-old boy with MMA, treated with a diet restricted in amino acids, later diagnosed with pancreatitis.
First child of non-consanguineous parents, diagnosed with MMA via neonatal screening. At 4 years old, after frequent incoherent vomiting and without metabolic decompensation, he was hospitalized for suspected acute pancreatitis, a common complication of MMA. Due to enteral feeding intolerance, PN was started with AA 18g (1.5g/kg, 60%), lipids 10g (0.85g/kg) and glucose 210g (17.9g/kg), totalling 86 kcal/kg and 150 ml/kg/day. After 4 days, enteral nutrition was gradually reintroduced using maltodextrin-based supplement at 5 ml per hour.
At the last follow-up, at the age of 7, the patient remained clinically and neurologically stable, with sustained oral tolerance and adequate growth [W 14.5kg (p5-10), H 102.5cm (p25-50), BMI 13.8 (p10).

Conclusion: Formulating PN in patients with MMA is particularly challenging, requiring precise modulation of protein intake while ensuring metabolic stability. The presence of recurrent pancreatitis, further complicates this process by requiring lipid restriction, making it difficult to achieve a nutritionally adequate formulation. This case highlights the feasibility of PN in critical situations, emphasizing the importance of individualized adjustments and close metabolic monitoring to optimize patient outcomes.

References:
(1) Kahler SG, et al. Parenteral nutrition in propionic and methylmalonic acidemia. J Pediatr. 1989 Aug;115(2):235-41;
(2) Walter JH, et al. Parenteral nutrition in propionic acidemia and methylmalonic acidemia. J Pediatr. 1990 Aug; 117 (2 Pt 1):338-9;
(3) Mahmud S, et al. Methylmalonic Acidemia. J Coll Physicians Surg Pak. 2015 Jun;25(6):462-4.

PO09

After all, Porphyria exists in Portugal! A three-year study

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Main category: Case series

Disease category: Metabolism of heterocyclic compounds

Introduction: Porphyrias are a group of eight rare inherited disorders, each caused by a defect in a specific enzymatic step of heme biosynthesis. These disorders are multisystemic, with variable symptoms, and represent a major burden for patients and families, with disabling chronic symptoms scattered with life-threatening acute attacks. There are two main clinical types of porphyria: acute porphyria and cutaneous porphyria. Acute porphyrias are often misdiagnosed because of their diverse clinical manifestations, which can mimic other diseases (1).

Methods: Porphyrin precursor accumulation patterns and total urine porphyrins (TUP) are the first-line laboratory tests. The determination of porphyrin profiles in biological samples and the plasmatic emission fluorescence peak are the second-line tests. The NGS porphyria panel is the third-line test.

Results/Case report: In Portugal, our unit (URN-INSA, Porto), also an associate member of IpNet (International Porphyria Network), is currently considered the reference laboratory for the biochemical and molecular characterization of porphyria. Since 2022, a cohort of 139 patients has been screened for porphyria. The development of acute and cutaneous diagnostic algorithms has resulted in 34 porphyrias: 5 cases of Acute Intermittent Porphyria (AIP), 1 Variegata Porphyria (VP), 2 Hereditary Coproporphyria (HCP), 23 Porphyria Cutanea Tarda (PCT) and 3 Erythropoietic Protoporphyria (EPP).

Conclusion: Even so, these figures are lower in comparison to other similar countries, as we should have a higher prevalence. This diagnosis was not available in our country, which is now possible at URN-INSA (2). From this work, we have concluded that the articulation between the clinician and the laboratory is crucial to choosing the right biochemical test to achieve the correct diagnosis and complete characterization of the disease. Porphyria exists; we just have to look for it (3)!

References:

(1) Stölzel et al., 2019. Clinical Guide and Update on Porphyrias. Gastroenterology 157:365-381;
(2) Brito-Avô Luís, Pereira Luísa, Oliveira Anabela, Ferreira Filipa, Filipe Paulo, Coelho Rodrigues Inês, Couto Eduarda, Ferreira Fátima, Airosa Pardal André, Morgado Pedro & Moreira Sónia, 2023. Portuguese Consensus on Acute Porphyrias: Diagnosis, Treatment, Monitoring and Patient Referral. Acta Med Port 36(11):753-764;
(3) Heymans B, Meersseman W. 2022. Porphyria: awareness is the key to diagnosis! Acta Clin Belg. 77:703-9.

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PO10

Review of ASMD adult patients from single reference center

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Main category: Case series

Disease category: Complex molecule and organelle metabolism

Introduction: Acid sphingomyelinase deficiency (ASMD) is an ultra-rare (1/100.000 to 1/1.000.000 births) pan-ethnic, autosomal recessive lysosomal storage disorder caused by mutations in the SMPD1 gene. In ASMD, there is a defect in the sphingomyelin degradation causing disfunction and multisystemic clinical manifestations. The clinical spectrum of ASMD ranges from the infantile severe and rapidly progressive neurologic neurodegenerative phenotype known as AMSD type A (NPD-A) to a milder, chronic, visceral and non-neurologic form classified as ASMD type B (NPD-B) with presentation in childhood or adultood.

Methods: Revision of the last evaluation performed in 2024, of the 5 adult patients with visceral ASMD type B, in actual follow up in a single reference center. The data collected included demographic, clinical, analytic, biomarkers and imagological parameters routinely used to assess the burden of disease.

Results/Case report: 3 of 5 patients are men and the median age is 33 years old (7 to 55 yo). All but 1 patient (due to splenectomy) have splenomegaly and hepatomegaly, but without liver structural disorder, other than steatosis. Elevated ALT was found in 2/5 patients, without liver disfunction. Thrombocytopenia was observed only in 1 patient.
Dyslipidaemia is present 4/5 patients and was well controlled in the 3/4 patients on treatment.
All patients have imagological signs of lung interstitial disease, more expressive in older patients with functional impact on DLCO (48 to 91%; mean 71% of theorical) and 6MWT (69 to 79% of theorical).
The most severe case, is the oldest patient (splenectomized) and chronic respiratory insufficiency but is improving on olipudase.
Disease biomarkers were greatly elevated (>50-80 ULN) in all patients except in patient on olipudase, with a less expressive elevation (<5xUL).

Conclusion: All of patients in this cohort have interstitial lung alterations and organomegalies that seems to aggravate with age. The elevated biomarkers indicate an active disease that could respond to specific therapy. Despite dyslipidaemia seems to be well controlled with the available medication, sphingomyelin accumulation still occurs with subsequent organ dysfunction. Currently ASMD type B have available enzymatic replacement therapy (olipudase alfa). The rate of progression of organ involvement and disease burden could be determinant to decide the right moment for the introduction of olipudase.

References:
(1) McGovern MM et al. Disease manifestations and burden of illness in patients with acid sphingomyelinase deficiency (ASMD). Orphanet J Rare Dis. 2017 Feb 23;12(1):41.
(2) Geberhiwot T et al. Consensus clinical management guidelines for acid sphingomyelinase deficiency (Niemann-Pick disease types A, B and A/B). Orphanet J Rare Dis. 2023 Apr 17;18(1):85.
(3) Wasserstein MP et al.

PO11

Forty-four years of newborn screening in Portugal: new challenges, the same commitment to the community

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Main category: Other

Disease category: Several disease categories

Introduction: The National Newborn Screening Program (PNRN) is a systematic program aimed at all newborns (NB) born in Portugal, and currently screening for 28 conditions: Congenital Hypothyroidism (CH), 24 Inborn Errors of Metabolism (IEM), Cystic Fibrosis (CF), Sickle Cell Disease (SCD) and Spinal Muscular Atrophy (SMA, still in pilot study). The addition of new conditions, the implementation of new screening strategies, the increasing genetic diversity of the Portuguese population, and the growing demands of modern society, represented important challenges to the program over the years.

Methods: More than 4,200,000 NB have been screened, using different strategies. Currently, immunological techniques (CH and CF), tandem mass spectrometry (IEM), capillary electrophoresis (SCD), and genetic testing (CF and SMA) are used. Constant development and increasingly quality control is performed.

Results/Case report: The anticipation of the collection date and the publication of results online were important organizational changes to the program. The modification of the sample's collection protocol for very low birth weight NB addressed the need to prevent false negative results in the screening of CH. The screening performance for 24 IEM was significantly improved with the introduction of various second-tier tests in the screening strategy. The recent change in the CF screening strategy (2023), with the inclusion of genetic testing, has greatly enhanced the performance of this screening. After a regional pilot study, SCD screening started nationally, to answer to recent population alterations in Portugal. These changes have increased the sensitivity and specificity in detecting the various screened conditions, and improved the program's response to the community.

Conclusion: The PNRN is a dynamic program in constant evolution, both in terms of its organizational and communication structures, as well as in the number of screened conditions and screening strategies employed. Over 2,700 positive cases have been identified and referred to specialized clinical centers (Reference Centers, if those are defined), enabling timely therapeutic interventions, thus benefiting both newborns and their families. The continuous update of screening programs, with incessant adaptation to new technological challenges and to the needs of the community, is essential for their success.

PO12

Rhabdomyolysis in Inborn Errors of Metabolism

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Main category: Other

Disease category: Intermediary metabolism: energy

Introduction: Rhabdomyolysis is the breakdown of skeletal muscle, leading to the release of muscle contents into the bloodstream. Common symptoms include weakness, myalgia, and myoglobinuria, with elevated plasma creatine kinase (CK) levels being a key laboratory finding. Inborn errors of metabolism (IEM) are a rare cause of rhabdomyolysis and can complicate diagnosis due to their variability. (1) This study aims to describe the characteristics of patients with metabolic myopathies and rhabdomyolysis.

Methods: A retrospective analysis was conducted on patients with metabolic myopathies at our reference center from 2009 to 2024.

Results/Case report: Twenty-two patients were included: 9 GSD (40.9%), 7 FAOD (31.8%), and 6 mitochondrial disorders (27.2%).
Three patients (13.6%) were diagnosed through the National Neonatal Screening Program. Symptoms included fatigue (54.5%), myalgias (45.4%), and dark urine (31.8%). 3 (13,6%) were asymptomatic. The age at presentation ranged from the neonatal period to adulthood (max 33 years); 41.7% were under 24 months old.
Triggers included exercise (36.4%) and infection (27.2%). CK levels exceeded 50xUNL in 50% of patients during crises. Normal CK levels were observed in 29.2% during asymptomatic periods. Hospitalization occurred in 63.6% of patients, and 3 patients died. Repeated rhabdomyolysis episodes affected 68.2%. Disease management included dietary treatment (45.4%), vitamin supplementation (22.7%), ezimatic substitution (4,5%) with 4 patients having specific crisis management.

Conclusion: Definitive identification of a specific metabolic myopathy is important as often leads to specific interventions, including lifestyle, exercise, and nutritional modifications, cofactor treatments, accurate genetic counselling, avoidance of specific triggers, and rapid treatment of rhabdomyolysis.

References:
(1) Scalco RS et al. Rhabdomyolysis: a genetic perspective. Orphanet J Rare Dis. 2015; May 2;10:51.

PO13

Serine metabolism disorder – one more metabolic aetiology of cerebral palsy

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Main category: Case report

Disease category: Disorders of amino acid metabolism

Introduction: Cerebral palsy (CP) refers to a group of neurological disorders caused by damaage or abnormalities of the developing brain, disrupting its ability to control movement and maintain posture and balance. Usually attributed to labour occurrences, metabolic and genetic disorders are increasingly being identified as main aetiological factors. Serine metabolism disorder involving SLC1A4 gene encoding for ASCT1 transporter are being described as one of the metabolic aetiologies associated to cerebral palsy.(1,2).

Results/Case report: We present a 21-year-old female, born at term from non-consanguineous parents. Low Apgar scores, diagnosed with dystonic cerebral palsy. She developed progressive microcephaly, severe psychomotor delay, no language, non-epileptic startle episodes, agitation, scoliosis, oropharyngeal dysphagia and MALT gastric lymphoma.
Brain MRI showed marked postero-anterior graded hypomyelination, thin corpus callosum, mild brainstem hypoplasia. Metabolic investigation showed normal mitochondrial respiratory chain activity and mild mtDNA depletion (60%). Mitochondrial disorders gene panel and clinical exome were inconclusive.
The patient was proposed to trio whole genome sequencing (WGS) in ZOEMBA® - International genomic discovery study, and two probably pathogenic biallelic variants c.272T>C (p.Leu91Pro) and c.1277del (p.Gly426Glufs*22) were identified in SLC1A4 gene, encoding for ASCT1 transporter.

Conclusion: ASCT1 transporter is a brain serine transporter encoded by SLC1A4 gene, and responsible for SPATCCM - spastic tetraplegia, thin corpus callosum, and progressive microcephaly disorder (MIM #616657).
Serine, although a non-essential aminoacid, needs to by synthesized in the brain and shuttle from astrocytes to neuron by this transporter. The clinical phenotype of ASCT1 defect is similar to defects in L-serine biosynthesis.(2)
Serine supplementation therapy was proposed as a possible therapeutic tool but only if started before neurological damage occurs.(1)

References:
(1) Damseh N, et al. Mutations in SLC1A4, encoding the brain serine transporter, are associated with developmental delay, microcephaly and hypomyelinationJ Med Genet 2015;52:541–547. doi:10.1136/jmedgenet-2015-103104;
(2) Heimer G. SLC1A4 mutations cause a novel disorder of intellectual disability, progressive microcephaly, spasticity and thin corpus callosum. Clin Genet . 2015 Oct; 88(4):327-35. doi: 10.1111/cge.12637.

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PO14

Protein intake and prevalence of overweight and obesity in patients with phenylketonuria: a 10 year-longitudinal TNSPKU study

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Main category: Clinical trial

Disease category: Intermediary metabolism: nutrientset

Introduction: Overweight (OVW) has been identified as a comorbidity associated with phenylketonuria (PKU). A systematic review with meta-analysis found that although patients with PKU had a similar body mass index (BMI) when compared to non-PKU controls, there was a significantly higher BMI in classical PKU (1). The aim of this detailed descriptive study was to identify the prevalence of OVW in patients with PKU followed in a Portuguese Reference Centre.

Methods: A retrospective longitudinal study was performed. Inclusion criteria were PKU diagnosis and completing an annual nutritional status evaluation, every 2 years, from 2009 to 2018. Information on anthropometric measurements, dietary intake and blood Phe concentrations were collected.

Results/Case report: The sample consisted of 94 patients (14.0 ± 7.8 years, 46 females, 18 HPA, 43 mild PKU, 28 classical PKU, 5 late treated). Over the study, there was a trend towards an increase in the prevalence of OVW (24.5 vs 33%, p=0.197). Compared to patients with normal weight, patients with OVW had significantly higher Phe levels in the 1st and 5th biennium [281.5 vs 467.3 (p=0.026) and 387.4 vs 524.9 umol/L (p=0.013)]. Total and natural protein intakes were significantly higher in patients with normal weight, at all timepoints, compared to patients with OVW. Univariate analysis showed that a higher protein intake (OR=0.02, 95%CI [0.00;0.15]), particularly of natural protein (OR=0.26, 95%CI [0.11;0.66]), was a protective factor against the development of OVW. This finding remained significant after adjusting total protein intake for age, gender, and metabolic control (OR=0.04, 95%CI [0.01;0.30]).

Conclusion: This study found a trend towards an increasing prevalence of OVW in patients with PKU. However, a higher protein intake appears to be a protective factor against OVW. Therefore, the nutritional status of these patients should be monitored frequently, and personalized nutritional advice should be given accordingly.

References:

Rodrigues, C., et L. Is the Phenylalanine-Restricted Diet a Risk Factor for Overweight or Obesity in Patients with Phenylketonuria (PKU)? A Systematic Review and Meta-Analysis. Nutrients, 13(10), 3443.

P015

Twenty Years of Newborn Screening for MCADD in Portugal: genetic data

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Main category: Other

Disease category: Intermediary metabolism: nutrients

Introduction: Medium-chain acyl-CoA dehydrogenase deficiency (MCADD) is an autosomal recessive inherited metabolic disorder that affects fatty acid oxidation metabolism. Most cases present the most common c.985G>A mutation in ACADM gene, while a few patients carry other rare mutations. In Portugal, MCADD has been included in the newborn screening program since 2004 and is the most frequently diagnosed inborn error of metabolism detected through this program, with an incidence of 1 in 6,433.

Methods: Approximately 1,762,713 newborns were screened for MCAD deficiency between October 2004 and January 2025, using tandem mass spectrometry (MS/MS) to detect elevated octanoylcarnitine (C8) levels and an increased C8/C10 ratio. Tandem mass spectrometry (MS/MS) results and genetic testing data were anal.

Results/Case report: Over the 20 years period, a total of 274 newborns were identified with high values of C8 and C8/C10 ratios from dried blood spots. Biochemical and molecular follow up confirmed the MCADD diagnosis in 273 cases. Molecular characterization was not available for 90 cases. Of the remaining 183 cases, which were studied at our Newborn Screening, Metabolism and Genetics Unit, 162 (88%) were homozygous for the c.985G>A mutation, while 22 were compound heterozygotes. Of these, 13 carried the c.985G>A mutation along with a another mutation, whereas 8 had two distinct mutations. Additionally, seven novel mutations were identified in this cohort: c.94G>C, c.113G>C, c.214G>T, c.532A>T, c.974A>G, c.1133G>A, and c.708+1G>A.

Conclusion: Newborn screening has been crucial for identifying and managing of MCADD in Portugal. Our study confirms the c.985G>A mutation as the most frequent pathogenic variant, consistent with previous reports. The identification of seven novel mutations expands the spectrum of known variants, underscoring the importance of comprehensive genetic analysis. These findings reinforce the importance of newborn screening in early diagnosis and intervention, while also contributing to a deeper understanding of the genetic diversity of MCADD, with implications for genetic counseling and long-term management.

PO16

Acetyl-Leucine as an adjunct therapy in Niemann-Pick Disease Type C: A Case Report

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Main category: Case report

Disease category: Complex molecule and organelle metabolism

Introduction: Niemann-Pick disease type C (NP-C) is a rare, autosomal recessive lysosomal storage disease, characterized by a wide range of progressive neurological symptoms. Currently, there is no cure for NP-C and treatment is limited to slowing disease progression with substrate reduction therapy using miglustat. However, ongoing research explores potential disease-modifying therapies.

Methods: A follow-up protocol (that included the SARA scale, modified NP-C clinical severity scale and the Quality--of-life EuroQol EQ-5D-Y scale) was implemented to monitor the effects of N-acetyl-Leucine (AL) on a NP-C patient followed at a Reference Center of Inherited Metabolic Diseases.

Results/Case report: We present the case of a 15-year-old female with a juvenile form of NP-C under miglustat for 3 years (since diagnose). With the agreement of the patient and family, it was decided to introduce AL alongside miglustat.
At the beginning of treatment, her neurological assessment revealed vertical supranuclear ophthalmoparesis, increased tendon reflexes and mild fluid dysphagia. There were no abnormalities in mobility, fine motor skills, speech or cognition and no signs of ataxia, dystonia, seizures, or gelastic cataplexy.
After 24 months of follow-up no neurological deterioration or adverse effects were observed. The patient reported better mood, increased energy and psychological well-being. EQ-5D-Y assessment showed a five-point improvement in perceived health following AL treatment.

Conclusion: N-acetyl-leucine has shown symptomatic and potential neuroprotective effects in various studies, including animal models, observational clinical reports and a multinational phase IIb trial. In this case, AL was associated with improved perceived health and clinical stability over two years. However, further long-term studies are required to evaluate its safety and efficacy in NP-C.

PO17

Early Diagnosis of Mucopolysaccharidoses in Pediatrics

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Main category: Case series

Disease category: Complex molecule and organelle metabolism

Introduction: Mucopolysaccharidoses (MPSs) are a group of Lysosomal Storage Disorders with multisystem involvement, presenting different degrees of severity and evolution. At early disease stages and late onset forms, diagnosis can be postponed for years or even missed. The FIND PROJECT was designed to claim awareness to the red flags of MPSs at pediatric age and to provide a useful tool for physicians to diagnose these pathologies, since most of them are amenable to enzyme replacement therapy.

Methods: MPSs clinical suspicious were addressed by performing seven distinct enzymatic assays in dried blood spots, in order to understand whether any of those specific enzymes was deficient. For positive cases, the identification of glycosaminoglycans and the molecular study is carried out.

Results/Case report: In the first eight years of the project, we have identified 12 patients (five MPS I; one MPS II; two MPS IIIB, one MPS IVA, two GM1 and one MPS VI) out of the 385 samples studied. In the majority of the patients identified, the age of diagnosis was less than 3 years of age, which is much lower when compared to the mean age of diagnosis of 6 years old, reported by Pinto et al, 2004.

Conclusion: These results, shows that this project was successful also in its educational component, by raising the concern and awareness for these multisystemic pathologies that are linked to high morbidity.

PO18

Gone with the Wind

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Main category: Case report

Disease category: Complex molecule and organelle metabolism

Introduction: The authors present the challenges faced by the metabolic and palliative care team in managing a child with infantile metachromatic leukodystrophy. The rapid neurological deterioration outpaced the capacity of the National Health Service to adequately meet the child's and family needs. The continuous adaptation to the "new" child, who presented progressively worsening complications, was a significant challenge. This included adjusting timelines, such as celebrating Christmas in November.

Methods: Clinical case presentation: An 18-month-old child presented with developmental regression. MRI findings were suggestive of metachromatic leukodystrophy, subsequently confirmed through biochemical and molecular studies.

Results/Case report: An 18-month-old child presented with developmental regression. She was evaluated by a neuropediatrician and a developmental pediatrician, who initially attributed her complaints to school adjustment difficulties. After parents and teachers observed language regression, she was taken to the emergency room in Apri. MRI findings were suggestive of metachromatic leukodystrophy, subsequently confirmed through biochemical and molecular studies in May.
Her decline was catastrophic: within two months, a nasogastric tube was required, followed by the need for gastrostomy feeding. Her analgesic regimen had to be increased daily, reaching a total of 300 mg of gabapentin four times a day.
She passed away in the hospital, as chosen by her parents, surrounded by close family members, just eight months after her diagnosis.

Conclusion: The progression of the disease was significantly faster than the National Health Service could accommodate, leaving gaps in meeting the child's and family's needs. However, the charity and support from the community were remarkable, addressing psychological and social aspects of care.
Metabolic and palliative care professionals face numerous challenges; only through teamwork can the profound emptiness of losing a child feel slightly less empty.

References:
(1) Thomas, S., et al. The burden of disease in metachromatic leukodystrophy: results of a caregiver survey in the UK and Republic of Ireland. Orphanet journal of rare diseases, 2024, 19(1), 87.

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PO19

Pediatric Smith-Lemli-Opitz Syndrome follow at a Portuguese Level III Hospital

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Main category: Case series

Disease category: Lipid metabolism and transport

Introduction: Smith-Lemli-Opitz syndrome (SLOS) is an autosomal recessive disorder caused by a mutation in the DHCR7 gene, which disrupts the final stages of cholesterol biosynthesis. This results in the toxic accumulation of bioactive precursor 7-DHC and 8-DHC, interfering with normal growth and development from the fetal stage onward.

Methods: This study retrospectively analyzes the phenotype, genotype and treatment options of SLOS pediatric patients currently followed at a Portuguese level III hospital. Data were collected from electronic medical records.

Results/Case report: Three male patients were included: two diagnosed in the first year of life and one in the third year. All were referred to the Reference Center after an established diagnosis to follow up and treatment. All patients showed prenatal abnormalities and were born at term, presenting with hypotonia and dysmorphic features, including microcephaly, bitemporal prominence, low-set ears, genital ambiguity, hypospadias, polydactyly, renal agenesis/hydronephrosis. Cognitive impairment was universal (global IQ score ranging from 20 to 70). One patient required gastrostomy feeding during the first year of life. All patients had elevated 7-dehydrocholesterol (disease-specific biomarker) and genetic confirmation of biallelic variants in DHCR7 gene. Cholesterol supplementation was initiated with good tolerance. Social and educational support was necessary for all families.

Conclusion: At birth, a hypotonic baby with genitourinary anomalies, craniofacial dysmorphisms, or major malformations may raise suspicion for SLOS, facilitating early diagnosis and treatment. Elevated 7-DHC and 8-DHC levels are disease-specific biomarkers. Molecular testing of the DHCR7 gene confirms the diagnosis. Treatment aims to increase cholesterol levels through dietary interventions and synthetic cholesterol supplementation.

References:

(1) Nowaczyk MJM, et al. Smith-Lemli-Opitz Syndrome. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]; 1993-2025;
2) Cardoso ML, et al. A síndrome de Smith-Lemli-Opitz; características fenotípicas e genotípicas dos doentes portugueses. Acta Pediatr Port 2012;43(2):47-52;
(3) Porter, F. Smith–Lemli–Opitz syndrome: pathogenesis, diagnosis and management. Eur J Hum Genet, 2008, 16, 535–541.

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PO20

When Does Klinefelter Syndrome Interfere with the Diagnosis of Fabry Disease?

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Main category: Case report

Disease category: Lipid metabolism and transport

Introduction: Klinefelter syndrome (KS) results from an extra X chromosome in males and is a common genetic cause of infertility (1). Fabry disease (FD) is an X-linked disorder caused by a pathogenic GLA variant, leading to α-galactosidase A(α-Gal) deficiency. FD, the most prevalent lysosomal disease in Portugal (13.2/100,000), causes globotriaosylceramide (Gb3) deposition leading to cardiac, renal, neurological complications and hearing loss (2). In the testis, Gb3 accumulation can cause infertility (3). We present a case in which FD biochemical findings led to confirmation of KS chromosomal abnormalities.

Methods: FD methods: 1) α-Gal activity in leukocytes/plasma (fluorimetric method, 4-MU-α-D-galactopyranoside); 2) urinary Gb3 (thin-layer chromatography and densitometric quantification); 3) GLA gene study (PCR, Sanger sequencing). KS method- karyotype analysed by GTG banding of cultured lymphocytes.

Results/Case report: An adult male was referred for cardiology assessment due to chest pain and resting dyspnoea. His medical history included hypertension, dyslipidemia, type 2 diabetes mellitus, sensory polyneuropathy in the lower limbs, and hypoacusis, along with a family history of FD and hemochromatosis. A history of infertility was also recorded. FD laboratory results revealed slightly reduced α-Gal activity in leukocytes, along with enzymatic plasma activity that remained within normal ranges. Urinary Gb3 excretion was increased. Genetic analysis identified an unexpected heterozygous pathogenic variant in the GLA gene (c.337T>C p.(Phe113Leu)). This heterozygosity raised suspicion of a concomitant syndrome, which was confirmed by karyotype analysis revealing a KS chromosomal mosaic anomaly: mos 47,XXY[24]/46,XY[12].

Conclusion: Given FD's X-linked inheritance, males with a heterozygous GLA variant should be evaluated for other syndromes, such as KS, which may explain preserved enzyme activity. In this patient (mos 47,XXY[24]/46,XY[12]), phenotypic expression depends on X-chromosome inactivation and tissue distribution. This male was proposed for enzyme replacement therapy to mitigate symptoms and prevent further events. This case highlights the importance of genetic consultation and counseling as symptoms, in X-linked disorders, may result from a combination of genetic conditions rather than a single disorder.

References:

(1) Sadick, VJ. et al. Klinefelter Syndrome with Fabry Disease – a case of nondisjunction of the X-chromosome with sex-linked recessive mutation. 2014, Vol. 23, pp. 1149 – 1152;
(2) Pinto R et al. Prevalence of lysosomal storage diseases in Portugal. Eur J Hum Genet. 2004;12, 87–92;
(3) Sansone L et al. Infertility in Fabry's Disease: role of hypoxia and inflammation in determining testicular damage. Front Endocrinol (Lausanne). 2024; Feb 22:15:1340188.

PO21

Longitudinal assessment of body composition in an infant with phenylketonuria treated at an early age

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Main category: Case report

Disease category: Intermediary metabolism: nutrients

Introduction: Early diagnosis in infants with phenylketonuria (PKU) should be followed by immediate implementation of a phenylalanine (Phe)-restricted diet, avoiding brain toxicity. There is ongoing discussion about the impact of this nutritional intervention on nutritional status. We aimed to describe, for the first time, the body composition assessment during the first 13 weeks of age, in an infant with PKU treated with a Phe-restricted diet.

Methods: Data on nutritional intake and metabolic control were collected since diagnosis. Body composition was measured using air displacement plethysmography (Pea Pod, Cosmed, Italy) at 3, 7, 10 and 13 weeks of life. Percentage of fat mass (%FM) and fat free mass (%FFM) were calculated by the device.

Results/Case report: An infant, born at 40 weeks gestational age, was diagnosed with PKU on the 5th day of life. He had a blood [Phe] of 694 umol/L, blood [tyrosine] of 40 umol/L, with a Phe/Tyrosine of 17.5. At the first appointment (8th day of life), blood [Phe] was 736 umol/L. Breastfeeding was allowed after a bottle feeding with a Phe-free protein substitute. During the study period, blood [Phe] was 205.3 ± 123.8 umol/L. At 13 weeks, intakes of natural protein, protein equivalent, Phe and energy were 1.47 g/kg/day, 0.83 g/kg/day, 334 mg/day (52 mg/kg/day) and 682 kcal/day, respectively. Z-scores for weight and length, at 13 weeks, were -0.0175 and 0.7381, respectively. From 1st to 4th assessment, %FM (z-score) varied from 15,6% (-0.05) to 22,9% (-0.45), fat mass (z-score) varied from 0.6362kg (-0.02) to 1.4590kg (-0.28) and fat free mass (z-score) varied from 3.4516kg (0.11) to 4.9199kg (0.68).

Conclusion: Nutritional intervention with a Phe-restricted diet allowed a metabolic control within the recommended target ranges, showing an adequate growth. Breastfeeding was the only dietary source of natural protein and Phe, allowing for adequate body composition development during the first 13 weeks of life. This novelty underlines the need for further studies aiming to investigate the role of increased amounts of protein equivalent (Phe-free amino acids) on body composition in infants with PKU.

PO22

Mapple Syrup Urine Disease – a diagnosis at an elderly age

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Main category: Case report

Disease category: Several disease categories

Introduction: Maple syrup urine disease (MSUD) is a rare autosomal recessive metabolic disorder caused by a deficiency in the branched-chain alpha-keto acid dehydrogenase complex, leading to toxic accumulation of branched-chain amino acids (BCAAs – leucine, isoleucine, valine), primarily in the central nervous system. In Portugal, its incidence is about 1 in 86,800 live births(1). Also called leucinosis, it presents five phenotypes classified by specific variants, residual enzyme activity, age of onset, treatment response, and symptom severity(2).

Results/Case report: A 78-year-old woman with a history of epilepsy since early adulthood, a protein self-restricted diet, and type 2 diabetes, with no known family history of metabolic disorders, was diagnosed with herpes zoster virus (VZV) infection and started on antivirals. She developed hypoglycemia, slurred speech, disorientation, psychomotor agitation, and focal seizures, leading to ICU admission for sedation and neurologic monitoring. Initial tests, including lumbar puncture and CT, were unremarkable and a nonconvulsive status epilepticus was diagnosed. Aminogram showed high BCAAs, a leucine/alanine ratio of 3.3, and elevated allo-isoleucine (58 µmol/L), indicating MSUD. Genetic testing confirmed a homozygous c.659C>T variant. Despite appropriate dietary management, she succumbed to refractory septic shock.

Conclusion: Most MSUD cases are diagnosed in newborns, but non-classical forms may appear later being this one of the most elderly presentation described on literature. This case highlights the need to consider inherited metabolic diseases early, as timely diagnosis and treatment are crucial to prevent severe neurological damage. Treatment includes a high-calorie, protein-restricted diet, specialized amino acid formulas, and family genetic counseling. Early intervention is key to improving outcomes and avoiding long-term complications.

References:

(1) Quental S et al. Incidence of maple syrup urine disease in Portugal, Mol Gen Metab. 2010; 100, 4, 385-387;
(2) Zhou M et al. Tissue-specific and nutrient regulation of the branched-chain α-keto acid dehydrogenase phosphatase, protein phosphatase 2Cm (PP2Cm), J Biol Chem. 2012; 287: 23397–23406;
(3) Miragaia P et al. Acute encephalopathy in a 10-year-old patient with Maple Syrup Urine Disease: a challenging diagnosis. Cureus. 2024; Jan 27;16(1): e53043.

PO23

Missense Mutation in the LYRM7 Gene: A Case of Leukoencephalopathy

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Main category: Case report

Disease category: Complex molecule and organelle metabolism

Introduction: Many inborn errors of metabolism are not detected by national early diagnosis programs. They can present with severe symptoms, leading to complications if not promptly identified. Mitochondrial complex III deficiency, nuclear type 8 (MC3DN8) is an autosomal recessive disorder (1) caused by a homozygous mutation in the LYRM7 gene on chromosome 5q23. Affected individuals show acute and recurrent neurological decompensation, hypotonia, hypertonia, spasticity, elevated lactate, and multifocal cystic lesions in brain imaging. (2).

Methods: We report a case of a patient who presented to the emergency department at Beja Hospital.

Results/Case report: We present a child, born to consanguineous parents, with a normal extended neonatal screening and a history of hospitalization at 9 months for vomiting, metabolic acidosis, and isonatremic dehydration. At 21 months, she presented to the emergency department at Beja Hospital with vomiting, diarrhea, prostration, and generalized hypertonia. Arterial blood gas revealed severe metabolic acidosis. After rapid progression to coma, she was transferred to the Pediatric Intensive Care in Lisbon, where MRI revealed cavitated leukoencephalopathy. Whole exome sequencing identified a homozygous missense variant in the LYRM7 gene, consistent with MC3DN8. Readmitted to Beja Hospital, with important global regression development. She regained skills but did not return to her previous condition. Currently, at 2 years and 6 months, she can stand with assistance, showing dystonic pattern and trunk ataxia.

Conclusion: We present this case due to its rarity, increased prevalence in consanguineous unions, its neurodegenerative nature, and the progressive decline observed with each acute episode, particularly those of infectious etiology, typically without a return to baseline health. It's crucial to remain vigilant with every intercurrent event and initiate supportive treatment promptly and intensively.

References:

(1) Invernizzi F et al. A homozygous mutation in LYRM7/MZM1L associated with early onset encephalopathy, lactic acidosis, and severe reduction of mitochondrial complex III activity. Hum Mutat. 2013; 34: 1619-1622. (2) Dallabona C et al. LYRM7 mutations cause a multifocal cavitating leukoencephalopathy with distinct MRI appearance. Brain. 2016; 139: 782-794. Note: Erratum: Brain 141: e82, 2018.

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PO24

Olipudase alfa enzyme replacement therapy. One-year outcomes in an adult patient with acid sphingomyelinase deficiency type B

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Main category: Case report

Disease category: Complex molecule and organelle metabolism

Introduction: Acid Sphingomyelinase Deficiency (ASMD) is a rare autosomal recessive lysosomal storage disorder caused by variants in the SMPD1 gene, leading to a deficiency in the activity of sphingomyelinase (ASM) that catabolizes sphingomyelin (SPM). ASMD Type B is a late-onset, severe disease characterized by progressive hepatosplenomegaly, gradual deterioration of liver and pulmonary function, osteopenia and an atherogenic lipid profile. Olipudase alfa is a recombinant human ASM enzyme replacement therapy indicated for the treatment of non-CNS manifestations of ASMD (1).

Methods: We report the 1-year outcome of an adult patient with ASMD Type B, confirmed by enzymatic assay and genotyping, treated with olipudase alfa. The drug was administered intravenously every 2 weeks, with the recommended gradual dose escalation over 14 weeks to 3 mg/kg, maintaining the dose afterword.

Results/Case report: We present the case of a 53 years old man diagnosed at the age of 37, when he complained of fertility problems and thrombocytopenia (76 to 145×109/L) and splenomegaly were found. A myelogram and bone biopsy revealed foam cells and the diagnosis was confirmed by a homozygous mutation c.1426C>T; p.R476W in the SMPD1 gene. He also presented interstitial lung disease with impaired diffusion capacity for carbon monoxide (DLco), bone involvement (BMS score 5 on MRI), osteopenia and dyslipidemia. At age 49, biclonal gammopathy was diagnosed IgG K e IgA k.
After one year treatment, there is near normalization of plasma lyso-sphingomyelin (from 300 to 17,2 MoM; ref:0,5--2,7), platelet counts normalization, reduction in spleen volume (from 900 to 529 mL), DLco normalization (from 57% to 78%), and a decrease in monoclonal free light K chains from 5.16 to 3.69 mg/dL. No adverse events were observed.

Conclusion: Treatment with olipudase resulted in clinical improvement: the patient no longer experienced gingival bleeding or epistaxis, feeling of abdominal fullness, began tolerating facial masks and noticed urodynamic improvement, incomplete bladder emptying sensation and pollakiuria resolved. The efficacy of olipudase alfa was evidenced by lyso SM509 reduction, improved DLco and decreased spleen volume. There were no variations in bone scores on MRI or densitometry. Chitotriosidase, was a low-sensitivity biomarker, remaining within normal values. Treatment with olipudase alfa was well tolerated.

References:

(1) Geberhiwot T, Wasserstein M, Wanninayake S, Christopher Bolton S,Dardis A, Lehman A, Lidove O, Dawson C, Giugliani R, Imrie J, Hopkin J, Green J, Vicente Corbeira D, Madathil S, Mengel E, Ezgü F, Pettazzoni M, Sjouke B, Hollak C, Vanier M, McGovern M, Schuchman E. Consensus clinical management guidelines for acid sphingomyelinase deficiency (Niemann–Pick disease types A,B and A/B). Orphanet Journal of Rare Diseases. 2023;18:85.

PO25

Macular Pattern Dystrophy as a Key Feature in Suspected Maternally Inherited Diabetes and Deafness (MIDD): A Case-Based Approach

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Main category: Case series

Disease category: Intermediary metabolism: energy

Introduction: Maternally Inherited Diabetes and Deafness (MIDD) is a mitochondrial disorder caused by mutations in mitochondrial DNA, most commonly m.3243A>G. It accounts for up to 1% of diabetes cases but remains underdiagnosed due to its variable presentation (1). While diabetes and sensorineural hearing loss are hallmark features, macular pattern dystrophy is a key ophthalmological clue. We present two cases where recognizing macular abnormalities facilitated the diagnosis of MIDD, emphasizing the importance of ophthalmological assessment in patients with atypical diabetes.

Methods: We describe two patients with diabetes, sensorineural hearing loss, and macular dystrophy. Both underwent ophthalmological examination with optical coherence tomography (OCT), and genetic testing for mitochondrial DNA variants. Genetic analysis confirmed the m.3243A>G variant in both cases.

Results/Case report: Case 1: A 64-year-old male with diabetes since 35, normal body mass index (BMI), and no known hearing loss had poor glycemic control (HbA1c 10.9%). MODY genetic testing was unremarkable. Fundoscopy showed pattern retinal atrophy and pigmentary changes without clear diabetic retinopathy. OCT revealed outer retinal atrophy, compatible with mitochondrial retinopathy. Targeted genetic analysis confirmed m.3243A>G (6% heteroplasmy).
Case 2: A 44-year-old female with diabetes diagnosed during pregnancy at 34, mild hearing loss, and progressive visual impairment since 3 years ago had a strong maternal family history of diabetes. The ophthalmological evaluation showed retinal pigment epithelium and outer retinal layer alterations, consistent with mitochondrial maculopathy. Genetic testing confirmed m.3243A>G (27% heteroplasmy), reinforcing the MIDD diagnosis.

Conclusion: MIDD is frequently underdiagnosed due to its heterogeneous presentation. Macular pattern dystrophy is a crucial phenotypic marker that should prompt genetic testing in atypical diabetes cases. Recognising ophthalmological features allows earlier diagnosis, personalised management, and genetic counselling. These cases underscore the need for multidisciplinary collaboration between endocrinologists, ophthalmologists, and geneticists to improve detection and optimise care for mitochondrial diabetes.

References:
(1) Murphy R, Turnbull DM, Walker M, Hattersley AT. Clinical features, diagnosis and management of maternally inherited diabetes and deafness (MIDD) associated with the 3243A>G mitochondrial point mutation. Diabet Med. 2008;25(4):383-99.

PO26

Dilated cardiomyopathy as a presentation of Neutral Lipid Storage Disease with myopathy: a diagnostic challenge

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Main category: Case report

Disease category: Lipid metabolism and transport

Introduction: Neutral Lipid Storage Disease with Myopathy (NLSDM) is an autosomal recessive disorder associated with variants in PNPLA2 gene, that causes lipid droplet accumulation in skeletal muscle and myocardium. Predominant cardiomyopathy phenotype with minimal to no skeletal manifestations is rare. Here, we report an otherwise healthy male diagnosed with dilated cardiomyopathy (DCM) following hospitalization for acute heart failure at age of 29. The apparent isolated cardiomyopathy, challenged the prompt diagnosis of NLSDM.

Results/Case report: Cardiac MRI showed significant left ventricular dilation and diffuse hypokinesis, with an LVEF of 21%. Late gadolinium enhancement revealed transmural subepicardial enhancement in the anterolateral segments. Endomyocardial biopsy confirmed fibrosis. Laboratory tests showed persistently elevated CK levels. Genetic multigene painel for DCM found no causal variants. Subsequently, a Hereditary Myopathies panel identified the pathogenic PNPLA2 variant c.792del p.Leu264Phefs*56, in apparent homozygosity, confirming NLSDM. Variant segregation confirmed the homozygosity. Despite the absence of musculoskeletal symptoms, neurological evaluation revealed mild scapular muscle atrophy with a normal biopsy. A peripheral blood smear showed pathognomonic Jordan's anomaly. After a 4-year follow-up, he underwent heart transplantation and, to this date, remains without symptoms of skeletal myopathy.

Conclusion: Elevated CK levels and progressive skeletal myopathy are the classic clinical manifestations of NLSDM. Cardiomyopathy is associated with approximately half of the cases (1) but rarely presents as the primary manifestation. Due to the varying phenotypic expression, NLSDM should be presumed as a potential diagnosis in individuals with persistently elevated CK levels and cardiomyopathy. Furthermore, it is important to consider different primary etiologies of cardiomyopathy, even in the absence of other signs or symptoms, broadening the genetic testing in selected cases.

References:

(1) Missaglia S et al. Neutral Lipid Storage Diseases as cellular model to study lipid droplet function. Cells. 2019; Feb 21;8(2):187.

PO27

Diagnosis of Niemann Pick disease type C in a patient with Charcot-Marie-Tooth neuropathy - the importance of valuing atypical signs

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Main category: Case report

Disease category: Complex molecule and organelle metabolism

Introduction: Niemann-Pick disease type C (NP-C) is an autosomal recessive lysosomal lipid storage disorder caused by mutation of NPC1 or NPC2 genes. Neurovisceral condition with manifestations depending on the age of onset. Neurological involvement predominates in late infantile and juvenile presentations with cerebellar ataxia, dysarthria, dysphagia, progressive dementia, dystonia and seizures. Vertical supranuclear ophthalmoparesis is a major characteristic sign. Diagnosis is based on biomarker screening (oxysterols, lyso-SM-509) confirmed by genetic testing. Treatment with miglustat increases survival.

Results/Case report: 15-year-old male, originally from Brazil, began follow-up in the pediatric neurology service due to clinical diagnosis of motor and sensory neuropathy. Charcot-Marie-Tooth disease type 1A was confirmed by PMP22 duplication. Besides gait difficulties, neurological observation revealed atypical signs like low cognition, speech difficulties and vertical ophthalmoparesis. A few months later, seizures, tremor, cognitive regression, increased speech and gait difficulties were noted, which led to the suspected diagnosis of NP-C. Increased lyso-SM-509 and heterozygous compound for two NPC1 pathogenic variants confirmed the diagnosis. Neuroaxis MRI revealed a diffuse alteration of supra tentorial white matter. Treatment with miglustat is proposed.

Conclusion: This case illustrates the importance of never disregarding atypical neurological signs during the observation of patients with chronic conditions as just another manifestation of the preexistent disease. A systematic approach of each patient is essential to provide the best care, appropriate and timely treatment and to improve the prognosis.

References:

(1) Patterson M. Niemann-Pick Disease Type C. GeneReviews® [Internet]. 2000.
Available from: https://www.ncbi.nlm.nih.gov/books/NBK1296/;
(2) Vanier MT. Niemann-Pick disease type C. Orphanet J Rare Dis. 2010 Jun 3;5:16;
(3) Nagappa M, et al. Charcot-Marie-Tooth Disease. StatPearls [Internet]. 2024 Jun 22.

PO28

Niemann-Pick Type B: A lifelong battle – Early diagnosis as the key for better outcome

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Main category: Case report

Disease category: Complex molecule and organelle metabolism

Introduction: Niemann-Pick type B (NP-B) is a lysosomal disorder caused by pathogenic variants in the SMPD1, resulting in deficient acid sphingomyelinase (ASM) activity. This deficiency leads to sphingomyelin accumulation and symptoms such as hepatosplenomegaly and pulmonary infiltration. Most patients reach adulthood with minimal central nervous system symptoms. Recently, Olipudase alfa, the first approved treatment for ASM deficiency, effectively reduces sphingomyelin levels and alleviates symptoms(1). The authors present two NP-B cases, highlighting the importance of recognizing this treatable condition.

Methods: Biochemical testing included enzymatic assays for sphingomyelinase in leukocytes, Lysosphingomyelins quantification in plasma (LysoSM, Lyso509) by tandem mass spectrometry. Additionally, beta-D-quitotriosidase activity was measured in plasma. SMPD1 Sanger sequencing led to genetic confirmation.

Results/Case report: Patient 1, a 76 years old female with chronic lung disease and splenomegaly, with a clinical suspition of Gaucher disease. Enzymatic determination revealed deficient sphingomyelinase activity, increased beta-D-quitotriosidase activity and increased levels of lysoSM and lyso509. Genetic analysis identified two pathogenic variants SMPD1, c.533T>A (p.Ile178Asn) and c.1829_31delGCC (p.Arg610del).
Patient 2, a 25 years old man from a consanguineous family, showed signs of swollen lymph nodes when he was 15. He exhibits hepatosplenomegaly and interstitial lung pathology. Laboratory findings displayed a decreased sphingomyelinase activity, significantly increased levels of lysoSM and lyso509, and increased beta-D-quitotriosidase activity. Genetic testing identified a pathogenic variant in the SMPD1 gene, a deletion (c.1829_31delGCC) leading to the loss of arginine at position 610 (p.Arg610del).

Conclusion: These cases illustrate the different clinical presentations of Niemann-Pick type B and the impact of early diagnosis on disease progression. Patient 1, diagnosed in late adulthood, experienced significant pulmonary complications that ultimately led to a fatal outcome, despite supportive care. In contrast, Patient 2, identified in a younger age, fills all the criteria to undergo enzyme replacement therapy. These findings reinforce the importance of early diagnosis in guiding treatment, improving quality of life, enabling genetic counselling and preventing familial cases.

References:
(1) Keam S. J. Olipudase Alfa: First Approval. Drugs. 2022;82(8): 941–947.

PO29

CPS1 diagnosed in adolescence

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Main category: Case report

Disease category: Intermediary metabolism: nutrients

Introduction: Carbamylphosphate synthase I (CPS1) deficiency is the most severe urea cycle disorder. It is caused by pathogenic variants in the CPS1 gene. Most cases described in literature present with the neonatal form, with severe hyperammonemia and irreversible neurological damages. Some cases can present late in life, with more unspecific manifestations, including failure to thrive, psychomotor retardation and late-onset acute metabolic decompensations. Low citrulline and high glutamine levels often accompany hyperammonemia. Molecular testing is essential for definitive diagnosis.

Results/Case report: 12-year-old girl, with short stature, presented to the emergency department with flu-like symptoms, prostration and disorientation. Brain CT was normal, and influenza B was diagnosed. There was clinical improvement after fluids, and she was discharged. Returned 4 days later for mental confusion and mydriasis. Blood analyses and drug screening were normal. Due to rapidly neurological worsening, she was transferred to PICU. Hyperammonemia (max. 276 umol/L) was confirmed, and sodium phenylacetate, sodium benzoate, arginine, and carglumic acid were started. She required hemodiafiltration for 3 days for unstable ammonia levels. Amino acid profile supported a urea cycle disorder. She had global clinical improvement, and was discharged with vegetarian diet, glycerol phenylbutyrate, carglumic acid, arginine, citrulline, with normal ammonia levels. Genetic testing confirmed the diagnosis of CPSI.

Conclusion: Clinical manifestations of CPSI deficiency are usually the most severe among urea cycle disorders, however, cases with late onset presentation have been described, usually with neurodevelopment disorder installed. A better understanding of possible presentation of metabolic disorders in older children/adolescents, particularly in a post-infectious context, is essential for timely diagnosis, to correct severe hyperammonemia as quickly as possible, for better neurological outcome and to reduce mortality. More studies are needed to correlate the genotype-phenotype of variants.

References:

(1) Wang S. et al. Clinical and genetic analysis of a case of late onset carbamoyl phosphate synthase I deficiency caused by CPS1 mutation and literature review. BMC Med Genomics. 2023; 16, 145;
(2) Noori M et al. Carbamoyl-phosphate synthetase 1 (CPS1) deficiency: A tertiary center retrospective cohort study and literature review. Mol Genet Metab Rep. 2024; Oct 18;41:101156.
(3) Fan L et al. Molecular, biochemical, and clinical analyses of five patients with carbamoyl phosphate synthetase 1 deficiency. J Clin Lab Anal. 2020; 34:e23124.

PO30

Tangier Disease: a rare disorder of lipid metabolism

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Main category: Case report

Disease category: Lipid metabolism and transport

Introduction: Tangier disease is a rare genetic disorder of lipid metabolism characterized by extremely low levels of circulating high-density lipoprotein (HDL) and tissue accumulation of cholesterol, especially in the reticuloendothelial system. It is inherited in an autosomal recessive manner, due to biallelic pathogenic variants in the ABCA1 gene. Its clinical expression is variable, and, despite low levels of cholesterol, premature coronary artery disease is frequently observed. There is no curative treatment available, and patients' management is mainly based on case reports and case series.

Methods: We present the case of a 50-year-old male, with a history of tonsillectomy at the age of 2 due to recurrent tonsillitis and long-term thrombocytopenia and splenomegaly of undetermined cause, in which the diagnosis of Tangier disease was recently confirmed.

Results/Case report: The patient was referred to Hematology consultation due to maintained splenomegaly and thrombocytopenia. Diagnostic work-up revealed thrombocytopenia (60-80000x10^9/L), mild hemolysis, iron overload (negative genetic study for hemochromatosis), splenomegaly (19cm), and severe hypocholesterolemia (total cholesterol 27 mg/dL. HDL 2 mg/dL, LDL 16mg/dL) with ApoA1<40mg/dL. He underwent bone marrow biopsy, which showed aggregates of xanthelasmized histiocytic cells. Genetic testing confirmed the presence of an unbalanced rearrangement in the ACB1 gene in homozigoty. Tangier Disease was confirmed. Ophthalmologic evaluation showed no corneal opacities. Cardiovascular evaluation revealed a high coronary calcium score (>400), with normal myocardial perfusion scintigraphy, and small carotid atherosclerotic plaques with no hemodynamic compromise. The patient has no cardiovascular symptoms.

Conclusion: Tangier disease should be suspected in the presence of very low HDL and Apo-AI circulating levels. In the lack of curative treatment, supportive care should be implemented, and a special focus should be placed on cardiovascular disease prevention through the control of cardiovascular risk factors. The role of lipid lowering treatments in the presence of very low LDL and triglyceride levels is still a matter of debate, and the decision of an antithrombotic strategy may be challenging, as this disease may present with thrombocytopenia and there are reports of increased hemorrhagic risk.

PO31

A challenging case of Classic Galactosemia

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Main category: Case report

Disease category: Intermediary metabolism: nutrients

Introduction: Classic galactosemia (CG) is a rare inherited disorder caused by a severe deficiency of galactose-1--phosphate uridyltransferase.
Clinical manifestations usually start a few days after birth due to galactose intoxication from breast milk or formula. Most neonates present with vomiting, failure to thrive/weight loss, cholestatic liver disease with hypoglycemia, proximal tubulopathy and susceptibility to gram-negative sepsis. In some cases the clinical presentation is less typical and diagnosis can be difficult.
It is not included in the Portuguese Neonatal Screening Program.

Methods: We describe a child with CG who presented at one month of age with multisystem involvement including severe ascites and an abnormal CDT type 1 profile, evocative of PMM2-CDG.

Results/Case report: First child of unrelated parents. Negative family history.
Due to failure to thrive on breastfeeding, infant formula was started at 2 weeks of age.
At 1 month of age, she was admitted with severe abdominal distension, noticed 3 days before. Pallor, mild jaundice, signs of malnutrition, collateral circulation and significant ascites requiring drainage were noted. Ophthalmological examination was normal.
On formula feeding, there was poor weight gain and occasional vomiting.
Investigation showed hypoalbuminemia, anemia (requiring infusion/transfusion), recurrent hypoglycemia, mild cholestasis and cytolysis and INR elevation, low antithrombin 3, normal anion gap metabolic acidosis, hyperlactacidemia, hyperaminoaciduria, 3 negative urine reducing sugar tests and CDT type 1 profile.
Clinical and laboratory improvement was observed with an elemental formula.
CG was diagnosed by WES.

Conclusion: This child had no history of vomiting before admission. Failure to gain weight was masked by ascites.
CG was considered in the differential diagnosis. Empirical use of a lactose-free formula was life-saving.
The aim of this report is to highlight the importance of considering CG in neonates/infants with clinical hepatorenal involvement.
Once CG is evoked, treatment must be initiated after blood sampling for galactosemia and Beutler test. These can be performed on DBS. Urine reducing sugar test is unspecific and too dependent on dietary galactose absortion.

References:
(1) Succoio M, Sacchettini R, Rossi A, Parenti G, Ruoppolo M. Galactosemia: Biochemistry, Molecular Genetics, Newborn Screening, and Treatment. Biomolecules. 2022;12(7):968;
(2) Welling L, Bernstein LE, Berry GT et al. International clinical guideline for the management of classical galactosemia: diagnosis, treatment, and follow-up. J Inherit Metab Dis. 2017;40(2):171-176;
(3) Badiu Tișa I, Achim AC, Cozma-Petruț A. The Importance of Neonatal Screening for Galactosemia. Nutrients. 2022;15(1):10.

PO32

Pompe disease: an Azorean family report

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Main category: Case series

Disease category: Intermediary metabolism: others

Introduction: Glycogen storage disease type II, also called Pompe disease, is a metabolic disease characterized by a deficit of the enzyme acid α-glucosidase, with an autosomal recessive pattern, caused by mutations in the GAA gene(1,2). The enzyme deficit leads to the accumulation of glycogen in lysosomes, especially in smooth and cardiac muscle and the peripheral nervous system(3). This disease has a heterogeneous clinical presentation, which mimics other neuromuscular diseases and is characterized by progressive proximal muscle weakness and altered ventilatory mechanics and cardiac function(2).

Methods: We present the cases of four siblings with Pompe disease. Diagnosis was based on clinical evidence and suggestive family history. Currently, three individuals have severe signs and symptoms and one has very mild signs of the disease. All are on an enzyme replacement programme.

Results/Case report: We report the cases of four siblings with late onset Pompe disease. Family history includes consanguinity and three family members with progressive proximal muscle weakness and persistent elevated CK. Clinical suspicion arose when the eldest brother presented proximal muscle weakness and sleep apnea. A few years later, similar complaints appeared in another sibling. Diagnosis began with genetic and enzyme activity studies. Two individuals are homozygous for the mutation c. -45T > G (IVS1-13T > G), with no enzymatic activity and two have compound heterozygosity for the mutation c. -45T > G (IVS1-13T > G) and c. 1941C>G (p.C647W) exon 14 with residual enzyme activity. Currently, three siblings present significant proximal weakness and different degrees of dysfunction in ventilatory mechanics and cardiac function. Nevertheless, all of them are undergoing enzyme replacement therapy.

Conclusion: The diagnosis of Pompe disease is based on genetic and enzymatic studies and requires a high degree of clinical suspicion. The correlation between genotype and enzyme activity is an important factor in grading the severity of the disease. These cases highlight the importance of genetic study, counselling and enzyme replacement therapy in managing clinical outcomes. It also explores the benefits of this therapy in slowing down the progression of the disease, especially when started early, although challenges remain in the treatment of late-onset cases.

References:

(1) Cupler, E. J., et al. Consensus Committee on Late-onset Pompe Disease, 2012. Consensus treatment recommendations for late-onset Pompe disease. Muscle & Nerve, 45(3), 319–333;
(2) Labella, B., et al. A Comprehensive Update on Late-Onset Pompe Disease. Biomolecules, 2023, 13(9), 1279;
(3) Stevens, D., et al. Pompe Disease: A Clinical, Diagnostic, and Therapeutic Overview. Current Treatment Options in Neurology, 2022, 24(11), 573–588.

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Document Reviewers: Dr Rui Mota (Head Chief of Neurology Department - Hospital do Divino Espírito Santo EPE, Ponta Delgada), Dra Marina Couto e Dr Pedro Miguel Lopes (both from the Neurology Department - Hospital do Divino Espírito Santo EPE, Ponta Delgada).

PO33

Genetic insights into adult cardiomyopathy: unraveling mitochondrial disorders through NGS

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Main category: Case report

Disease category: Several disease categories

Introduction: Unclear presentations of inborn errors of metabolism (IMDs) in adults, especially those with multi-organ involvement, create diagnostic challenges. Next-generation sequencing (NGS) has emerged as a key tool in resolving complex genetic etiologies. Early identification of mitochondrial disorders facilitates personalized management and genetic counseling. In this case, NGS was essential in diagnosing a mitochondrial disorder with cardiac manifestations, highlighting the importance of advanced genetic testing in adult patients with metabolic and multi-systemic involvement.

Methods: An 80-year-old male with hypertrophic cardiomyopathy and severe aortic stenosis was referred for genetic evaluation. Whole-exome sequencing (WES) revealed a homoplasmic variant in MT-ND6, suggesting a mitochondrial disorder. Mitochondrial studies, via skin biopsy, are ongoing, with results pending.

Results/Case report: Cardiac assessments showed severe concentric hypertrophy of the septal wall (17mm), resulting in left ventricular diastolic dysfunction. The patient had a history of deafness diagnosed at 59 years old, hypertension, dyslipidemia, and benign prostatic hyperplasia. There was no significant personal or family history of mitochondrial disease. WES identified the m.14484T>C variant in MT-ND6, which is associated with Leber Hereditary Optic Neuropathy (LHON) and Leigh syndrome. However, neurological and neuro-ophthalmological assessments, including retinography and brain MRI, were normal. The ongoing mitochondrial studies aim to clarify the variant's impact through skin biopsy analysis.

Conclusion: Pathogenic variants in MT-ND6 result in diverse mitochondrial disorders, such as LHON and Leigh syndrome, with variable phenotypes and age of onset. The m.14484T>C variant's association with isolated cardiac abnormalities and favorable visual outcomes underscores its clinical relevance. This case demonstrates the importance of NGS in diagnosing complex IMDs in adults and the necessity of mitochondrial studies, like those currently underway, to further understand and characterize the impact of such variants.

PO34

WES revisited – solving an unsolved inherited retinal disease case

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Main category: Case Report

Disease category: Disorders of amino acid metabolism

Introduction: Inherited retinal diseases (IRDs) are amongst the most prevalent Mendelian human disorders in humans. Most IRDs are incurable and caused by monogenic defects leading to progressive photoreceptor degeneration, making IRDs a leading cause of unavoidable blindness in the working population (1). Advances in genetic research have revealed significant clinical and molecular diversity, with over 300 disease loci and genes identified to date (2). Genetic and phenotypic overlap is common with few unique genotype-phenotype associations.

Methods: This study was performed in agreement with the tenets of the Declaration of Helsinki. Molecular analysis was performed at the Institute of Molecular and Clinical Ophthalmology of Basel and previously described [3]. Clinical evaluation was performed at ULS São José and ULS Stª Maria.

Results/Case report: A moleculary unsolved IRD case in a 27 year old (yo) woman was reviewed. She was a high myope. Nyctalopia and peripheral visual field loss became symptomatic around 14yo. At 21yo performed cataract surgery. Fundoscopy showed chorioretinal atrophy with a relatively preserved fovea. Initial whole exome sequencing (WES) did not reveal any disease causing variants in IRD associated genes. Despite the absence of typical scalloped areas of chorioretinal atrophy, other findings were compatible with gyrate atrophy. Plasma amino acid chromatography was performed and showed hyperornitinemia (832 mmol/L). Original OAT gene WES data was reviewed in detail and complemented with Sanger sequencing revealing a known pathogenic variant (ClinVar:1376471) and a known VUS (ClinVar:806581) which according with ACMG criteria was reclassified as likely pathogenic. Segregation confirmed compound heterozygosity.

Conclusion: Gyrate atrophy of the choroid and retina (GACR) is caused by biallelic mutations in OAT, which encodes ornithine aminotransferase. GACR's manifestations are mainly ocular and it is one of the few IRDs with a unique phenotype-genotype association since atrophic areas display a pathognomonic scalloped pattern(4). This pattern was not present in our patient. Probably due to progressive coalescence of these areas with loss of the preserved interstitial chorioretinal tissue. GACR is one of the few actionable IRDs since restriction of dietary protein can decrease disease progression rate(5).

References:

(1) Verbakel SK, et al. Non-syndromic retinitis pigmentosa. Prog Retin Eye Res. 2018 Sep;66:157-186. doi: 10.1016/j.preteyeres.2018.03.005. Epub 2018 Mar 27. PMID: 29597005;
(2) https://retnet.org/disease;
(3) Peter VG, et al. The first genetic landscape of inherited retinal dystrophies in Portuguese patients identifies recurrent homozygous mutations as a frequent cause of pathogenesis. PNAS Nexus. 2023 ;2(3):pgad043;
(4) Brands M, et al; GACR Bird's Eye View Consortium. A mini-review on the international gyrate atrophy.

Acknowledgements: We would like to thank the patient and her family for participating in this study.

PO35

Reverse phenotyping after NGS panel of X-linked intellectual disability unravels creatine transporter (slc6a8) deficiency

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Main category: Case report

Disease category: Cofactor and mineral metabolism

Introduction: X-linked intellectual disability (XLID) is characterized by extensive genetic heterogeneity. Next-generation sequencing (NGS) have been used in these cases as a cost-effective diagnosis approach. Genetic findings often reveal variants unforeseen during clinical investigation, prompting the need for reevaluation of specific features designated as reverse phenotyping (RP). X-linked creatine transporter deficiency (CTD) is a potentially treatable intellectual disability caused by pathogenic variants in the SLC6A8 gene leading to impaired creatine transport into the brain.

Results/Case report: A 7-year-old boy with intellectual disability, speech delay, hyperactivity and epilepsy was referred to Metabolic and Neuropediatric Clinic.Family history identified a mother with learning difficulties and a maternal uncle with intellectual disability, indicating a possible X-linked inheritance. NGS intellectual disability panel identified a variant classified as probably pathogenic(c.880_881del (p(Lys294Alafs*2))in the SLC6A8 gene, in hemizygosity which prompted referral to Metabolic and Neuropediatric Clinic.Reverse phenotyping was carried out with biochemical and imaging assessment that showed: high urinary Creatine-Creatinine ratio (2.17;RV 0.04-1.07) with normal guanidinoacetate acid and absence of creatine peak in brain MRI spectroscopy, confirming the diagnosis. Genetic studies on female family members are ongoing. Recently he started treatment with creatine, arginine and glycine.

Conclusion: X-linked CTD is a rare disease that has been reported in more than 150 individuals worldwide. We present a case in which the diagnostic approach was reverse phenotyping, through biochemical and imaging studies, after the identification of pathogenic variants in SLC6A8 by NGS panel. The efficacy of its treatment remains controversial with variable results, and a close evaluation will be needed.

PO36

Early diagnosis of acid sphingomyelinase deficiency (ASMD) through biomarkers analysis

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Main category: Case report

Disease category: Complex molecule and organelle metabolism

Introduction: Acid sphingomyelinase deficiency (ASMD), historically known as Niemann–Pick disease (NPD) types A, A/B, and B, is a rare, progressive, potentially fatal lysosomal storage disease caused by pathogenic variants in SMPD1 gene. It presents a wide spectrum of symptoms, age of onset, and degree and type of organ effected.
The disease manifestations frequently involve hepatosplenomegaly with progressive organ dysfunction, interstitial lung disease, and bleeding.
In this work, we will present a patient whose lysosomal biomarkers study allowed the diagnosis of ASMD.

Methods: This patient had hepatosplenomegaly, elevated transaminases in which the primary clinical suspicion was an acid lipase deficiency. By the analysis of our multiplex biomarker panel by LC-MS/MS analysis, we were able to do a differential diagnosis.

Results/Case report: The lysosphingomyelin (lysoSM) and lysosphingomyelin-509 (lysoSm-509) were approximately 100 a 150x than normal, suggestive of Niemann–Pick disease. The diagnosis of ASMD was confirmed by reduced acid sphingomyelinase enzyme activity measured in peripheral blood leukocytes and the presence of a pathogenic variant in both alleles in the SMPD1 gene.

Conclusion: ASMD can be underestimate and the diagnostic odissey arise from an overlap in symptomology with other diseases, including primary hepatic disease, Gaucher disease, Niemann–Pick disease, and lysosomal acid lipase deficiency.
The multiplex biomarker panel, with different lysolipids, allows simultaneously diagnosis of different LSDs, in a timely manner, leading to an early intervention, before the appearance of more deleterious symtpoms.

PO37

Neurocognitive outcomes and personality traits in 28 adult PKU patients from new-born screening

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Main category: Basic science study

Disease category: Several disease categories

Introduction: Phenylketonuria (PKU) is a rare autosomal recessive disorder caused by phenylalanine hydroxylase deficiency, leading to elevated phenylalanine levels and neurological issues. Early treatment with a Phe-restricted diet prevents severe impairments, but adherence often declines over time, causing cognitive deficits and neuropsychiatric symptoms. This study explores neurocognitive outcomes and personality traits in adult PKU patients, highlighting the need for ongoing support to improve daily functioning and quality of life.

Methods: Study of 28 PKU patients (18F, 10M, 18–36 yrs) assessed diet control (Phe levels), IQ (WAIS-III), personality (16 PF-5), education, and career using SPSS 20, exploring diet-cognition-life outcome links.

Results/Case report: Our results showed a specific neurocognitive profile and some personality traits in adult PKU patients that may jeopardise the therapeutic goals. These results allowed a better understand of the difficulties in their psychosocial behaviour and suggested the need of a special multidisciplinary supervision throughout life.

Conclusion: These results allowed a better understand of the difficulties in their psychosocial behaviour and suggested the need of a special multidisciplinary supervision throughout life.

PO38

A rare complication of Diabetes Mellitus – The Mauriac Syndrome

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Main category: Case report

Disease category: Several disease categories

Introduction: Glycogenic hepatopathy, or Mauriac Syndrome, is a rare complication of type 1 diabetes mellitus (T1DM) seen in children or young adults with poor glycemic control. It is marked by growth failure, cushingoid appearance, hepatomegaly, and hypertransaminasemia. Glycogen deposition in the liver during hyperinsulin episodes results from glycogenesis activation and inhibition of glycogenolysis(1). Elevated lactate levels occur when the Krebs cycle is saturated, leading pyruvate to undergo lactic acid fermentation.

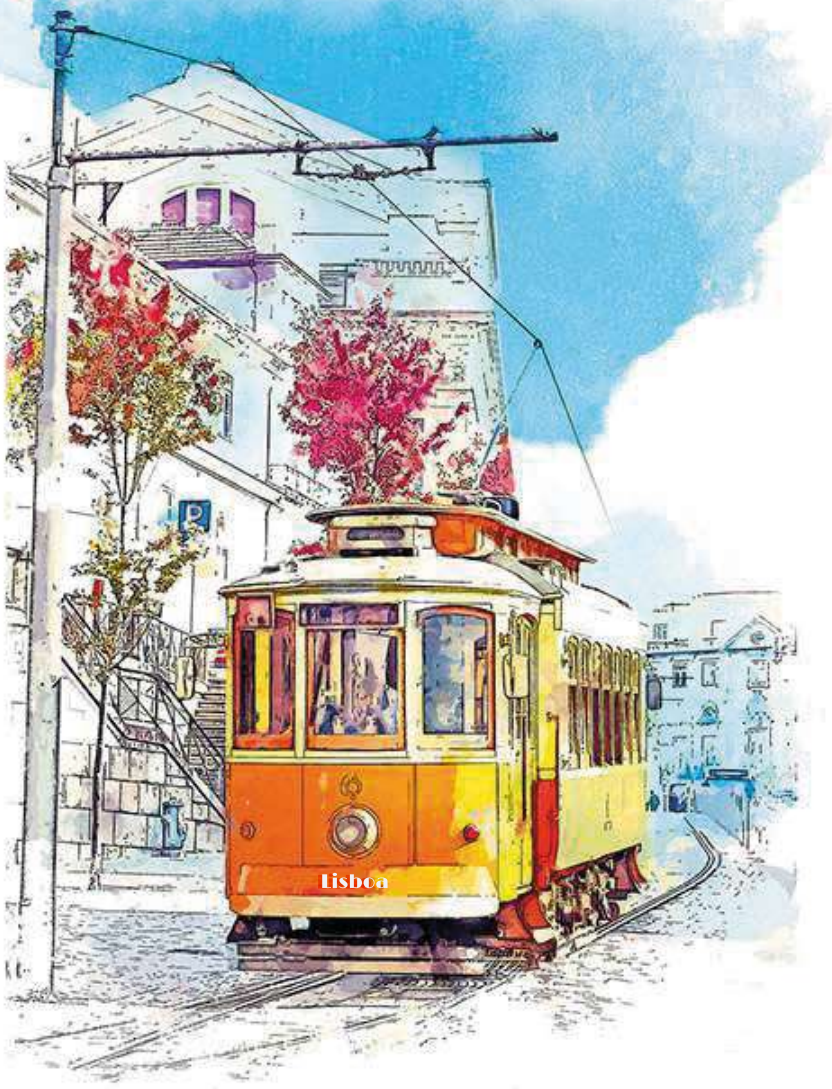
Results/Case report: We report a 20-year-old female with T1DM since age 2, complicated by severe retinopathy (two past surgeries), delayed puberty, and short stature. She presented to the Emergency Department with abdominal pain and vomiting. Blood tests revealed elevated lipase, and CT showed hepatomegaly and peripancreatic edema, leading to a diagnosis of acute pancreatitis. Her C-peptide was extremely low, and hemoglobin A1C was 11.3%. During hospitalization, hyperlactacidemia coincided with hyperglycemia, alongside hepatomegaly, suggesting Mauriac syndrome. Liver biopsy confirmed glycogen accumulation. Organic acid analysis suggested mitochondrial cytopathy (traces of fumaric acid, 2-hydroxyisovaleric acid, and 2-hydroxybutyric acid), but mitochondrial DNA sequencing was normal. The insulin regimen was adjusted, achieving glycemic control, and she was discharged for outpatient follow-up.

Conclusion: The improvement in devices monitoring glucose levels and insulin has allowed for better control of patients with T1DM, making conditions like Mauriac syndrome increasingly rare. So, it is extremely important the early recognition of the syndrome, appropriate multidisciplinary management based in therapeutic education, a good doctor-patient relationship, and family support (2).In time, with glycemic control, the liver damage can be reversed (3).

References:

(1) Soulaimane M, Elouali A, Najioui Y, et al. Mauriac syndrome or hepatic glycogenosis: a rare complication of unbalanced diabetes (about two clinical cases). Journal of Clinical and Translational Endocrinology: Case Reports. 2022;24:100111;
(2) Jemai C, Fakhfakh Y, Hadj Ali Z, Htira Y, Ben Mami F. Hepatic Glycogenosis: A Rare Complication of Type 1 Diabetes Mellitus. Cureus. 2024;16(11):e74766;
(3) In: Farrell M, Bucuvalas J - Liver disease in children: Systemic disease and the liver. Philadelphia: Lippincott Williams and Wilkins, 2001.

SESSION VI



DEVELOPMENT AND CHALLENGES FOR NEW THERAPIES IN IMD

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The basis for mRNA-based therapies in IMD

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Messenger RNA (mRNA) plays a crucial role in cellular function by acting as the intermediary between DNA and the proteins that carry out essential cellular activities.

Many lives were lost during COVID-19 pandemic but many more would have been lost if mRNA-based vaccines had not been developed and approved within an unimaginable short time never seen in the history of medicine. These vaccines, tested on tens of thousands of volunteers and administered to millions within an unprecedented timeframe, proved to be a ground-breaking success in global public health. However, this achievement was only possible due to decades of prior research into the use of synthetic mRNA for disease treatment and prevention.

Since the 1960s, scientists have explored ways to develop mRNA technology, facing numerous challenges in their effective deliver. Significant breakthroughs in the last decade, have now paved the way for large-scale production of safe and effective mRNA medicines. Between 1990 and 2019, mRNA technology advanced rapidly, finding applications in functional protein expression, vaccines, cancer immunotherapy, and gene editing. The approval of COVID-19 mRNA vaccines marked a turning point, demonstrating the real-world potential of mRNA-based therapies in treating diseases beyond infectious outbreaks offering promising avenues for treating genetic metabolic disorders among other diseases. By directing cells to produce specific proteins, mRNA can replace missing or defective proteins in genetic diseases. This adaptable, precise, and highly targeted approach revolutionizes treatment options, making mRNA a viable and safer alternative not only to traditional vaccines but also to enzyme replacing therapies, avoiding the need for complex protein production and administration, and to gene therapies, as mRNA do not integrate into the genome, reducing the risk of unintended genetic alterations. mRNA-based therapies are now being explored for a range of genetic disorders in which treatment options are limited or unavailable, such as inherited metabolic diseases (IMD), including hereditary tyrosinemia type 1, arginase deficiency, phenylketonuria, methylmalonic acidemia, propionic acidemia, glycogen storage disease type 1a, Fabry disease, and ornithine transcarbamylase deficiency.

With extensive knowledge gained from COVID-19 pandemic response efforts, the potential applications of mRNA in medicine continue to expand. In the coming years, mRNA-based treatments will likely revolutionize personalized medicine, accelerate drug development, and lower barriers to innovation in addressing rare genetic diseases, including IMD and many other medical challenges.

mRNA therapy for lysosomal disorders

Sandra Alves

Instituto Nacional de Saúde Dr. Ricardo Jorge, Porto, PT

Antisense oligonucleotide (ASO) therapies are experiencing a remarkable surge in development, offering new hope for patients with rare and often fatal diseases. ASOs are short, synthetic single-stranded DNA or RNA molecules designed to selectively bind to target RNA sequences, enabling the downregulation of gene expression or modulation of splicing. Their accuracy in targeting disease-related genes makes them a powerful tool in precision medicine, particularly for rare diseases. As the therapeutic potential of ASOs expands, numerous ongoing clinical trials and several approved therapies are already showing positive outcomes for patients.
Some of the most impactful applications of ASO therapies have been in previously incurable, congenital, and progressive neurodegenerative diseases that had devastating, often fatal consequences for patients. Notable breakthroughs include treatments for spinal muscular atrophy and a specific form of amyotrophic lateral sclerosis. Additionally, ASOs have proven effective in addressing ultra-rare diseases, which previously lacked viable commercial solutions for treatment.
One major advantage of ASO-based therapies is their ability to efficiently reach the central nervous system (CNS) via intrathecal administration, making them particularly valuable for neurological disorders. Among lysosomal storage disorders, mucopolysaccharidoses (MPS), particularly type III, present severe neurological decline due to the accumulation of glycosaminoglycans (GAGs), such as heparan sulfate, in the CNS. These characteristics make MPS III an ideal candidate for ASO-based therapeutic strategies. MPS IIIC is a priority among the MPS subtypes because, unlike other types, it is caused by defects in an enzyme that presents unique challenges: acetyl-CoA:α--glucosaminide N-acetyltransferase. Unlike most MPS-related enzymes, this enzyme is not a lysosomal hydrolase but rather a transmembrane protein of the lysosome. As a result, therapeutic options for MPS IIIC are much more limited, as enzyme replacement therapy is not viable for these patients.
In our research, we are using ASOs to downregulate key genes involved in the biosynthesis of heparan sulfate, whose accumulation is particularly detrimental to the brain and CNS of MPS IIIC patients. Our aim is to reduce pathological HS accumulation, offering the possibility of alleviating disease symptoms. Looking ahead, our strategy holds promise not only for older patients by helping to slow disease progression but also for younger patients who are awaiting more permanent solutions, such as gene therapy or gene editing.

Mitochondrial Disorders: Hope for the Future

Shamima Rahman

UCL Great Ormond Street Institute of Child Health, London, UK

The field of mitochondrial medicine is young yet is governed by complexity at all levels. It is less than 50 years since the mitochondrial genome was first sequenced in its entirety (the first completed "Human Genome Mapping Project"), 37 years since the first pathogenic variants in mitochondrial DNA were identified and only 30 years since the first mutation was reported in a nuclear encoded subunit of an oxidative phosphorylation enzyme. In the first two decades following the discovery of these genetic diseases, patients faced lengthy diagnostic odysseys and were counselled of a likely poor prognosis. Now 50% of patients receive a genetic diagnosis, sometimes within days of their clinical presentation, and a wealth of pharmacological and genetic therapies are being developed. Questions remain about the underlying disease mechanisms, best outcome measures and optimal clinical trial design, and very few therapies are even close to being licensed. In this talk I will discuss recent innovations in diagnostics, therapy development and international consortia focussed on clinical trials that I believe provide hope for the future of mitochondrial medicine.

New treatment approaches for CDG

Dulce Quelhas

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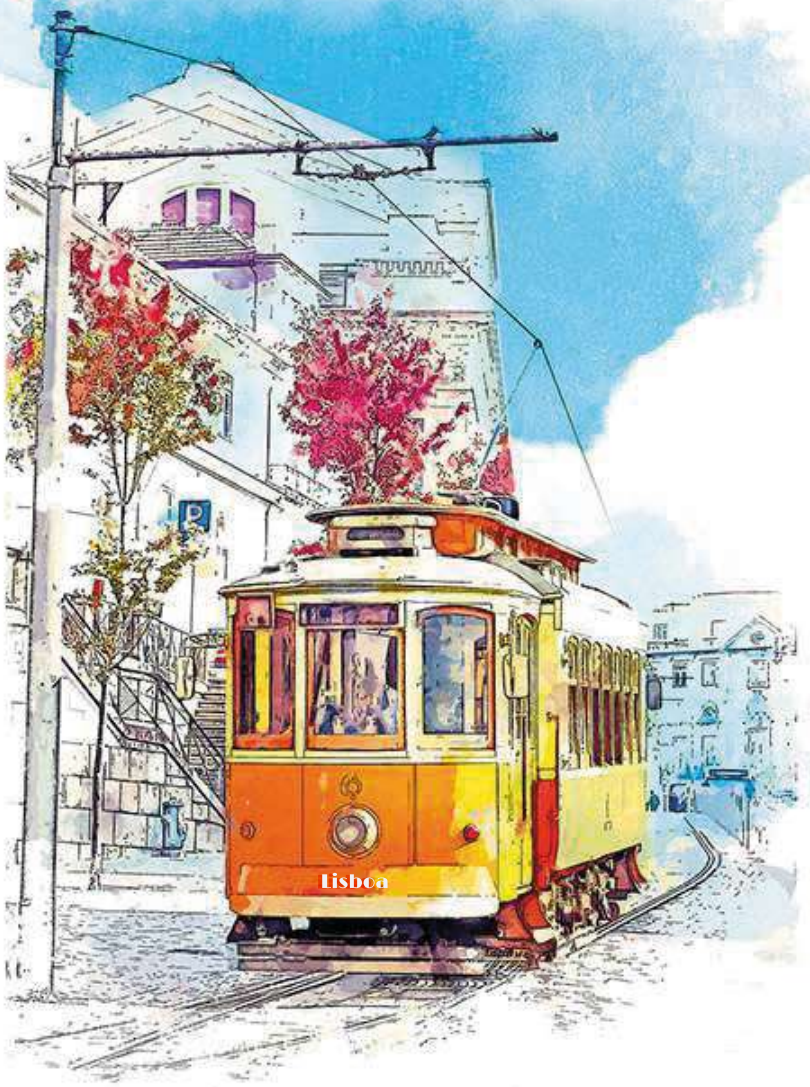
While the identification and diagnosis of congenital disorders of glycosylation (CDG) have rapidly progressed, available treatment options are still quite limited. Mostly, until recently, we were only able to manage the disease symptoms rather than to address the underlying cause.
However, in the past decade, advancements in novel treatments for CDG have accelerated, targeting the root cause and affected pathways. They brought remarkable advances for some CDG, and fortunately, some innovative therapies, have transitioned from the research stage to clinical practice.
Clinical trials are essential for drug approval. However, designing clinical trials for inherited metabolic diseases, such as CDG, can be challenging because of the small subject pool and the need to include control groups in randomized controlled trials.
This presentation aims to provide an overview of current treatments developments in CDG and the rising concepts that are used to treat these ultra-rare diseases, including disease models.

SESSION VII



REVISITING NUTRITIONAL APPROACHES IN IMD

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Exploring asymptomatic childhood methionine cycle disorders

Patrícia Lipari Pinto

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S-adenosylhomocysteine hydrolase (SAHH) deficiency is a rare inborn error of methionine metabolism characterized by elevated methionine, SAM and SAH levels, with a wide clinical spectrum ranging from severe neonatal disease to asymptomatic cases.
We describe two siblings of Pakistani origin diagnosed with SAHH deficiency during childhood, both carrying the homozygous pathogenic AHCY variant c.146G>A (p.Arg49His). Despite being clinically asymptomatic, both presented with chronic liver dysfunction, elevated creatine kinase, and biochemical markers consistent with SAHH deficiency. Brain MRI revealed mild, reversible leukodystrophy in the older sibling following methionine-restricted dietary treatment. Our findings support the existence of a mild, likely underdiagnosed phenotype and reinforce a genotype-phenotype correlation associated with this South Asian hotspot variant.
This work raises important questions about therapeutic strategies in asymptomatic individuals to prevent long-term complications such as myopathy and hepatocellular carcinoma.

Supplementation for performance and health in patients with phenylketonuria

Domingo González-Lamuño

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Phenylketonuria (PKU) is an inherited disorder that affects phenylalanine (Phe) metabolism, caused by Phe hydroxylase enzyme (PAH) deficiency. Treatment with a low-Phe diet, often supplemented with protein substitutes, is necessary to prevent Phe accumulation in the brain. In other hand, it is well known that proteins are vital for athletes, supporting muscle growth, minimizing catabolism, and aiding muscle repair and glycogen replenishment post-exercise. Since patients with PKU need to restrict their daily protein intake and take commercial preparations of Phe-free amino acid or glycomacropeptide supplements tailored to variables such as age and patient status are crucial for improving performance and health in PKU patients. Tailored to meet nutritional needs, these substitutes lack Phe but fulfill protein requirements.
Various factors affect tolerated Phe levels, including supplement quantity and age. Adhering to supplement regimens optimizes performance and addresses PKU challenges. Strategically-timed protein substitutes can safely enhance muscle synthesis and sports performance. Individualized intake is essential for optimal outcomes, recognizing proteins' multifaceted role. Due to limited supplement availability, athletes with PKU may need higher protein intake.
Overall, individuals with PAH have similar nutrient requirements to the general population. However, they may have higher protein needs due to reduced protein availability in protein substitutes and possible mitigation of protein catabolism by supplements.
In athletes with PKU, optimal nutritional management is challenging but feasible. An exercise-based approach tailored to individual needs can help improve adherence to dietary recommendations and protein substitutes, which are crucial for both performance and health. Here, we review the use of protein substitute supplementation in PKU patients in the context of physical activity, considering limited evidence.

Personalised parenteral nutrition for Inherited Metabolic Disorders during acute decompensations

Marjorie Dixon

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Parenteral Nutrition (PN) is the administration of nutrients into the blood stream through a venous catheter. PN is invasive and has associated risks, so should only be used when it is not possible to supply nutrients by the gastrointestinal tract. To achieve optimal nutrition and outcome, PN is best managed by a multidisciplinary nutrition support team.

PN has been used in the management of inherited metabolic disorders (IMD) since the 1980's, but there are few publications, and most are case studies.

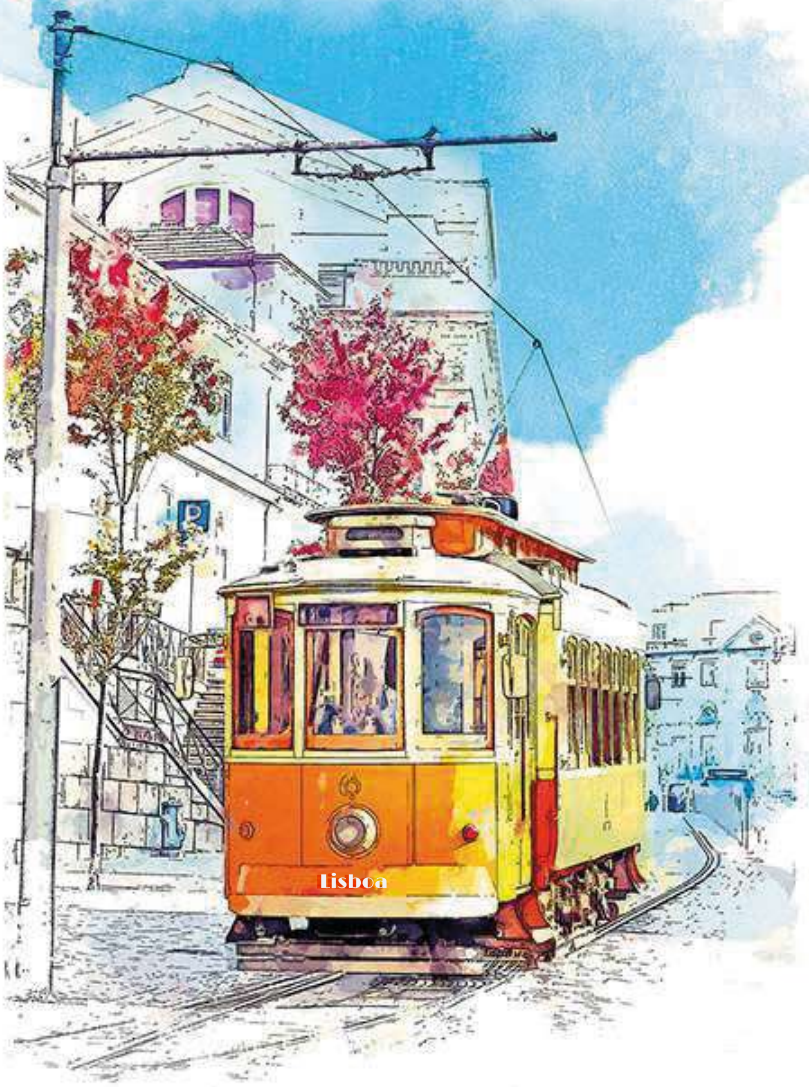
PN is often used to promote anabolism during episodes of intercurrent illness in organic acidaemias (OA) or urea cycle disorders (UCD), as such forming part of the treatment or prevention of metabolic decompensation when the usual enteral feeds or diet are not tolerated. Our centre's experience is mainly with short-term use of PN during episodes of recurrent vomiting and metabolic acidosis, and/or pancreatitis in children with OA.

There are no PN specific solutions for different IMD, making provision for disorders such as MSUD a major problem. Composition of commercial amino acid and lipid solutions vary, some may be considered more suitable for specific disorders.

PN prescriptions need to be individually tailored for the child, considering their disorder, age, weight, height, clinical condition, biochemical findings, usual diet prescription, fluid allowance and venous access route. For OA and UCD, standard PN solutions can be used. For macronutrients our practice is to limit the amino solution acid to provide only the child's usual daily protein intake, glucose and lipid amounts (g/kg/day) are generally increased over two to three days to meet energy requirements. Protein intake may need to be increased further in some situations such as on-going pancreatitis.

This presentation will focus on indications, provision, composition, monitoring of PN and titration plans back to enteral feeding.

SESSION VIII



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POC01

CYP46A1 Expression Partially Improves Intracellular Traffic in Niemann-Pick Type C Disease

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Main category: Basic science study

Disease category: Lipid metabolism and transport

Introduction: Niemann-Pick Type C Disease (NPC) is an autosomal recessive disorder arising from loss-of-function mutations in either the NPC1 or NPC2 protein, leading to unesterified cholesterol and glycosphingolipids accumulation in late endosomes (LE)/lysosomes (LY) (1). Compromised autophagy has also been reported (2). Recently, we showed that the cholesterol 24-hydroxylase (CYP46A1) ectopic expression in cellular and animal models of NPC was able to promote cholesterol metabolism and its redistribution from LE/LY (3). Thus, we aimed to study a potential role in also rescuing autophagic mechanisms.

Methods: To investigate how CYP46A1 improves NPC features, we used the NPC1-KO HeLa cell line overexpressing CYP46A1 by adenoviral or lentiviral-mediated expression. Additionally, we investigated the effect of CYP46A1 in Npc1tm(I1061T) mice that received an injection of CYP46A1-coding adeno-associated vector.

Results/Case report: Preliminary results show that NPC1-KO HeLa cells transduced with CYP46A1-encoding vector have decreased LC3II/I ratio in comparison with cells transduced with the control vector. However, we did not detect any differences in p62 levels, suggesting only a partially resolved autophagy block. To evaluate the various steps of autophagy flux we performed colocalization studies, using antibodies against LC3 (autophagosomes) and Rab7 (LE). We detected an increase in the percentage of anti-Rab7 signal overlapping that of anti-LC3, suggesting that CYP46A1 expression may promote amphisome formation. Conversely, we failed to observe an effect during double immunofluorescence of anti-LC3 with anti-LAMP2 (lysosomes). We further dissected the effect of CYP46A1 ectopic expression in the cerebellum of Npc1tm(I1061T) mice, by accessing p62 levels by immunoblotting and of LC3 by immunohistochemistry.

Conclusion: Our preliminary results hint that CYP46A1 may only partially resolve impaired autophagy featured in cellular and animal models of NPC. Specifically, in NPC1-KO HeLa cells we observe that CYP46A1 may induce the earlier stages of autophagy flux, whereas it does not seem to have an effect in the clearance of the autophagic cargo, namely the cargo receptor p62. More efforts will be needed to fully uncover the role of CYP46A1 ectopic expression in cellular models and in Npc1tm(I1061T) mice.

References:

Vanier M T. Niemann-Pick disease type C. Orphanet journal of rare diseases. 2010; 5(16);

Sarkar S, Carroll B, Buganim Y, Maetzel D, Ng A H, Cassady J P, Cohen M A, Chakraborty S, Wang H, Spooner E, Ploegh H, Gsponer J, Korolchuk V I, Jaenisch R. Impaired autophagy in the lipid-storage disorder Niemann-Pick type C1 disease. Cell reports. 2013;5(5):1302–1315;

Nunes M J, Carvalho A N, Reis J, Costa D, Moutinho M, Mateus J, Mendes de Almeida R, Brito S, Risso D, Nunes S, Castro-Caldas M, Gama M J, Rodrigues C M P, Xapelli S, Diógenes M J, Cartier N, Chali F, Piguet F, Rodrigues E. Cholesterol redistribution triggered by CYP46A1 gene therapy improves major hallmarks of Niemann-Pick type C disease but is not sufficient to halt neurodegeneration. Biochimica et biophysica acta. 2024; 1870(3).

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POCo2

Unveiling lipid profile alterations in MCADD patients: Insights from Red Blood Cell Lipidomics

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Main category: Basic science study

Disease category: Intermediary metabolism: energy

Introduction: Medium-chain acyl-CoA dehydrogenase deficiency (MCADD) is the most common fatty acid oxidation disorder (FAOD), characterized by the accumulation of medium-chain acylcarnitines, the basis of neonatal screening. Changes in the lipid homeostasis have been reported in plasma of MCADD patients (1). Red blood cells (RBC) lipidome remains relatively constant throughout their lifespan. It is less influenced by dietary changes than plasma and reflects long-term metabolic alterations. In this study the plasticity of the RBC lipidomic profile in MCADD patients compared to controls was assessed.

Methods: The lipidomic profile of RBC samples, using C18-liquid chromatography-mass spectrometry, was analyzed. The study included 35 MCADD patients treated at the Reference Center for Hereditary Metabolic Diseases in Coimbra, Portugal, and 38 controls.

Results/Case report: We identified significant alterations in 240 lipid species in MCADD, in particular an upregulation of sphingolipids – including sphingomyelins (SM) and ceramides – as well as of lysophospholipids, such as lysophosphatidylcholines and lysophosphatidylethanolamines. These changes suggest a possible pathophysiological link with oxidative stress, inflammation. Concurrently, the depletion of PUFA-containing phospholipids - phosphatidylcholines (PC) and phosphatidylethanolamines (PE) - and plasmalogens may compromise the antioxidant defences and potentially exacerbate oxidative stress. Furthermore, the altered PC/PE and PC+SM/PE+PS (phosphatidyserine) ratios observed in MCADD patients may cause changes in RBC (and presumably other cells) membranes properties, such as fluidity and asymmetry.

Conclusion: The observed imbalance in lipid composition of RBC, together with compromised antioxidant defences, enhanced oxidative stress and inflammatory state, may underlie long-term complications in MCADD patients. These changes may have a particular impact on the nervous system, given the high proportion of complex lipids in its composition. Therefore, his study highlights the utility of RBC lipidomics as a robust tool for understanding the pathophysiology of MCADD and suggests its potential for monitoring disease progression in MCADD.

References:

(1) Guerra, I. M. S.; et al. Plasma Lipidomics Analysis Reveals Altered Profile of Triglycerides and Phospholipids in Children with Medium-Chain Acyl-CoA Dehydrogenase Deficiency. Journal of Inherited Metabolic Disease 2024;47(4):731-745.

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POC03

New Zebrafish Models for Mitochondrial Diseases

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Main category: Translational science study

Disease category: Intermediary metabolism: energy

Introduction: Mitochondrial diseases (MD) are rare disorders with clinical and genetic heterogeneity and no effective therapies. Next Generation Sequencing has advanced MD diagnosis, although the interpretation of variants of unknown significance (VUS) remains a challenge (1). Functional validation is crucial for determining VUS pathogenicity, and zebrafish has emerged as a valuable organism to model MD, due to its conserved physiology and genetic similarity to humans (2).
This project aims to functionally characterize four previously identified VUS in ACAD9 and TSFM using zebrafish as an in vivo model.

Methods: Translational/splice blocking morpholino oligonucleotides (MO) were designed to knockdown ACAD9 and TSFM in zebrafish. MO concentrations will be optimized, and specificity confirmed with controls. Rescue experiments by co-injecting MOs with wild-type or mutant human cRNA will assess genetic rescue.

Results/Case report: Our project is ongoing and we are successfully generating zebrafish models for ACAD9 and TSFM genes, using a MO-induced knockdown strategy. We are currently determining the optimal concentration for knockdown that minimizes overt toxicity or nonspecific binding effects, as well as comparing survival outcomes between injected and non-injected embryos. The pathogenicity of the VUS will be verified if the phenotype resulting from the genetic knockdown cannot be rescued by the introduction of the mutated transcripts, but only when the wild type zebrafish and human transcripts are introduced. As such, the resulting behaviors and phenotypes of the developing embryos will be monitored and registered.

Conclusion: This research project will allow the implementation of a fast and reliable tool to functionally validate potentially pathogenic VUS, using a MO-mediated genetic rescue approach in new zebrafish models. This approach will have a high impact for the patient to obtain certainty about the cause of the disease, for the clinician to be able to provide optimal care to the patient and to predict the disease course, as well as for the clinical geneticist for genetic counseling of the patient and family members.

References:
(1) Nogueira et al., The genetic landscape of mitochondrial diseases in the next-generation sequencing era: a Portuguese cohort study. Front Cell Dev Biol, 2024, 23;12:1331351
(2) Adamson et al., Use of zebrafish models to investigate rare human disease. J Med Genet, 2018, 55(10):641-9.

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POC04

SIRT5-Mediated Regulation of Mitochondrial Acylations and MCAD Activity

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Main category: Basic science study

Disease category: Intermediary metabolism: energy

Introduction: Metabolic regulation involves genomic, proteomic and metabolic adjustments, several of which become compromised in disease states. Non-enzymatic PTMs, like succinylation and glutarylation, have emerged as important regulators of mitochondrial enzymes (1, 2). Their extent correlates with metabolite accumulation, such as succinyl-CoA and glutaryl-CoA, during fasting, caloric restriction, and metabolic diseases. These modifications are tightly controlled by SIRT5, a mitochondrial deacylase. Yet, structural and functional effects on mitochondrial proteins, and regulation by SIRT5 remains unclear.

Methods: To asses acylation's impact on mitochondrial proteins such as medium chain acyl-CoA dehydrogenase (MCAD), we employed biochemical and spectroscopic methods. Additionally, we are using HEK293 and SIRT5-KO HEK293 cell lines to investigate the physiological relevance of acylations.

Results/Case report: Our work has shown that MCAD is heavily succinylated and glutarylated in various conditions, in vitro. Interestingly, despite being similar, and despite not heavily affecting MCAD's structure, these modifications have different functional impact. Whilst succinylation increases MCAD's activity for all tested substrates, glutarylation only increases MCAD's activity for long chained substrates. Importantly, MCAD acylation is reverted, in vitro, by SIRT5, the deacylase responsible for removing negative charged acylation in the mitochondria in vivo, leading to a decrease in activity to unmodified MCAD levels. Currently, we are establishing protocols to profile these acylations in cellular models (HEK293 and Sirt5 knockout HEK293) under different nutrient availability. We will identify conditions that promote acylations and assess the impact of acylation level on mitochondrial homeostasis.

Conclusion: Overall, our results shed light on the importance of non-enzymatic PTMs, in particular negative charge acylations, as fine regulators of mitochondrial energy metabolism, by uncovering the first example of a β-oxidation enzyme presenting increased activity upon modification. Ongoing cellular studies will provide crucial insights into how acylations impact metabolic pathways and mitochondrial function in health and disease.

References:

(1) Wagner, G. R. et al., A Class of Reactive Acyl-CoA Species Reveals the Non-enzymatic Origins of Protein Acylation. Cell Metab. 2017;25(4):823-837;
(2) Bhatt, D. P. et al. Deglutamylation of glutaryl-CoA dehydrogenase by deacylating enzyme SIRT5 promotes lysine oxidation in mice., J. Biol. Chem. (2022) 298(4) 101723.

Acknowledgements: Fundação para a Ciência e Tecnologia (FCT/MCTES, Portugal) for grants: Scientific Employment Stimulus--Individual Call 2021.02218.CEECIND (to B.J.H), centre grants UIDB/04046/2020 and UIDP/04046/2020 (to BioISI). Sociedade Portuguesa de Doenças Metabólicas for Bolsa SPDM de apoio à investigação Dr. Aguinaldo Cabral. This research is partially funded by the European Union (TWIN2PIPSA, GA101079147). 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.

POC05

ETF-derived peptides rescue the unstable and prone to aggregation medium-chain acyl-CoA dehydrogenase variant, p.K329E

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Main category: Basic science study

Disease category: Lipid metabolism and transport

Introduction: In mitochondrial fatty acid β-oxidation, medium-chain acyl-CoA dehydrogenase (MCAD) catalyzes the first step of medium-chain fatty acids (MCFA) catabolism. MCFA oxidation results in FAD (MCAD cofactor) reduction, that is reoxidized by the electron transferring flavoprotein (ETF). MCAD deficiency (MCADD) is caused by ACADM gene mutations, with c.985A>G (p.K329E) as the most prevalent. The p.K329E is characterized as unstable and prone to aggregation, thus impairing enzyme activity. No pharmacological therapy is available for MCADD and stabilizing compounds are an attractive strategy.

Methods: Three short peptides (SPep), derived from the MCAD-ETF docking site were designed to rescue the p.K329E variant stability. The effect of SPep on p.K329E was explored, focusing on changes in structure, thermal stability, aggregation profile and enzyme activity.

Results/Case report: Recombinant wild-type and p.K329E MCAD were expressed and purified. Only the active tetrameric MCAD form was used. All assays were performed with synthetic SPep (100 and 500 uM) and compared with non-incubated MCAD.
The secondary structure content of MCAD was analyzed by circular dichroism. Thermal denaturation curves were obtained by CD and by the FAD-associated and the intrinsic tryptophan fluorescence. In isothermal denaturation assays, MCAD unfolding, particle size, and aggregation were monitored for 2 h at 37 °C. While not altering the MCAD secondary structure, SPep had a modest effect on p.K329E stability and aggregation profiles. SPep2 and SPep3 increased the p.K329E activity and also improved the kinetic inactivation parameters obtained after 2 hours incubation at 37°C.

Conclusion: The p.K329E MCAD variant is described as unstable and prone to aggregation. The tested SPep had a subtle effect on the variant's stability against thermal denaturation and aggregation. We postulate that those stability changes result in the increase of the enzymatic activity of p.K329E variant after incubation with SPep2 and SPep3. Further studies must be performed to confirm the predicted binding region between MCAD and the SPep, thus validating the strategy used to design stabilizing compounds based on the sequence/structure of interacting regions from protein partners, such as ETF.

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POC06

Invariant natural killer T (iNKT) cells in α-Gal knockout mice

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Main category: Basic science study

Disease category: Complex molecule and organelle metabolism

Introduction: Fabry disease (FD) is a rare X-linked lysosomal storage disease caused by mutations in the GLA gene, encoding enzyme α-Galactosidase (α-Gal), responsible for catalyzing glycosphingolipids (1). α-Gal knockout (KO) mice have a progressive accumulation of globotriaosylceramide and invariant natural killer T (iNKT) cells are reduced in spleen, thymus and liver (2). iNKT cells are lipid reactive, CD1d-restricted T cells, expressing semi-invariant T cell-receptor (TCR). In mice, iNKT cells are either CD4+ or CD4- CD8- (Double negative, DN), expressing none to negligent CD8+ iNKT cells (3).

Methods: Herein, α-Gal KO mice and control wild type (WT) mice with C57BL/6 129Sv background aged between 10-12 months were used. Spleen, liver and thymus were retrieved, processed, stained and the cells characterize through flow cytometry equipped with spectral technology (Cytek Aurora).

Results/Case report: The results show that when comparing α-Gal KO and WT mice, there is a significant decrease in iNKT cell frequency in the spleen and liver of α-Gal KO mice and the same tendency is observed for thymus. Nonetheless, no major differences were seen in the TCR usage, activation state (CD69/CD25/iCOS %), Ki-67 and PD-1 expression, NKT functional subsets and in the CD4/CD8 profile of iNKT cells when α-Gal KO and WT mice were compared. Surprisingly, detectable amounts of CD8+ iNKT cells were observed not only in α-Gal KO mice (not published results from our group) but also in WT mice. There was a statistically higher CD8+ iNKT % in αGal KO mice housed in high security barrier (Rederivation room) when compared to WT animals. No differences between WT and α-Gal KO on the phenotype of CD8+ iNKT cells. CD8+ iNKT cells are phenotypically and functionally different from CD4+ and DN iNKT cells.

Conclusion: There is a lower iNKT cell % in α-Gal KO mice (spleen and liver; tendency in thymus), which could be due to the lipid accumulation, characteristic of these animals. Alterations in iNKT cells are important to be explored as these cells are immunoregulatory and they can play a role in the physiopathology of Fabry disease. There are no major differences in iNKT cell characterization when comparing α-Gal KO and WT mice. In addition, there was a higher CD8+ iNKT cell % in α-Gal KO mice from Rederivation room. CD8+ iNKT cells are phenotypically and functionally different from CD4+ and DN iNKT cells.

References:

(1) Desnick RJ, et al. α-Galactosidase A Deficiency: Fabry Disease. In: Valle DL, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA, eds. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill Education; 2019.
(2) Macedo MF, et al. Enzyme replacement therapy partially prevents invariant Natural Killer T cell deficiency in the Fabry disease mouse model. Mol Genet Metab. 2012;106(1):83-91.
(3) Lee H, et al. The presence of CD8+ invariant NKT cells in mice. Exp Mol Med. 2009;41(12):866-72.

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POC07

Fabry Disease Screening in patients with idiopathic HCM or idiopathic LVH: data from the multicentric nationwide F-CHECK Study

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Main category: Case series

Disease category: Complex molecule and organelle metabolism

Introduction: Fabry disease (FD) is a rare lysosomal storage disorder caused by mutations in an X-linked gene that encodes the alpha-galactosidase A (GLA) enzyme. The most common cardiac manifestation of FD is hypertrophic cardiomyopathy (HCM). Because the clinical presentation of FD can be non-specific, the best way to improve diagnosis rates is to systematically screen patients exhibiting compatible phenotypes. In this multicenter registry, we aim to report the findings from a nationwide FD screening initiative (F-CHECK) conducted in Portugal, to gather more data on the incidence of this rare disease.

Methods: Patients diagnosed with idiopathic HCM, idiopathic left ventricular hypertrophy, dilated phase of hypertrophic cardiomyopathy (dHCM), ot dilated cardiomyopathy with delayed enhancement in the inferolateral segment, underwent Dried Blood Spot or genetic testing between January 2021 and December 2024.

Results/Case report: The study included 265 patients, 163 males (61.5%), with a median age of 65 years [18-93]. A total of 10 patients were diagnosed with FD (3.8%), with 6 distinct mutations of the GLA gene, 4 with F113L, 2 with N215S and 4 with other pathogenic mutations. Among 131 patients who underwent DBS, enzyme activity was reduced in 17 patients, with further genetic FD confirmation obtained in 7 cases. In FD patients, cardiovascular symptoms or signs were present in 9 patients (90.0%), and 4 had previous cardiovascular events (40.0%). FD patients compared with those without the disease had larger QRS duration (139 vs 104ms p=0.022), and higher prevalence of right bundle branch block (66.7 vs 9.5%, p<0.001), fascicular block (33.3 vs 4.7%, p=0.011) and LGE inferolateral (70.0 vs 18.6%, p<0.001). Additionally, the use of B-Blockers and ACE/ARA was less common in the FD patients.

Conclusion: In this screening study including centres in the Northern region of Portugal with distinct cardiac phenotypes, FD was diagnosed in a significant percentage of patients, 60% with non-F113L mutation, highlighting the importance of FD screening in patients with HCM or idiopathic LVH.

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F-CHECK Group:
Centro Hospitalar Universitário de São João (CHUSJ); Centro Hospitalar Universitário do Porto (CHUP); Hospital Pedro Hispano (HPH); Centro Hospitalar do Tâmega e Sousa, EPE; Unidade Local de Saúde de Gaia/Espinho, EPE; Centro Hospitalar De Trás-Os-Montes E Alto Douro, EPE; ULS de Barcelos/Esposende; Centro Hospitalar Universitário de Coimbra (CHUC); Hospital de Santa Maria (HSM)

POCo8

Shaping gut microbiota: the impact of protein substitutes used in the treatment of Phenylketonuria

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Main category: Basic science study

Disease category: Disorders of amino acid metabolism

Introduction: Phenylketonuria (PKU) is an inborn error of phenylalanine (Phe) metabolism. Although the Phe-restricted diet is recognized as the mainstay of therapy [1], the impact of protein substitutes (Phe-free L-amino acid supplements (L-AAs) or casein glycomacropeptide with amino acids (CGMP-AAs)) on gut microbiota composition is not established. Thus, our aim was to identify the impact of L-AAs and CGMP-AAs on growth parameters of three representative gut bacteria: Escherichia coli (commensal), Lactobacillus paracasei (probiotic), and Shigella flexneri (pathogenic).

Methods: Bacterial growth was assessed in vitro. Bacterial suspensions were grown in broth supplemented with water (control), L-AAs, CGMP-AAs, digested whey protein (DWP), or whey protein (WP). Optical densities at 600 nm were measured every 30 minutes for 24 hours.

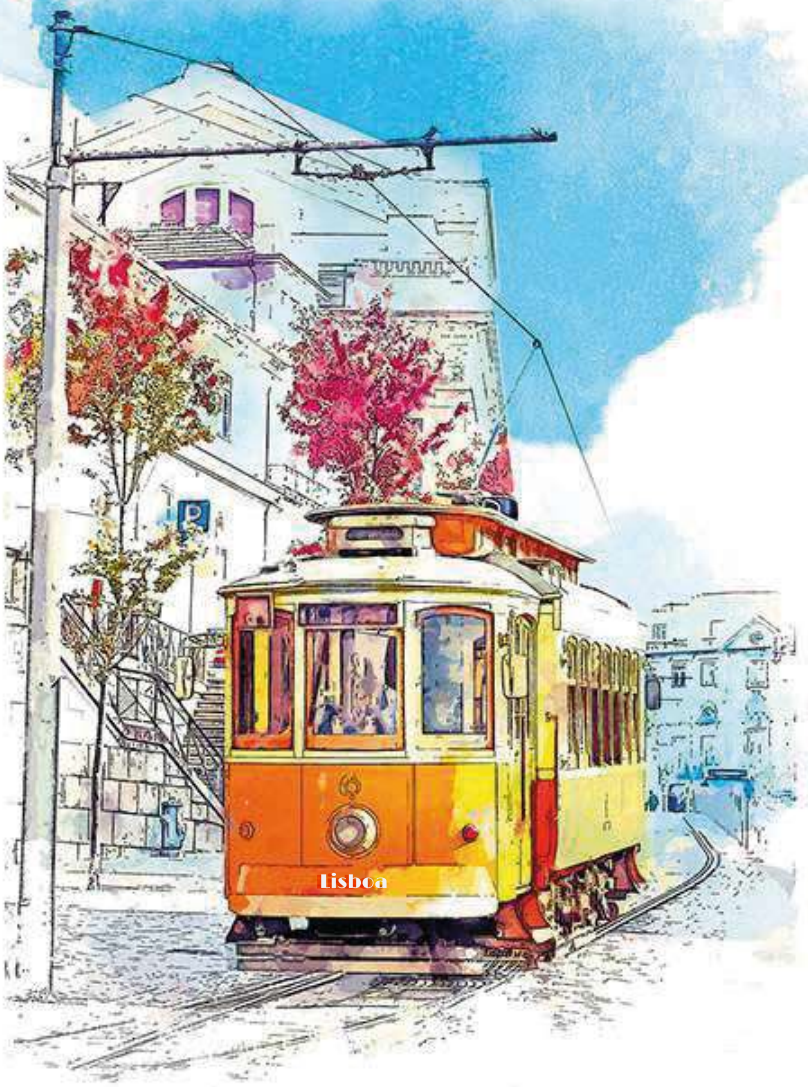
Results/Case report: Exposure to different sources of protein significantly increased the bacterial area under the growth curve compared to water. For all bacteria, this increase was more pronounced after exposure to L-AAs, compared to CGMP-AAs (E. coli: 694.4 ± 2.7 vs 658.6 ± 3.3, $p<0.001$; L. paracasei: 607.5 ± 5.9 vs 540.0 ± 4.0, $p<0.001$; S. flexneri: 892.5 ± 4.6 vs 853.8 ± 2.3, $p<0.001$).
Additionally, the growth rate was significantly increased by L-AAs, DWP, and WP compared to water, for all bacteria. Interestingly, CGMP-AAs selectively increased the growth rate of L. paracasei. This seems to be explained by the potential prebiotic effect of CGMP-AAs, and the decrease in gastrointestinal symptoms reported by patients with PKU who consume CGMP-AAs [2,3].

Conclusion: Protein substitutes promote the overall growth of intestinal commensal bacteria. This effect appears to be of greater magnitude in L-AAs, compared to CGMP-AAs. However, CGMP-AAs selectively increases the growth rate of the probiotic bacteria L. paracasei, compared to commensal and pathogenic bacteria. Future studies are underway to understand the impact of these protein substitutes on global gut microbiota composition and metabolomic profile of patients with PKU.

References:

(1) van Wegberg et al. The complete European guidelines on phenylketonuria: diagnosis and treatment. Orphanet J Rare Dis. 2017; 12:162;
(2) Daly et al. Glycomacropeptide in PKU-Does It Live Up to Its Potential? Nutrients. 2022;14(4):807;
(3) Zaki et al. The Use of Glycomacropeptide in Dietary Management of Phenylketonuria.J Nutr Metab. 2016; 2016: 2453027.

SESSION IX



MOVING FROM RESEARCH AND CLINICAL PRACTICE TO DIGITAL HEALTH AND DECISION

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The European Health Data Space: impact for disease management at the individual and population level

Cátia Sousa Pinto

SPMS, EPE - Serviços Partilhados do Ministério da Saúde (Head of Global Digital Health and International Affairs), Lisbon, PT

This lecture will examine the impact of the European Health Data Space (EHDS) on disease management, focusing on both individual and population-level approaches. It will explore Portugal's approach to leveraging health data for digital transformation and public health, with a particular focus on the role of the Electronic Health Record (EHR), national strategies, and alignment with the EHDS. The EHDS seeks to enhance interoperability and facilitate access to health data across Europe, aiming to optimise healthcare delivery and improve patient outcomes. By creating a framework for seamless data exchange, the EHDS is poised to improve the coordination of care, enable more personalised treatments, and support better clinical decision-making.

The presentation will provide particular insights into the implementation of the EHDS in Portugal, with a focus on the pivotal role of the Shared Services of the Ministry of Health (SPMS) in driving forward this agenda. The presentation will highlight key initiatives such as MyHealth@EU and HealthData@EU, emphasising their crucial role in shaping a global digital health ecosystem and advancing cross-border healthcare solutions.

Furthermore, the lecture will highlight SPMS's contributions to international initiatives that foster digital health transformation, emphasising the importance of cross-border collaboration in advancing healthcare solutions. A key focus will be Portugal's National Strategy for Digital Transformation in Health, which reflects the country's commitment to advancing digital health solutions and promoting international cooperation to strengthen the European health data infrastructure.

The lecture will reflect on Portugal's role in shaping the future of the EHDS, addressing the challenges and opportunities of cross-border health data exchange and reinforcing the country's commitment to a patient-centred, innovation-driven healthcare system.

Using data science for better healthcare and opportunities in IMD

João Guimarães

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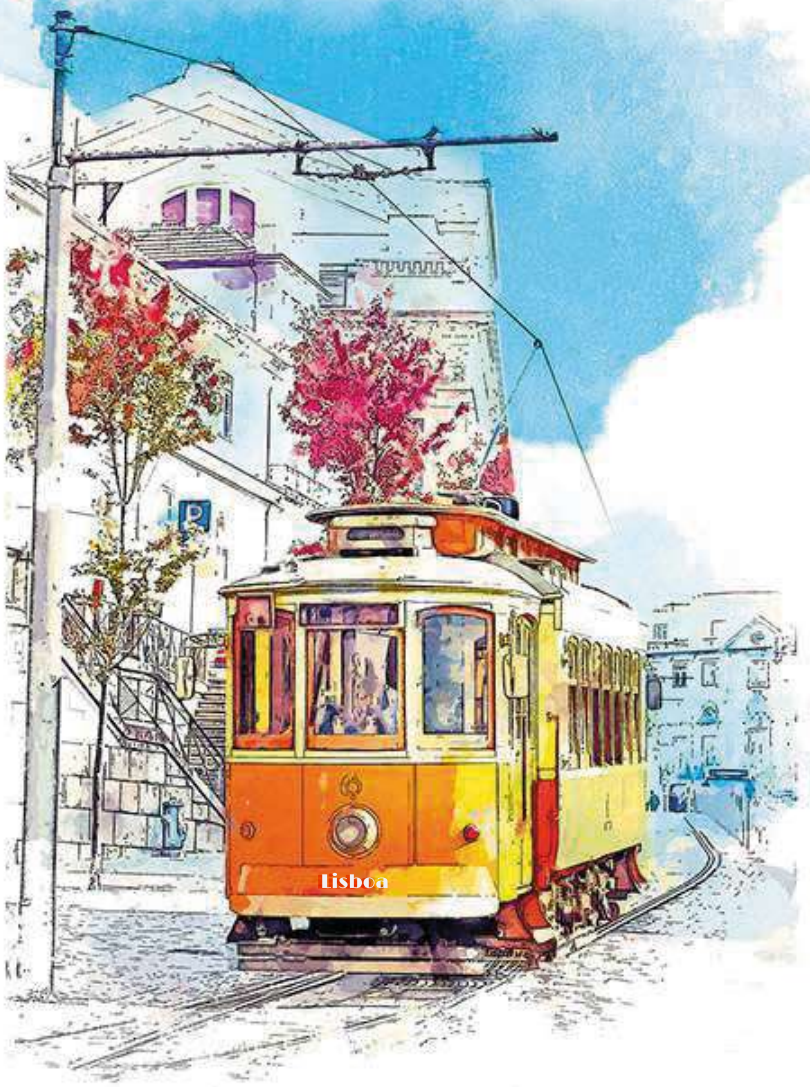
Modern clinical care generates a plethora of complex and heterogeneous types of data such as medical images, clinical notes from physicians, monitoring data from wearable sensors or genomic data. Finding relationships between vast amounts of data and a given clinical outcome of interest is very challenging and often beyond human capacity. Machine learning has the potential to revolutionize healthcare and biomedicine by training computational models that learn from examples rather than being explicitly programmed. Machine learning can identify patterns from thousands of clinical data points and infer relevant relationships in the training data. Potential applications for machine learning include the development of decision support systems for clinicians, as well as the design of predictive models for biological systems that can be exploited by the biomedical industry. Our research program on health data science and genomics seeks the development of machine learning models that integrate distinct health-related data modalities to understand human physiology in normal and pathological conditions.

Sustainability in the development of the treatments for IMD

Rui Santos Ivo

INFARMED- Autoridade Nacional do Medicamento e Produtos de Saúde, I. P. (President); European Medicines Agency, EMA (President of the Management Board); Lisbon, PT

SESSION X



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Can enzyme replacement therapy revert iNKT cell dysfunction in acid sphingomyelinase deficiency patients?

Fátima Macedo

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Acid sphingomyelinase deficiency (ASMD) is a lysosomal storage disease caused by deficient activity of the enzyme acid sphingomyelinase (ASM), resulting in an abnormal accumulation of sphingomyelin in lysosomes. The abnormal accumulation of sphingomyelin, a crucial cell membrane component, ultimately impairs pulmonary, hepatic, and sometimes neurological functions, with severe forms of the disease being fatal in the first years of life.
Invariant Natural Killer T (iNKT) cells are lipid-reactive T cells that play a central role in a wide range of immune responses including cancer, infection and inflammation. iNKT cells are restricted to CD1d, depending on the presentation of lipids by this molecule for their function. Sphingomyelin is a lipid with affinity for CD1d and its accumulation in ASMD influences the role of iNKT cells by impairing normal lipid antigen presentation to these cells (1). Interestingly, ASM-/- mice have reduced number of iNKT cells and impaired iNKT cell activity, in ASMD patients a reduced frequency of iNKT cells is also observed (1). Noteworthy, enzyme replacement therapy (ERT) with recombinant ASM can prevent iNKT cell deficiency in ASM-/- mice (1). In the current study we are investigating the effect of ERT on iNKT cells in ASMD adult patients.
So far, five ASMD patients were recruited, having three initiated ERT with Olipudase alpha. Patients iNKT cells were analyzed pre-therapy and every 3 months after ERT started. In addition, twenty-two healthy donors were analyzed as controls.
The basal characterization of ASMD patients, before ERT, confirms patients' lower iNKT cell frequency. In addition, patients iNKT cells have a more immature profile indicated by lower CD161 and higher CD4 expression and increased activation state accessed by ICOS expression than control subjects.
During the course of these study three patients treated with ERT were recruited. So far patients have been on therapy for 3, 9 and 20 months. The two patients treated longer show improvement in the disease biomarker lyso-sphingomyelin and clinical features. Despite these improvements no recovery in the percentage or phenotype of iNKT cells was observed so far. It will be important to recruit more and younger patients and continue patient follow-up for a longer duration.

Acknowledgments: This work was supported by "Bolsa SPDM Aguinaldo Cabral 2022"

Reference:

[1] Melum, et al Blumberg (2019)Nature Immunology, doi:10.1038/s41590-019-0504-0.

Functional and structural impact of 10 ACADM missense mutations on human medium chain acyl-CoA dehydrogenase

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The acyl-CoA dehydrogenases (ACADs) family are flavin adenine dinucleotide (FAD)-dependent enzymes that includes 11 mitochondrial members, from which three have a stablished key role in mitochondrial fatty acid (FA) β-oxidation (mFAO), namely the short (SCAD), medium (MCAD) and very long (VLCAD) chain acyl-CoA dehydrogenases. Besides being responsible for the first step of mFAO, SCAD, MCAD and VLCAD are also involved in ATP production as upon dehydrogenation of ACAD substrates, electrons accepted by the FAD cofactor are transferred to the electron transferring flavoprotein (ETF), which in turn interacts with ETF:ubiquinone oxidoreductase establishing an electron flux towards the respiratory chain. Impaired ACADs activity have been associated with human diseases, such as MCAD deficiency (MCADD), the most frequent mFAO disorder. MCADD patients may develop severe clinical manifestations, particularly during metabolic stress that can lead to coma and sudden death. Till present no pharmacological therapies are available for MCADD. MCAD is encoded by the ACADM nuclear gene and to be biologically active assembly into homotetramers, FAD incorporation and interaction with ETF is necessary. To understand the impact of ACADM missense mutations on MCADD pathogenesis, 10 MCADD--associated amino acid changes scattered along the protein domains were studied by producing and characterizing the recombinant MCAD variants at the structural level (oligomeric profile, secondary structure, thermal stability, and susceptibility to proteolysis), FAD content and binding affinity, and at the functional level (enzyme activity for different chain-length substrates, thermal inactivation, and ETF interaction).

Most of the studied pathogenic MCAD variants presented disturbed Vmax and/or Km, FAD misincorporation, changes in the affinity for different chain-length substrates (indicating a change in the architecture of the active center) and impaired MCAD/ETF interaction. Our studies also highlighted the need for a carefully evaluation of the enzymatic assay conditions usually performed in patient cells for MCADD diagnosis, as these assays are usually performed at Vmax conditions with saturating concentrations of substrate and from our data each variant will present its optimal working range. Disturbed ETF interaction and impaired FAD incorporation was observed also on MCAD variants with amino acid substitutions distant from the FAD-binding pocket or the MCAD/ETF interacting region. Furthermore, for some variants the presence of FAD increased protein stability, suggesting that in mitochondria, the activity of those variants and their ability to perform protein-protein interactions will depend on FAD availability, thus impacting the patient phenotype. The evident importance of a suitable MCAD/ETF interaction also support these protein interfaces as candidate pharmacophoric site for MCADD drug development.

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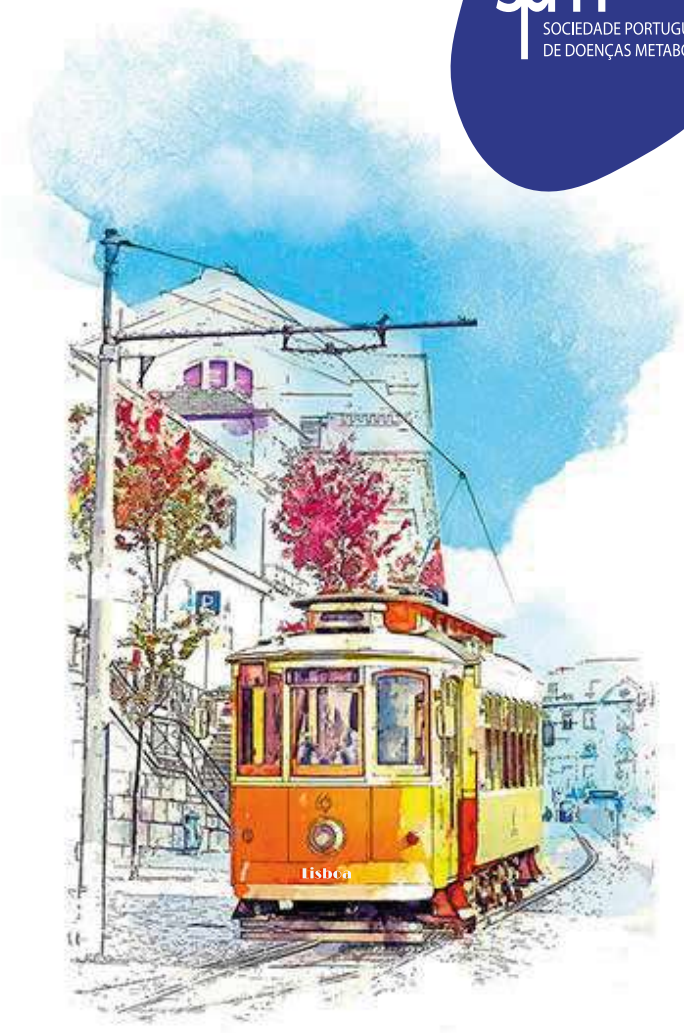

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