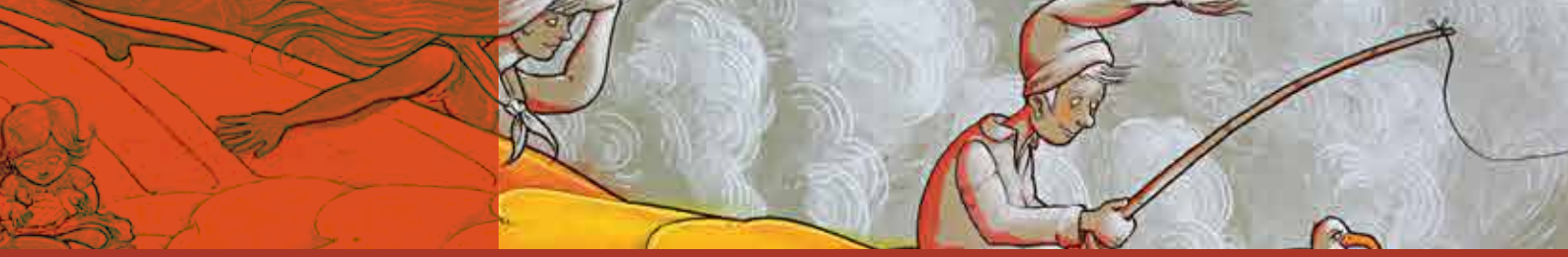
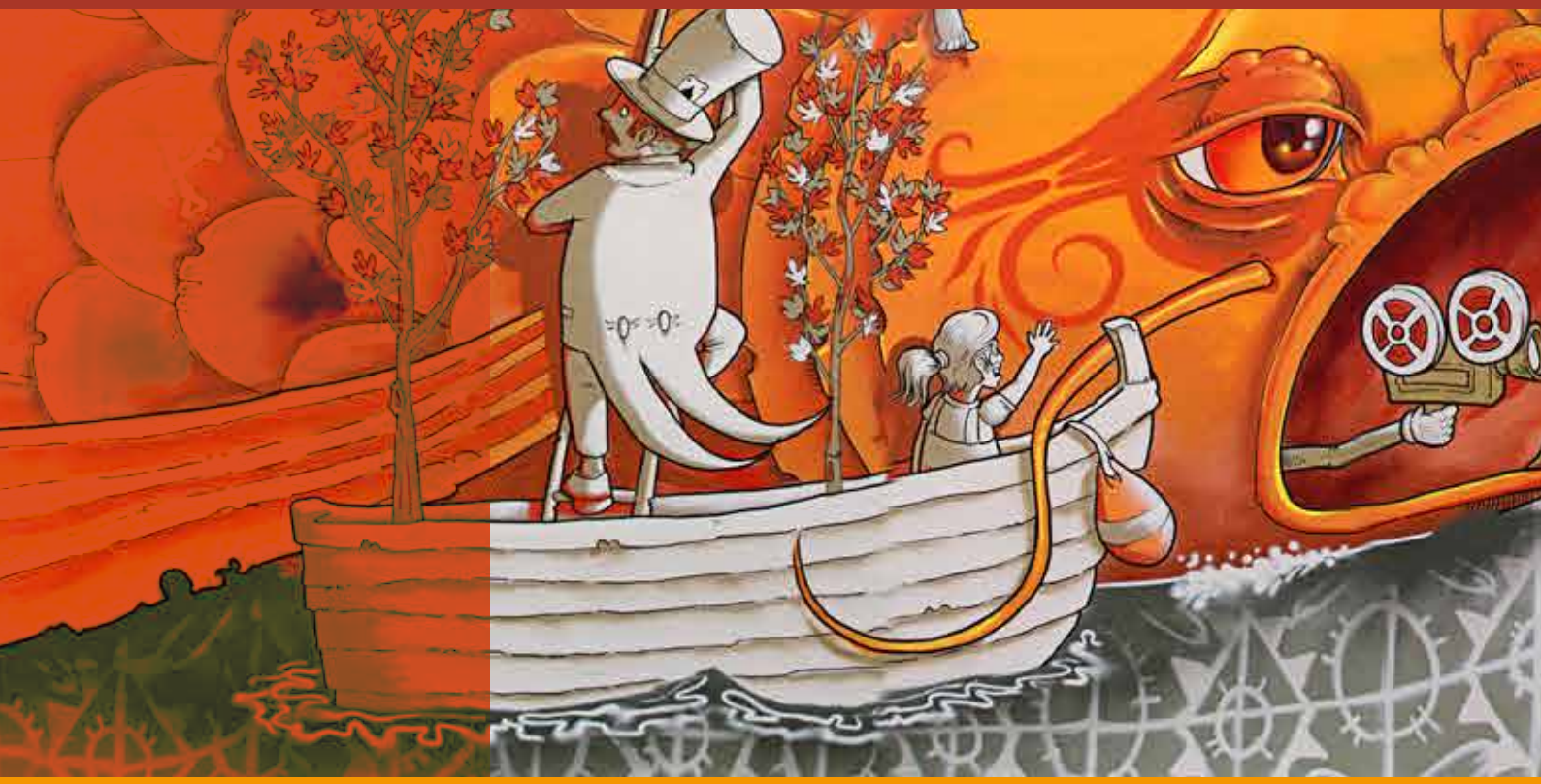


19TH INTERNATIONAL SYMPOSIUM OF THE PORTUGUESE SOCIETY FOR METABOLIC DISORDERS



THE NEXT STEPS IN INBORN ERRORS OF METABOLISM: FROM NEWBORN SCREENING TO PALLIATIVE CARE

29–31 MAR 2023

EUROSTARS OASIS PLAZA - FIGUEIRA DA FOZ - PT

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spdm
SOCIEDADE PORTUGUESA DE DOENÇAS METABÓLICAS

WELCOME ADDRESS

Dear Colleagues and Friends,

On behalf of the Organizing Committee, it is a great pleasure to welcome you to the 19th International Symposium of the Portuguese Society for Metabolic Disorders (SPDM).

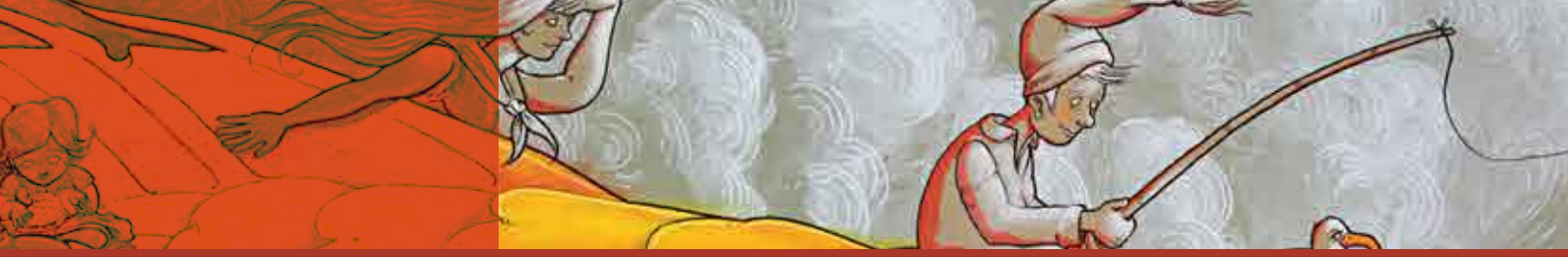
This year´s programme focus on "The next steps in Inborn Errors of Metabolism: from newborn screening to palliative care", with the scope to raise awareness of Inborn Inherited Diseases (IMD) and expand the field to other areas of medical expertise. The Symposium programme has the privilege to count on the participation of outstanding world experts who will bring you the most recent scientific advances in the IMD field, including aging, innovative therapies, bigdata and artificial intelligence and unmet needs in IMD. Moreover, it dedicates two sessions for the presentation of short oral communications and allocates time for poster visit and discussion, giving the opportunity to promote the work done in Portugal in the field.

The symposium has an hybrid format with a platform that will allow the intervention of all participants, either in person or virtually. We hope that most of the participants can get together in person, so important for exchange of ideas in an informal environment. The Eurostars Oasis Plaza offers ideal conference conditions in a modern and pleasant Atmosphere.

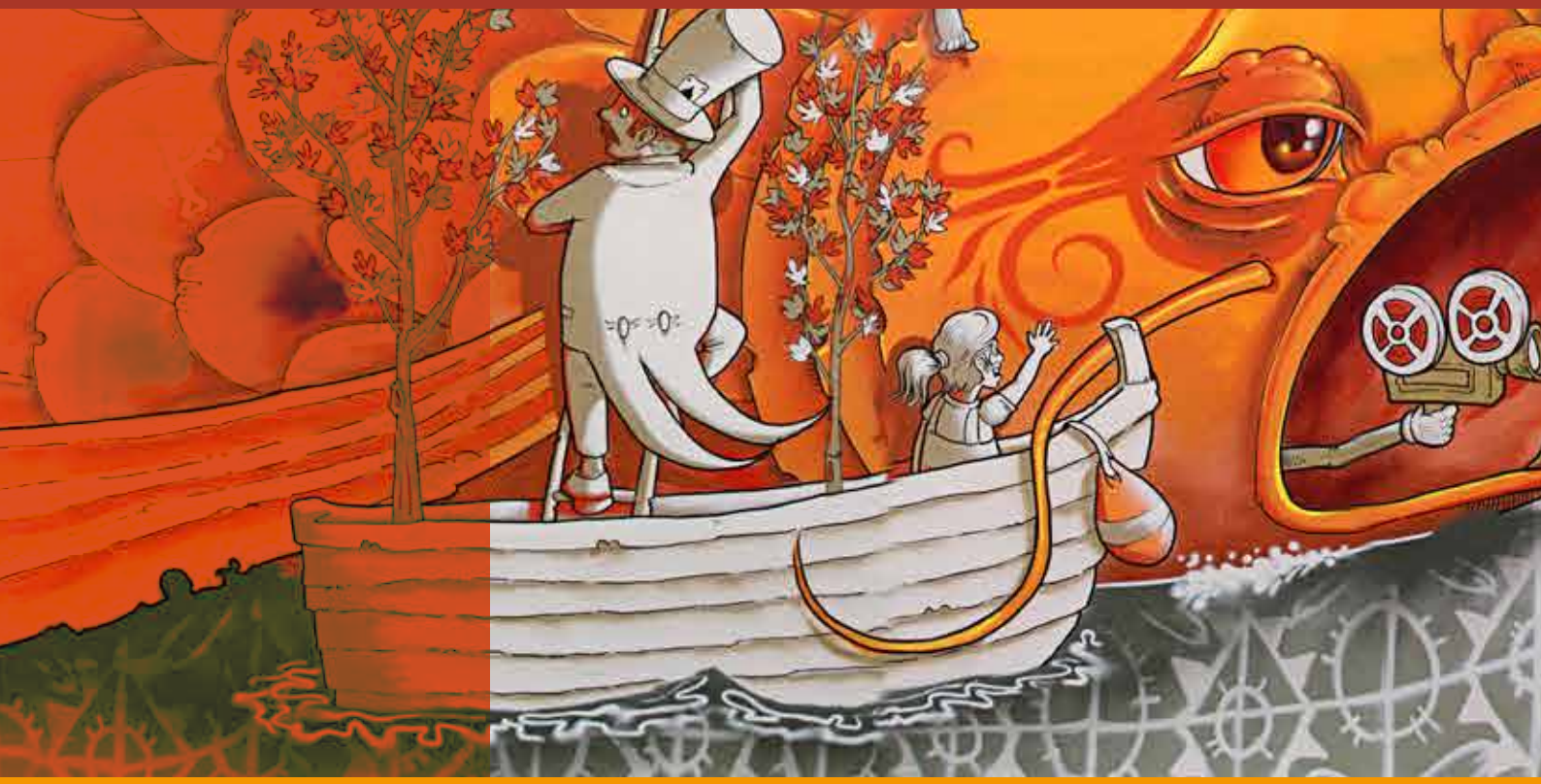
This meeting has been made possible by the support of the sponsors, which we acknowledge.

We are delighted to be hosting the 2023 SPDM Annual Symposium, hoping that it will be a success, and very much look forward to welcome all of you in Figueira da Foz.

Luísa Diogo
2023 Symposium President



19TH INTERNATIONAL SYMPOSIUM OF THE PORTUGUESE SOCIETY FOR METABOLIC DISORDERS



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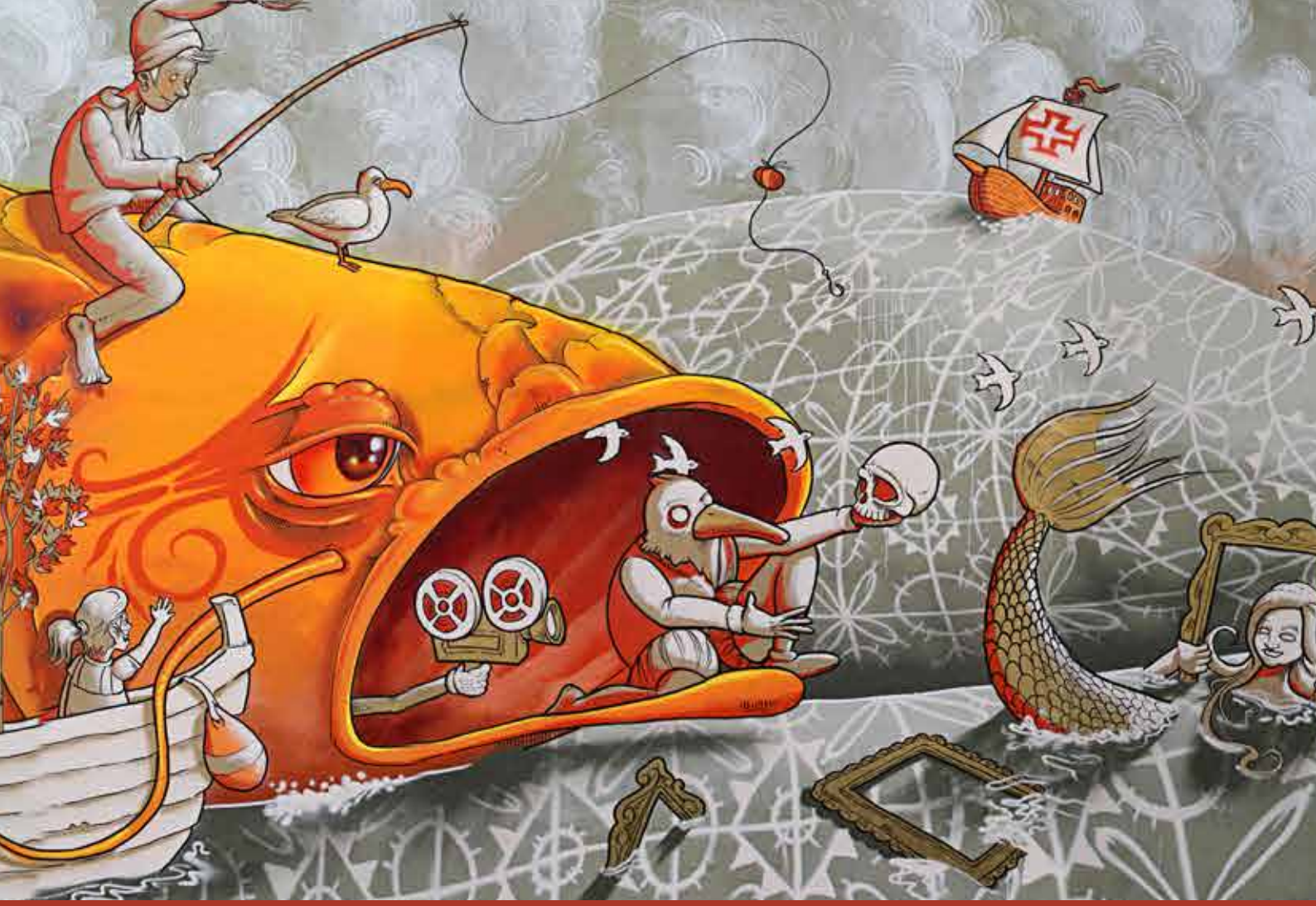


PROGRAMME

SCIENTIFIC PROGRAMME

WEDNESDAY, 29TH MARCH

17:00	SPDM Nutrition Group Meeting
17:45	SPDM Working Groups meetings

THURSDAY, 30TH MARCH

08:30	Registration opening *Symposium Chairperson*
09:00	Symposium Opening – Welcome address on behalf of the SPDM
	SESSION I – INHERITED METABOLIC DISEASES IN THE LIFETIME *Chairpersons: João Durães, Coimbra; Lelita Santos, Coimbra; Maria João Guedes, Coimbra*
09:10	Dietary management during the lifetime for IMD - *Júlio Rocha, Lisbon*
09:30	Reproductive health and other challenges in adults with an IMD - *Elaine Murphy, London*
09:50	Neurometabolic disorders in adults: IMD and beyond - *Fanny Mochel, Paris*
10:10	Palliative care for IMD patients - *Cândida Cancelinha, Coimbra*
10:30	Discussion
10:50-11:20	Coffe Break and Poster View
	SESSION II - FAMILIAL DYSLIPIDAEMIAS *Chairpersons: Ana Gaspar, Lisbon; Anália Carmo, Coimbra; M. Teresa Cardoso, Porto;*
11:20	Defects of lipoprotein metabolism: from the genes to the clinic *Adriaan Holleboom, Amsterdam*
11:40	Familial hypercholesterolaemia in children and adolescents - better safe than sorry *Albert Wiegman, Amsterdam*
12:00	The Portuguese screening program for familial dyslipidaemias - *Mafalda Bourbon, Lisbon*
12:20	Discussion
12:20 - 14:30	Lunch and Satellite Symposium
	SESSION III – ARE WE MOVING FORWARD IN LYSOSOMAL STORAGE DISORDERS? *Chairpersons: Esmeralda Rodrigues, Porto; Lúcia Lacerda, Porto; Sandra Alves, Porto*
14:30	The future of enzyme replacement therapy - *Eugen Mengel, Hochheim*
14:50	The path to gene therapy in lysosomal storage disorders - *Francesca Tucci, Milan*
15:10	Registries in inherited metabolic diseases: how to move forward? - *Nadia Belmatoug, Paris*
15:30	Discussion
16:00-16:30	Coffe Break and Poster View
16:30	**SESSION IV – ORAL COMMUNICATIONS I** *Chairpersons: Isabel Rivera, Lisbon; Sara Ferreira, Coimbra*
17:30	**SPDM GENERAL ASSEMBLY**
19:00	**DEPARTURE TO THE SYMPOSIUM DINNER**

SCIENTIFIC PROGRAMME

FRIDAY, 31ST MARCH

	SESSION V – NEW APPROACHES IN PORPHYRIAS *Chairpersons: Arlindo Guimas, Porto; Eulália Costa, Coimbra; Sónia Moreira, Coimbra*
09:00	Acute hepatic porphyria – The experience of a reference center in Brazil - *Charles Marques Lourenco, Ribeirão Preto*
09:20	Biochemical and molecular update on porphyria diagnosis - *Filipa Ferreira, INSA Porto*
09:40	The RNAi therapeutics revolution: from bench to bedside and back again - *Pedro Moreno, Porto*
10:00	Discussion
10:30-11:00	Coffe Break and Poster View
	SESSION VI – THINKING BIG AND BOLD IN INHERITED METABOLIC DISEASES *Chairpersons: Ana Cristina Ferreira, Lisbon; Anabela Oliveira, Lisbon; Laura Vilarinho, Porto*
11:00	Challenges and opportunities for using of real world data in metabolic medicine - *Mário Silva, Lisbon*
11:20	Newborn screening by WGS: opportunities and challenges - *David Bick, London*
11:40	Aging in IMD: uncovering new phenotypes - *Charles Lourenço, Ribeirão Preto*
12:00-12:20	Discussion
	SESSION VII – ORAL COMMUNICATIONS II *Chairpersons: Joana Salgado, Coimbra; João Gomes, Coimbra*
13:00-14:30	Lunch
	SESSION VIII – UNMET NEEDS IN INHERITED METABOLIC DISEASES *Chairpersons: Fátima Ventura, Lisbon; Paulo Gonçalves, Lisbon; Rui Tato Marinho, Lisbon*
14:30	Unmet needs for the patient and the family - *José Vilhena, Coimbra*
14:50	The pharmacist and the specificities of IMD - *Sara Dias, Lisbon*
15:10	Reference centres of IMD in Portugal - challenges and opportunities - *Luisa Diogo, Coimbra*
15:30-15:50	Discussion
	SESSION IX – SPOTLIGHT I *Chairpersons: M. Helena Santos, Vila Nova de Gaia; Nanci Batista, Coimbra*
15:50	Diet quality and saproterin dihydrochloride (BH4) use in children with phenylketonuria (PKU) - *Maria Inês Gama, Lisbon*
16:10	Novel insights into treatment strategies for hyperammonemia-associated urea cycle disorders and organic acidurias. - *Margarida Silva, Lisbon*
16:30-17:00	Coffee Break and Poster View
	SESSION X – SPOTLIGHT II *Chairpersons: Paula Leandro, Lisbon; Paulo Castro Chaves, Portugal*
17:00	Something stinks': impaired hydrogen sulfide and cysteine persulfide production by cystathionine β-synthase variants identified in classical homocystinuria patients - *João Vicente, Lisbon*
17:20	Improve management of MADD patients: a curated database with clinical, molecular and cellular information - *Bárbara Henriques, Lisbon*
17:40	**AWARDS AND FINAL REMARKS**
18:00	**END OF THE SYMPOSIUM**

ORAL COMMUNICATIONS

THURSDAY, 30TH MARCH

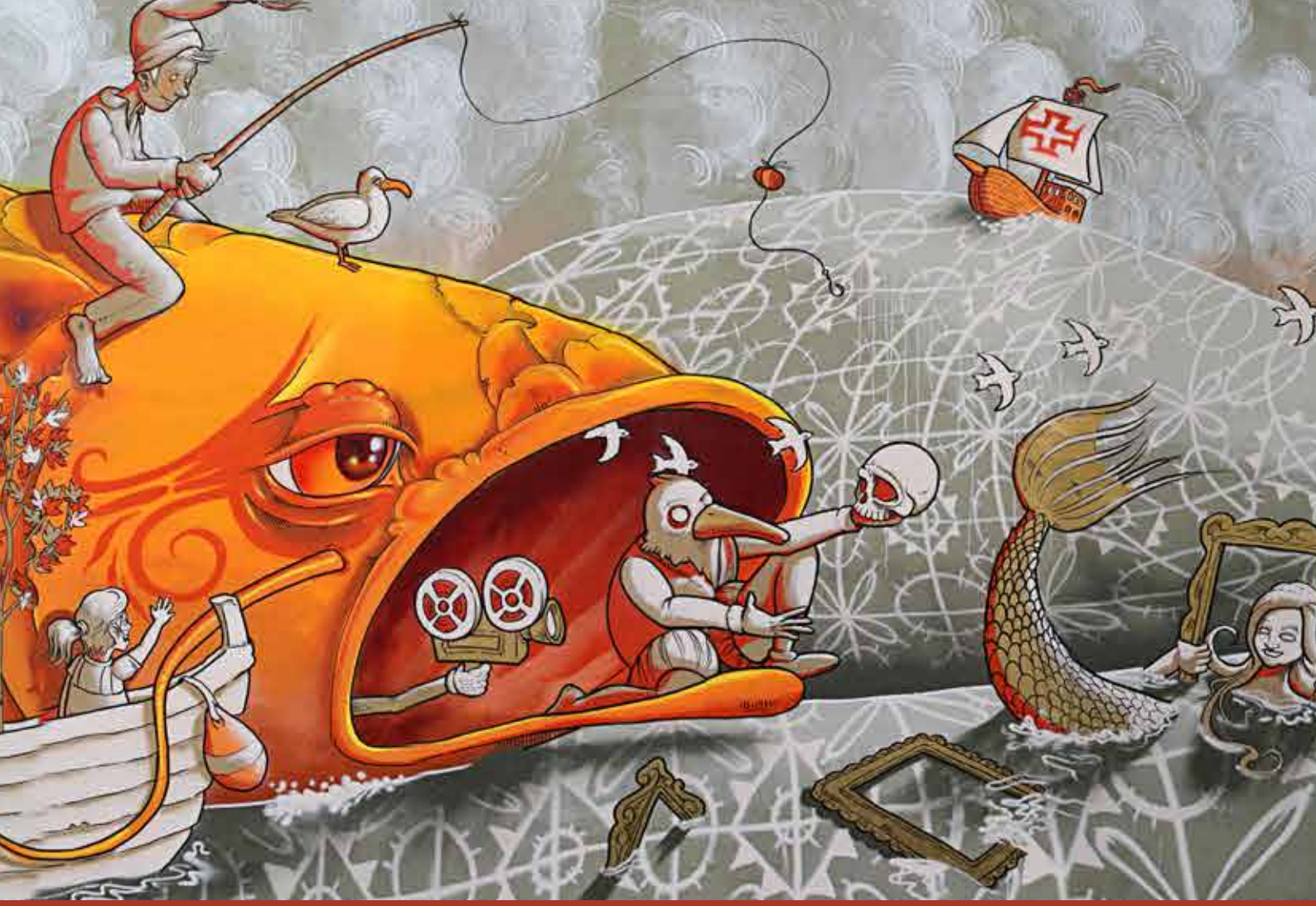
16h30 – 17h30 | Session IV

OC 01	Impact of structural GLA protein changes on peripheral GLA activity and substrate accumulation in Fabry disease patients
OC 02	MCADD patients: how to face cardiac function biomarkers during acute episodes?
OC 03	Help comes from unexpected places: how a tiny fairy and a tropical fish may help us model Mucopolysaccharidoses
OC 04	Clinical and laboratory findings in Glycogen Storage Disease Type V: results from a retrospective observational study in a tertiary hospital
OC 05	Glutaric acidemia type 1: diagnosis, clinical features, and outcome in a Portuguese cohort
OC 06	Forty-three Years After The Start Of Neonatal Screening In Portugal: The Results of a Retrospective Cohort Study with 113 Adult PKU Patients

FRIDAY, 31ST MARCH

12h20 – 13h00 | Session VII

OC 07	The hole in the whole: mitochondrial DNA deletions screening
OC 08	Restoring cholesterol homeostasis in neurons by AAV-mediated CYP46A1 delivery is not sufficient to stall the progression of Niemann-Pick type C disease
OC 09	Palliative care in children with inherited metabolic diseases: why does it matter?
OC 10	Boosting insights on the immunopathology of PMM2-CDG



SPEAKERS

ADRIAAN HOLLEBOOM
AMSTERDAM,
THE NETHERLANDS

Adriaan G. (Onno) Holleboom, MD, PhD

Is an internist registered in Vascular Medicine and Endocrinology, faculty member of the Department of Vascular Medicine and Assistant Professor at Amsterdam UMC. He heads a multidisciplinary outpatient clinic for NAFLD together with hepatology and including clinical trials. Within the NAFLD-NL consortium and supported by the Dutch MLDS gastroenterology and hepatology foundation, his team develops care paths for NAFLD together with LUMC and Radboud MC. Together with prof. Max Nieuwdorp, he runs a research group with 7 PhD candidates focussing on genetic and gut microbial drivers of NAFLD in three cohort studies, as well as more fundamental work on pathways around lipophagy and liver sinusoidal endothelium. He has published 69 peer-reviewed articles, including in Circulation and Cell Metabolism and received various prestigious grants, a.o. from The Netherlands Organization for Scientific Research and the Amsterdam UMC Fellowship.
By applying iPSC-derived hepatocyte models, he has deciphered molecular mechanisms underlying hypocholesterolemia in type 1 congenital disorders of glycosylation (Van den Boogert et al, Circulation et al 2019) and severe steatohepatitis phenotypes in V-ATPase assembly defects (Larsen et al, CMGH 2021).

ALBERT WIEGMAN
AMSTERDAM,
THE NETHERLANDS

Albert Wiegman, MD, PhD

Born in Amsterdam, the Netherlands, became a pediatrician and member of the staff at the Amsterdam University Medical Centers in March 1991.
In January 1993, he completed his sub-specialization in pediatric cardiology. In that year, the pediatric-lipid department came under his care, and he started his research into the treatment of familial hypercholesterolemia in children, in close co-operation with Prof. John J.P. Kastelein, head of the department of vascular medicine. He brought the research to completion in his thesis: 'Pediatric implications of heterozygous Familial Hypercholesterolemia'.
In March 2020, he was appointed associate professor and principal investigator.

BÁRBARA HENRIQUES
LISBON, PORTUGAL

Bárbara J. Henriques, PhD

Is Principal Investigator at Biosystems & Integrative Sciences Institute, Faculty of Sciences University of Lisboa (BioISI-FCUL). In 2010 she obtained a Ph.D. in Biochemistry/Structural Biochemistry, at New University of Lisboa (ITQB/UNL). Bárbara's research interests are focused on establishing molecular mechanisms underlying protein misfolding and functional deficiency in the context of rare metabolic disorders, resorting to patient profiling and biochemical and cellular models. This follows international experience obtained during training periods at Aarhus University Hospital (Denmark) and Université Paris Descartes (France), and +18y research experience in rare metabolic diseases. Main scientific contributions translate to establishing the molecular and biochemical basis of therapeutic potential of dietary vitamins, definition of genotype-phenotype relationships, and profiling protein dysfunction in mitochondrial disease. Current research focus is on fatty acid beta oxidation disorders caused by defects on ETF and ETF:QO, and also on leukodystrophies, neurometabolic rare diseases caused by defects in mitochondrial aminoacyl-tRNA synthetases. Bárbara has published +18 articles in international peer-review journals, 4 book chapters, and presented her work in + 50 international meetings. In the last 8Y she raised over 435 kEUR in national competitive calls as PI in 6 research projects, and supervised +20 young researchers, currently 2 PhD and 1 MSc students.

CÂNDIDA CANCELINHA
COIMBRA, PORTUGAL

Cândida Cancelinha, MD
Paediatrician with competence in Palliative Medicine.
Coordinator of the Intra-Hospital and Paediatric Home Palliative Care Team - Paediatric Hospital - University Hospital Centre of Coimbra
Invited assistant of Paediatrics - Faculty of medicine - University of Coimbra
Vice President of the Portuguese Association of Palliative Care
Member of the Work group of Palliative Care - Regional Health Administration
Secretary - Centre Region of Paediatrics Portuguese Society

CHARLES MARQUES LOURENÇO
RIBEIRÃO PRETO, BRAZIL

Charles M Lourenço, MD, PhD
is a Professor of Clinical Genetics and Hereditary Metabolic Disorders in the Neurogenetics Unit - Inborn Errors of Metabolism Clinics at the National Reference Center for Rare Diseases, Faculty of Medicine of São José do Rio Preto.
He is the coordinator of the Inborn Errors of Metabolism and Neurogenetics Outpatient Clinics of the Hospital de Base and Hospital Materno-Infantil at Faculty of Medicine of São José do Rio Preto, where he is also a member of the Lysosomal Unit, being involved in the care of patients with lysosomal storage disorders. He is also the consultant clinical geneticist at National Reference Center for Rare Diseases in the same university.
Dr Lourenço is a clinical biochemical geneticist with a special interest in genetic neurodegenerative disorders. He obtained his Medical Degree at the Federal University of Bahia, Brazil, in 2002, and underwent postgraduate training in medical genetics and then neurogenetics at the Clinical Hospital of the State University of São Paulo, and then the Hospital of Ribeirão Preto, University of São Paulo.
Professor Lourenço holds a PhD in neurogenetics and his PhD thesis focused on spinocerebellar ataxia of early onset, especially on a subset of patients with ataxia and hypogonadism. Most recently, he has been involved in a new multidisciplinary clinic at his hospital, which mainly focuses on investigation of childhood neurodegenerative disorders, and in particular patients with early-onset cerebellar ataxia and genetic white matter disorders.
Dr Lourenço's interests include the clinical and molecular aspects of leukodystrophies, hereditary spastic parapareses, metabolic causes of neonatal cholestasis, hereditary spinocerebellar ataxias, genetic epileptic encephalopathies, lysosomal disorders of the brain (neurolipidoses) and inborn errors of metabolism with adult presentation.
Most recently, he has been involved in a new multidisciplinary clinic at Faculdade de Medicina de São José do Rio Preto (FAMERP), which focuses primarily on investigation of childhood neurodegenerative disorders and, in particular, patients with early-onset cerebellar ataxia and genetic white matter disorders.
Dr Lourenço is a member of many professional societies, including the Brazilian Clinical Genetics Society, the American Society of Human Genetics, the International Skeletal Dysplasia Society, the Society for the Study of Inborn Errors of Metabolism, and the Latin American Society of Inborn Errors of Metabolism and Newborn Screening. He has published extensively in journals and books, and serves as a peer reviewer for *Neurology Genetics* and the *Journal of Inherited Metabolic Disease*.
Dr Lourenço is also Medical Consultant in Specialized Education at DLE/Grupo Pardini, in Personalized Medicine area producing online content regarding hereditary metabolic disorders for experts and non experts in the field

DAVID BICK
LONDON,
UNITED KINGDOM

David Bick, MD

Is the Principal Clinician for the Newborn Genomes Programme at Genomics England. Prior to his work in England, he was the Chief Medical Officer and a faculty investigator at the HudsonAlpha Institute for Biotechnology. Dr. Bick also served as the Medical Director of the Smith Family Clinic for Genomic Medicine at HudsonAlpha and the Laboratory Director of the HudsonAlpha Clinical Services Laboratory.

He came to HudsonAlpha from the Medical College of Wisconsin where he was Professor in the Department of Pediatrics and the Department of Obstetrics & Gynecology and Director of the Clinical Sequencing Laboratory, Director of the Advanced Genomics Laboratory, Medical Director of the Genetics Clinic at Children's Hospital of Wisconsin, and Chief of the Division of Genetics in the Department of Pediatrics at Medical College of Wisconsin. Dr. Bick is board certified in Pediatrics, Clinical Genetics, and Clinical Molecular Genetics.

Dr. Bick has published numerous peer-reviewed articles, chapters, and reviews. His laboratories at the Medical College of Wisconsin and Children's Hospital of Wisconsin were the first in the world to offer whole genome sequencing as a clinical test. He also developed the first Genomic Medicine Clinic in the United States.

ELAINE MURPHY
LONDON,
UNITED KINGDOM

Elaine Murphy, MD, PhD

Qualified from Trinity College, Dublin. She trained in chemical pathology / metabolic medicine at Imperial College NHS Trust, London and developed a specialist interest in inherited metabolic disease. She has worked as a consultant at the Charles Dent Metabolic Unit, based at the National Hospital for Neurology and Neurosurgery, Queen Square since 2008. The unit manages over 1400 adult patients with rare inherited disorders of metabolism, including phenylketonuria, glycogen storage disorders, urea cycle defects, galactosemia, fatty acid oxidation defects, peroxisomal disorders and inherited hypophosphatemia. Staff at the unit specialize in the dietary management of specific inherited disorders of metabolism. It is also an NHS England specialized service for the management of patients with lysosomal storage disorders. The unit has a long history of participation in clinical trials of new treatments for these rare disorders. Dr Murphy has been the chair of the British Inherited Metabolic Disease Group (2019-2022) and is currently a member of the Royal College of Physicians Young Adult and Adolescent Steering Group.

EUGEN MENGEL
HOCHHEIM, GERMANY

Eugen Mengel, MD, PhD

Has studied medicine on the Goethe-University, Frankfurt and the Phillipps-University, Marburg in Germany. From 1993 to 2001 he was educated in pediatriacs on the Children´s Hospital, University of Mainz (Germany). Specialized education was performed in pediatric metabolic medicine and hematology. In 1994 he joined the lysosomal storage disorders group named Villa metabolica of Michael Beck with special interests in sphingolipidosis. From 2001 - 2019 he was consultant of pediatric inborn errors of metabolism. In international clinical trials concerning ASMD, Pompe disease, Gaucher disease, LALD, Mannosidosis, NPC and Morquio disease he acted as Principal Investigator. He is following a German cohort of LSD patients with more than 200 adult and pediatric patients. In 2019 he founded the independent clinical research institute SphinCS performing investigator initiated studies as well as international multicenter Phase 2 – 4 trials with promising IMPs in the field of LSDs including novel blood-brain barrier crossing ERT with fusionproteins. He is an active member of the EWGGD, ESGLD and SSIEM.

FILIPA FERREIRA
PORTO, PORTUGAL

Filipa M.B. Ferreira, PhD

Works in the Newborn Screening, Metabolic and Genetics Unit of Human Genetics Department of National Institute of Health Dr. Ricardo Jorge, in Porto. She received her PhD in Biology, in 2011 from Faculty of Sciencies - University of Porto (FCUP). Filipa Ferreira has a Biology degree with a Zoology specialization and she also has a Master degree from FCUP. Her research interests focuses from behavioural ecology, cyanobacteria metabolites, hazard assessment of endocrine disrupting chemicals in aquatic environment, development of some techniques for parasite growing, and more recently in the diagnostic approach of some rare inherited inborn errors of metabolism diseases. She is the author of approximatly 40 scientific publications in national and international journals.

FANNY MOCHEL
PARIS, FRANCE

Fanny Mochel, MD, PhD

Fanny Mochel 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 inborn errors of metabolism. Prof. Mochel leads the French reference center on Neurometabolic diseases in adults and co-leads a research team ("Immunity, Metabolism and Neurodegeneration") at the Paris Brain Institute of La Pitié-Salpêtrière University Hospital in Paris. She is chair of the adult section of the Society for the Study of Inborn Errors of Metabolism (SSIEM) and co-chair of the French society for inborn of errors of metabolism in adults. Her research is 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.

FRANCESCA TUCCI
MILAN, ITALY

Francesca Tucci, MD

Started her scientific career as an intern student at the Department of Pediatrics, II Policlinico (Naples, Italy) working in laboratory focusing her research on genetics and gene expression studies of coeliac disease in pediatric patients. She graduated in 2010 at the University of Naples Federico II with a thesis entitled "Potential Celiac Patients: A Model of Celiac Disease Pathogenesis" (final grade 110/110 with honors) under the supervision of Prof. L. Greco. Thereafter, she started her Specialization in Pediatrics at the University of Naples, focusing on clinical and technical management of onco-haematological patients and terminal children with extensive experience treating pediatric patients with leukemias and lymphomas at AORN Santobono-Pausilipon Hospital, Naples.

She also practiced medicine in settings of limited resources and management of the most common pediatric tropical diseases and malnutrition in 2014 at Saint Mary's Hospital Lacor, Uganda where she mainly focused on clinical management of onco-haematological patients and terminal children leading ward rounds, providing clinical care and conducting invasive procedures primarily for Burkitt's lymphoma treatment.

During the Specialization, she spent 7 months at G. Gaslini Children's Hospital, Genova, under the supervision of Dr. C. Dufour, focusing on clinical management of in and out-patients affected with malignant and non-malignant hematological diseases and research activities in patients with previously unclassified inherited bone marrow failure. In 2016, she completed her Specialization in Pediatric with a thesis under the supervision of Prof. V. Poggi (Title: "Next-Generation Sequencing In Patients With Previously Unclassified Inherited Bone Marrow Failure"; final grade 50/50 cum laude).

In 2016 she moved to the San Raffaele Hospital (Milan, Italy), where she took the position of Consultant Pediatrician at the Immunohematology Unit, under the supervision of prof. A. Aiuti and started her clinical activity on hematopoietic stem cell-gene therapy in pediatric immunodeficiencies and metabolic disorders and on allogeneic bone marrow transplantation in non-malignant disorders.

In 2018 she completed her Master in Pediatric Hematology at University of Rome "Sapienza" with a thesis under the supervision of prof. A. Aiuti (title: "Bone Marrow Hematopoietic Stem Cell Harvesting From Patients Affected By Severe Combined Immunodeficiency Caused By Adenosine Deaminase Deficiency, Wiskott Aldrich Syndrome And Metachromatic Leukodystrophy Undergoing Gene Therapy").

From 2020 she took the position of Permanent Staff Pediatrician at the Immunohematology Unit.

She is sub-Investigator in several phase I/II gene therapy clinical studies in particular in the protocol "A phase I/II study evaluating safety and efficacy of autologous hematopoietic stem and progenitor cells genetically modified with IDUA lentiviral vector encoding for the human alpha-L-iduronidase gene for the treatment of patients affected by Mucopolysaccharidosis Type I, Hurler variant". She is also part of the medical investigator staff of several phase I/II and III studies on Duchenne Muscular Distrophy.

JOÃO VICENTE
LISBON, PORTUGAL

João B. Vicente, PhD

Earned his European Label PhD in Biochemistry from NOVA University of Lisbon (Portugal) and Sapienza University of Rome (Italy) in 2007. After a post-doc in Stanford University (USA) and a researcher position at iMed.ULisboa and the School of Pharmacy, Lisbon University (Portugal), he started a position as Auxiliary Investigator in the Macromolecular Crystallography Unit at NOVA Instituto de Tecnologia Química e Biológica António Xavier (Portugal).

Currently, Vicente leads the Applied Protein Biochemistry Lab at ITQB. His research team combines protein biochemistry and biophysics with structural biology to investigate molecular details of protein function and structure, and to tailor and target proteins with biotechnological applications.

One of the main research interests is the study of molecular mechanisms underlying human hydrogen sulfide (H_2S) metabolism. Particularly, his team is interested in understanding how the metabolic pathways leading to the production and breakdown of H_2S are regulated by endogenous physiologically relevant modulators. Through a network of collaborators, he aims to position these metabolic pathways and their regulatory mechanisms as key determinants in the context of various human diseases. Moreover, he is committed to the discovery and development of pharmacological and diagnostics tools to improve therapeutics.

JOSÉ VILHENA
COIMBRA, PORTUGAL

José Vilhena, MsC, MBA

José Vilhena was born in Coimbra on October 10, 1976, the city where he grew up and developed his studies in Environmental Engineering. He has, however, a very strong family and emotional connection to Almeida, a smal village in the interior of Portugal, where he spent most of his free time until his daughter Margarida was diagnosed with Tay Sachs Disease.

Together with his wife and other parents affected by Gangliosidosis, they founded DOCE and, since its foundation, he has been chairman of the board.

With the structure of DOCE, a national struggle to publicize the disease of Tay Sachs, Sandhoff and GM1 was developed; a structure is developed to look for affected families and to provide them with the support they may lack; bases are developed for hosting clinical trials for Portuguese patients; understandings are also developed with pediatric palliative care units to support their families.

Work
Head of Parks and Gardens Division of Coimbra's City Hall (MsC, MBA)

JÚLIO C. ROCHA
LISBON, PORTUGAL

Júlio César Rocha, PhD
Professor of Nutrition and Metabolism
NOVA MEDICAL SCHOOL | Faculdade de Ciências Médicas, Universidade Nova de Lisboa, PT
Clinical Nutritionist Specialist, PhD
Reference Centre of Inherited Metabolic Diseases, Centro Hospitalar Universitário Lisboa Central, PT
Researcher
Center for Health Technology and Services Research, PT

Júlio César Rocha is a Professor of Nutrition and Metabolism, graduated in Nutritional Sciences (0438N – specialist in Clinical Nutrition), with a post graduate qualification in Clinical Nutrition from the Faculty of Nutrition and Food Sciences – University of Porto (UP) and he has also a PhD in Metabolism, at the Faculty of Medicine, UP.
He has been working in the field of inborn metabolic diseases since 2003. He is Professor of Nutrition and Metabolism at NOVA Medical School teaching in the field of Nutrition and Metabolism to Medicine and Nutrition students. He is also member of the multidisciplinary clinical team at the Reference Centre of Inherited Metabolic Diseases at Centro Hospitalar Universitário Lisboa Central, one of the 5 Portuguese Reference Centres for the follow-up of patients with Inherited Metabolic Diseases. He is also a researcher at CINTESIS (Center for Health Technology and Services Research).
He is council member of the SSIEM (Society for the Study of Inborn Errors of Metabolism), Chair of the Dieticians Group of the SSIEM (SSIEM-DG), Chair of the Nutrition Group of the Portuguese Society of Metabolic Disorders (SPDM-GN) and President of the Portuguese Society of Clinical Nutrition and Metabolism (SPNCM). He is also member of the working group of the European Phenylketonuria Guidelines (EPG 2.0) under the umbrella of the ESPKU (European Society for Phenylketonuria and Allied Disorders Treated as Phenylketonuria). He has been also member of the PKU European Parliament Cross Party Alliance, a joined group of Members of the European Parliament (MEP), experts and civil society.
He is author of more than 70 international, indexed, scientific publications and he has done more than 100 oral presentations/lectures/conferences in more than 13 different countries.

LUÍSA DIOGO
COIMBRA, PORTUGAL

Luísa Diogo, MD, PhD
Senior Hospital Assistant of Pediatrics - Hospital Pediátrico - CHUC Coordinator of the Reference Centre of Inherited Metabolic Diseases - CHUC, member of MetaERN.
Invited Associated Teacher of Biochemistry – Faculty of Medicine, University of Coimbra
Degree in Medicine - Faculty of Medicine - University of Coimbra (FMUC) - 1982.
Pediatrician - Coimbra Paediatric Hospital, since 1991.
Since 2011- Invited Associated Teacher of Biochemistry – FMUC. (1984 - 2010 Invited Assistant).
Since 1993: Head of the "Metabolic Unit" - Paediatric Department – Coimbra University Hospital Centre - CHUC
Since 2015: Coordinator of the Reference Centre of Inherited Metabolic Diseases – CHUC, member of MetaERN since 2016.
Since 2002, member (founder associate) of the Portuguese Metabolic Diseases Association (SPDM). Member of the directive board until 2015 (President - 2014-15).
Member of the Society for the Study of Metabolic Diseases (SSIEM); Portuguese corresponding member: 2007-2016.

MAFALDA BOURBON
LISBON, PORTUGAL

Mafalda Bourbon, PhD
Is a senior researcher at the National Institute of Health, Portugal (INSA) and a research and invited professor at Biosystems & Integrative Sciences Institute (BioISI), Faculty of Sciences, University of Lisbon. She completed her PhD in Clinical Sciences in 2006 at Imperial College Faculty of Medicine - Hammersmith Campus. She is the Chair of the Familial Hypercholesterolaemia Variant Curation Expert Panel at Clinical Genome Resource and the National lead Investigator of 2 international FH registries (FH Studies Collaboration and International Children FH Registry). She also participates in the 1 Million Genomes Initiative in the country mirror groups on sequencing and interpretation standards and complex disorders and is part of the Public Health Group at FH Europe, a patients association initiative. She is a board member of the Iberoamerican FH network and is part of the Scientific Committee of the Portuguese Atherosclerosis Society. Her main field of research is genetic dyslipidaemia with a special focus on Familial Hypercholesterolaemia (FH) developing and applying methods to identify, functionally characterize and interpret variants found in clinical FH patients and other dyslipidaemia patients. She is founder and coordinator of the Portuguese Familial Hypercholesterolaemia (FH) Study (1999-present) and the Rare Dyslipidaemia Study (2012-present). She is also working on a personalized medicine model for FH. She published more than 70 peer review articles in international scientific journals and 3 book chapters.

MARGARIDA SILVA
LISBON, PORTUGAL

Margarida F. B. Silva, PhD
Is an Assistant Professor at the Department of Pharmaceutical Sciences of the Faculty of Pharmacy, Universidade de Lisboa. Holding a Ph.D. in Biochemistry (2002) she is also a scientist at the Research Institute of Medicines (iMED.Ulisboa) working in translational research in the fields of Inborn Errors of Metabolism and Biochemical Pharmacology. Throughout her career, she has been focused on elucidating mechanisms of mitochondrial dysregulation where mass spectrometry-based biomarkers development have played a key role. Her studies involving metabolic intermediates and signaling molecules have prompted progresses in new bioanalytical methods. In recent years, her research interests approached pathophysiological mechanisms, from liver to brain, aiming the modulation of metabolism, and the improvement of therapies in synergy with pharmacological interventions.

MARIA INÊS GAMA
LISBON, PORTUGAL

Maria Inês Gama, MSc
Is currently a Master student in Human Nutrition and Metabolism at NOVA Medical School | Faculdade de Ciências Médicas da Universidade NOVA de Lisboa. She has spent the past year developing a research project in Phenylketonuria (PKU) at Birmingham Children's Hospital, UK. She has received the 2021 Recordati Rare Disease Award, published papers on PKU, presented at scientific meetings and participated in numerous inherited metabolic disorders (IMD) related courses and events. Maria Inês has been interested in IMD, since her bachelor's degree, having spent part of her training at the IMD Reference Centre of the Centro Hospitalar Universitário do Porto. She described herself has a "PKU enthusiast" and thrives to get better care and treatment for all IMD patients.

MÁRIO SILVA
LISBON, PORTUGAL

Mário J. Gaspar da Silva, PhD

Is a Full Professor in Computer Science and Engineering (Information Systems) at Instituto Superior Técnico (U. Lisboa) and a researcher of its Information and Decision Support Systems Laboratory (IDSS Lab).

He is currently involved in IntelligentCare, a CMU-Portugal initiative where he is developing a patient centric solution to help manage multimorbidity (MM) using analytical methods to explore data from the electronic health records. This initiative has been focusing on records of MM patients with heart failure and diabetes. He is also participating in the Genomic Data Infrastructure (GDI) project, an initiative for enabling access to genomic and related phenotypic and clinical data across Europe. GDI is doing this by establishing a federated, sustainable and secure infrastructure to access the data.

He is a PhD in Electrical Engineering and Computer Science from UC Berkeley (1994). His main research interests include Web Engineering and NLP: information retrieval and text mining, information integration (mainly biologic and geographic); computational biology and bioinformatics; sentiment analysis in social networks; and digital libraries.

NADIA BELMATOUG
PARIS, FRANCE

Nadia Belmatoug, MD

is a specialist in rheumatology and internal medicine at the Assistance Publique-Hôpitaux de Paris. She is the coordinator of a French Reference Centre for Lysosomal Diseases. Her centre belongs to the european rare disease network "Metab-ERN".

She is mainly involved in the diagnosis, monitoring, evaluation of clinical and biological characteristics, as well as the pathophysiology of Gaucher disease. Her centre has developed with other experts of the "French Evaluation Committee of Gaucher Disease" the national recommendations for the management of Gaucher disease (PNDS)*. She has developed a close collaboration with the French association of patients with lysosomal disorders "Vaincre les Maladies Lysosomales" (VML) and with the "International Gaucher Alliance" (IGA) to improve the management of patients. Her centre has organized numerous multidisciplinary congresses on Gaucher disease.

She is the scientific director of the academic French Gaucher Registry (600 patients) the one of the largest in Europe certified by the INSERM institution. She participates in different academic (Ra-Di-Co MPS) and industrial registries (International Collaborative Gaucher Group "ICGG", Gaucher Outcome Survey "GOS").

Since 2004, she has participated in the construction of the French Rares Diseases Plan for the Ministry of Health and works as an expert of lysosomal diseases for the Social Security.

She was awarded the title of Knight of the Legion of Honour in December 2009.

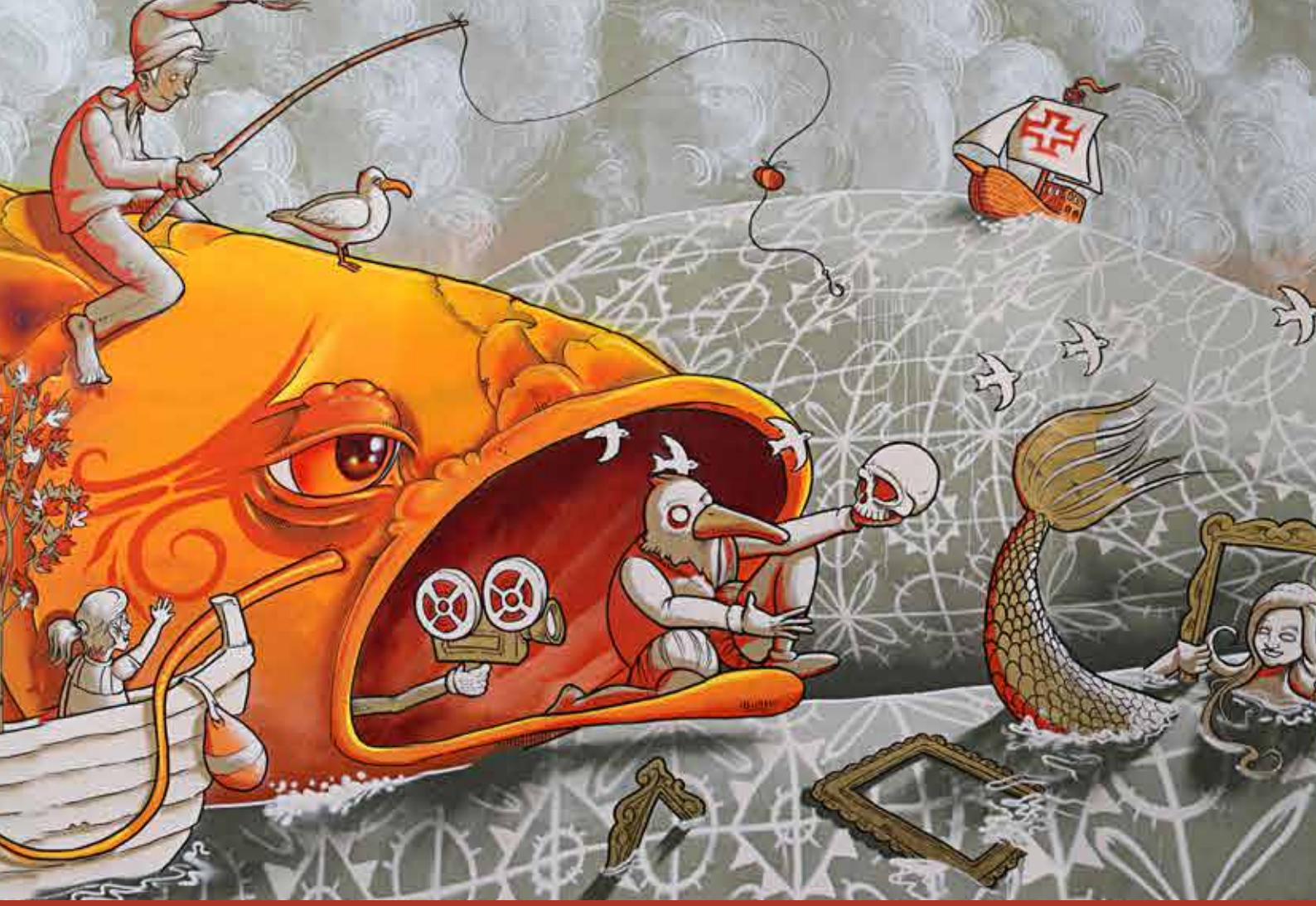
*PNDS : Protocole National de Diagnostic et de Soins :
https://www.has-sante.fr/jcms/p_3339127/fr/maladie-de-gaucher

PEDRO MORENO
PORTO, PORTUGAL

Pedro Moreno, PhD
I3S - Instituto para a Investigação e Inovação em Saúde, Universidade do Porto
nanoBiomaterials for Targeted Therapies Group
Pedro Moreno is a senior researcher at the Institute for Research and Innovation in Health (i3S) at the nanoBiomaterials for Targeted Therapies group.
Pedro has a Biochemistry degree from the University of Coimbra and a PhD in Cell and Molecular Biology from the Karolinska Institute, where he initiated his research work in genetic therapies and gene delivery.
In 2013 he was awarded a Marie Curie European fellowship from the European Commission to proceed his studies at the Institute of Biomedical Engineering (INEB) in Porto.
Currently at i3S he focus his research on development of novel RNA therapeutics and nanodelivery vectors for neuro-regeneration and cancer therapy. Pedro has published more than 30 research papers in his subject, several book chapters and is named inventor in two awarded international patents and one provisional patent application. Additionally, he also collaborates with industry as a consultant and advisor in the field of RNA therapeutics.
In 2021 he was the promoter and successfully set-up the first international symposium on oligonucleotide therapeutics in Portugal (OTP2021).

SARA DIAS
LISBON, PORTUGAL

Sara Raquel Gonçalves Dias, PharmD,
Centro Hospitalar Universitário Lisboa Norte, Hospital Santa Maria
Sara Dias graduated in Pharmaceutical Sciences in 2012 at the Faculty of Pharmacy of University of Coimbra.
Sara has been Hospital Pharmacist since 2017 and specialist since 2022.
Tutor of the discipline of Clinical Therapeutic Practice II at the Faculty of Pharmacy, University of Lisbon since 2022.
She currently integrates the Compounding Department and the Pediatric Pharmacy Unit.



SESSION I

INHERITED METABOLIC DISEASES IN THE LIFETIME

CHAIRPERSONS

JOÃO DURÃES,
Centro de Referência de Doenças Hereditárias do Metabolismo - Centro Hospitalar Universitário de Coimbra - MetabERN, PT

LELITA SANTOS,
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MARIA JOÃO GUEDES,
Centro de Referência de Doenças Hereditárias do Metabolismo - Centro Hospitalar Universitário de Coimbra, Coimbra - MetabERN, PT

DIETARY MANAGEMENT DURING THE LIFETIME FOR IEM

Júlio César Rocha

Several inherited metabolic disorders can be treated by life-long nutritional interventions aiming to prevent severe clinical manifestations, allowing as much as possible an appropriate growth and development. For some disorders, newborn screening has allowed prompt intervention, changing the landscape of patient's clinical evolution. For many other disorders, improved diagnostic techniques, the availability of new pharmaceutical treatment options and transplantation creates a plethora of diverse clinical scenarios that need personalized nutritional interventions. Dietary management, mainly focused on dietary restrictions and/or nutritional supplementation, should nowadays give the stage to the clinical nutrition aligned with the nutrition care process model. Recognising the huge phenotypic variability within the same condition, any nutritional intervention should be anticipated by a deep nutritional assessment that can define a concrete nutritional diagnosis. Simultaneously with the nutritional intervention, it should be defined a monitoring and reassessment step that aims to analyse if objectives of nutritional intervention were accomplished, redefining the need for a subsequent intervention. Beyond the impact on patient's metabolic control, a comprehensive analysis of nutritional and metabolic status is recommended in order to anticipate any unwanted iatrogenic consequences of the nutritional intervention.

REPRODUCTIVE HEALTH AND OTHER CHALLENGES IN ADULTS WITH IMD

Elaine Murphy

There is increasing awareness of the specific needs of women with inherited disorders of metabolism (IMD). IMD can affect all aspects of reproduction from ovarian and follicle development, menarche (eg. Galactosemia), pregnancy, fetal growth and teratogenicity (eg. Phenylketonuria), and breastfeeding. Certain times of a woman's life may make her more susceptible to complications (eg. post-partum metabolic decompensation in urea cycle defects, adenoma growth during pregnancy in Glycogen Storage Disorders). In addition, limited data are available on the impact of IMD and their complications on later stages of life eg. post-menopausal bone loss and sarcopenia in women on life-long protein restricted diets.

In this presentation I will discuss these issues, with examples, and consider the available evidence and guidelines available to support the life-long optimisation of women's health and reproductive options.

NEUROMETABOLIC DISORDERS IN ADULTS: IMD AND BEYOND

Fanny Mochel

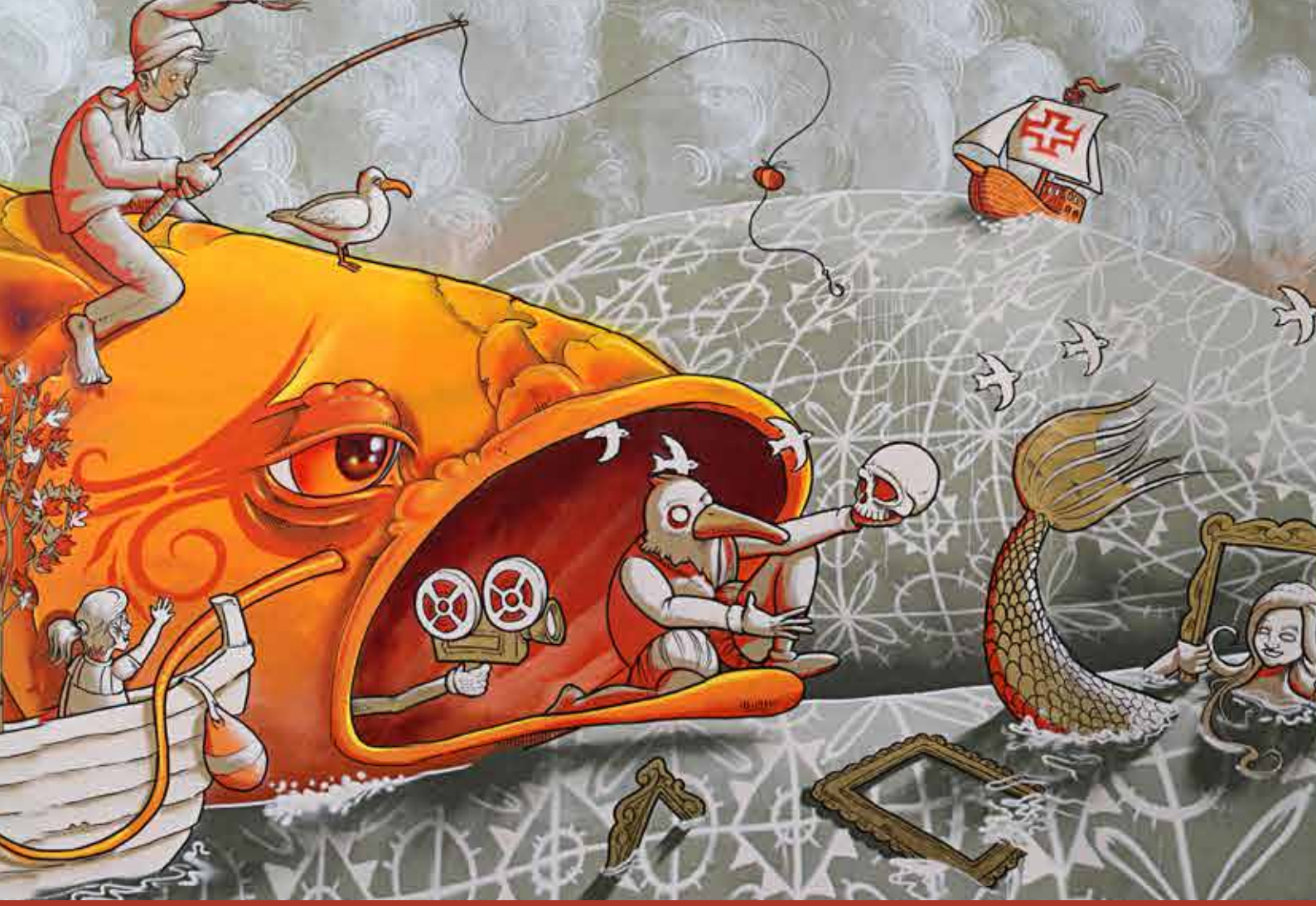
We are seeing a greater awareness of inherited metabolic diseases (IMD) in adult medicine, especially with the increased access to next generation sequencing. However, delays to diagnose patients with IMD are still substantial despite the availability of sensitive and clinically available biomarkers. This is especially regretful for disorders that can be treated, provided that the diagnosis is made at an early stage. Therefore, there still an important need to promote knowledge and training about IMD in all the fields of adult medicine, especially neurology, internal medicine, endocrinology, hepatology, intensive care, but also ophthalmology, cardiology and nephrology. This talk will specifically address ongoing efforts to improve diagnosis and treatment of neurometabolic disorders in adults. It will also provide an example about how IMD can enlighten our understanding of neurodegenerative disorders.

PALLIATIVE CARE FOR IMD PATIENTS

Cândida Cancelinha

In parallel with the increase in the number of children with life-limiting or life-threatening diseases, the need for and right to pediatric palliative care (PPC) is also increasing.

However, most data on symptoms and needs of children in PPC refer to those with cancer, whereas the majority of the children is living with or dying from LLCs other than cancer.
In the subgroup of children with inborn errors of metabolism (IEM) such as mitochondrial disorders, peroxisomal diseases or certain lysosomal storage diseases, for whom curative treatment is not possible, almost all present with severe neurological impairment and are nonverbal.
Caring for a child with incurable IEM and neurological impairment and, thus, impaired communication, confronts caregivers and treating physicians with some substantial challenges, namely regarding correct identification and interpretation of distressing symptoms.
Symptom burden is high with neurologic, respiratory and gastrointestinal symptoms being the most frequent and most of those being difficult to treat, as well as potential technology dependence.
Early PPC involvement provides best understanding of child and family needs as well as a multidimensional approach, increasing quality of life, reducing burden of treatment and burden of care. In these children, particular attention needs to be addressed to advance care planning in order to reduce inadequate interventions.



SESSION II

FAMILIAL DYSLIPIDAEMIAS

CHAIRPERSONS

ANA GASPAR,
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Centro Hospitalar Universitário Lisboa Norte, Lisboa - MetabERN, Portugal

ANÁLIA CARMO,
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Centro Hospitalar Universitário de Coimbra, Coimbra, Portugal

M. TERESA CARDOSO,
Centro de Referência de Doenças Hereditárias do Metabolismo -
Centro Hospitalar Universitário São João, Porto - MetabERN, Portugal

DEFECTS OF LIPOPROTEIN METABOLISM: FROM THE GENES TO THE CLINIC

Adriaan Holleboom

As defined comprehensively in Harrison's Principles of Internal Medicine, lipoproteins are 'large macromolecular complexes composed of lipids and proteins that transport poorly soluble lipids (primarily triglycerides, cholesterol, and fat-soluble vitamins) through body fluids (plasma, interstitial fluid, and lymph) to and from tissues.'

Common dysmetabolic conditions such as obesity, diabetes mellitus type 2 and non-alcoholic fatty liver disease are characterized by insulin resistance and drive disturbance of lipoprotein metabolism, with higher plasma concentrations of triglyceride-rich VLDL particles and small dense LDL and lower HDL-cholesterol, a shift known to induce atherosclerosis. This large-scale clinical relevance has spurred extensive study of lipoprotein metabolism, and in these studies, lessons from rare genetic dyslipoproteinemias have been invaluable.

There is a multitude of genetic defects in the pathways of lipoprotein metabolism, which lead to specific hyper- and hypolipidemias and accumulation of lipid and lipoprotein subtypes in a variety of tissues and organs, most notably the arterial wall, brain, cornea, gut, liver, kidney, muscle tendons, pancreas, tonsils or skin. Some of these accumulations are mere diagnostic clues to the particular specific genetic dyslipidemia involved, without compromising organ function, such as eye lid xanthelasmata and lipoid corneal arc in familial hypercholesterolemia. Yet most accumulations unfortunately compromise organ function, leading to variable degrees of neurocognitive impairment, dementia, blindness, atherosclerotic cardiovascular disease (ASCVD), steatohepatitis and liver fibrosis, pancreatitis, diarrhea and malnutrition or renal function decline.

Familial hypercholesterolemia is among the commonest inherited disorders and multiple pharmacological options are available to treat this genetic hyperlipidemia and to prevent its most feared complication, i.e. ASCVD. Yet other genetic dyslipidemias are extremely rare, sometimes a few dozen cases worldwide, and targeted treatments are still in development. Thus, these extremely rare dyslipidemias to date still lead to potentially severe organ damage, often at quite early ages and clearly constituting an assignment for medical science to develop the required targeted treatments.

Together, this makes the genetic dyslipoproteinemias an intriguing group of metabolic diseases. Firstly, they indicate the importance and intricate regulation of lipoprotein metabolism in physiology. Secondly, their study may not only benefit treatment development for the rare patients involved, but also for the common dysmetabolic dyslipidemias, as evidenced by the advent of PCSK9 inhibitors for hypercholesterolemia in recent years.

FAMILIAL HYPERCHOLESTEROLAEMIA IN CHILDREN AND ADOLESCENTS - BETTER SAFE THAN SORRY

Albert Wiegman

Familial hypercholesterolemia (FH) is a genetic disorder characterized by elevated low-density lipoprotein cholesterol (LDL-C) levels and premature cardiovascular disease (CVD). Both the heterozygous form and the very severe homozygous form can be diagnosed by genetic testing and by clinical criteria. The genetic screening program for familial hypercholesterolemia (FH) in the Netherlands, that was embraced by the Dutch Ministry of Health from 1994 to 2014, has led to twenty years identification of at least 1500 FH cases per year. Although funding by the government was terminated in 2014, the approach had proven its effectiveness and had built the foundation for development of more sophisticated diagnostic tools, clinical collaborations and new molecular-based treatments for FH patients. As such, the community was driven to continue the program, insurance companies were convinced to collaborate and multiple approaches had been launched to find new index cases with FH. Additionally, the screening was extended, now also including other heritable dyslipidemias. For this purpose, a diagnostic next-generation sequencing (NGS) panel had been developed that not only comprises the culprit LDLR, APOB and PCSK9 genes but also 24 other genes that are causally associated with genetic dyslipidemias. Moreover, the NGS technique enabled further optimization by including pharmacogenomic genes in the panel. Using such a panel more patients that are prone for cardiovascular diseases are being identified nowadays and receive more personalized treatment. Loss of function effect of mutations compared to gain of function effect of mutations even leads to new types of treatment (PCSK9 inhibition, ANGPTL3 inhibition).

Genetic testing can discern FH in a form caused by complete absence of the LDL-receptors, the negative variant, and a form leading to reduced activity of the LDL-receptors, the defective variant. The aim of this study is to provide more insight in the genotype-phenotype correlation in children and adolescents diagnosed with heterozygous FH (HeFH) and with homozygous FH (HoFH), specifically in relation to the clinical and therapeutic consequences of the negative and defective variant of FH. Data of 5904 children with a tentative diagnosis of FH referred to our center for genetic testing were collected. A lipid-profile was present in 3494 children, who became the study cohort. In this large cohort of children, which includes 2714 HeFH and 41 HoFH patients, it is shown that receptor negative variants are associated with significant higher LDL-C levels in HeFH patients than receptor defective variants (6.0 mmol/L versus 4.9 mmol/L; $p<0.001$). A negative/negative variant is associated with a significant higher LDL-C level in HoFH patients than a negative/defective variant, which in itself has a higher LDL-C level than a defective/defective variant. Significantly more premature CVD is present in close relatives of HeFH children with negative variants compared to close relatives of HeFH children with defective variants (75% vs 59%; $p<0.001$).

Performing genetic testing and identifying the type of underlying genetic variant is of added value to distinguish between pediatric patients with higher risk of premature CVD and to identify those that will benefit most from new types of lipid-lowering therapies. Since in children the phenotype of FH is less affected by environmental factors, the study substantiates the genotype-phenotype correlation in this large pediatric population.

THE PORTUGUESE SCREENING PROGRAMS FOR FAMILIAL DYSLIPIDAEMIAS

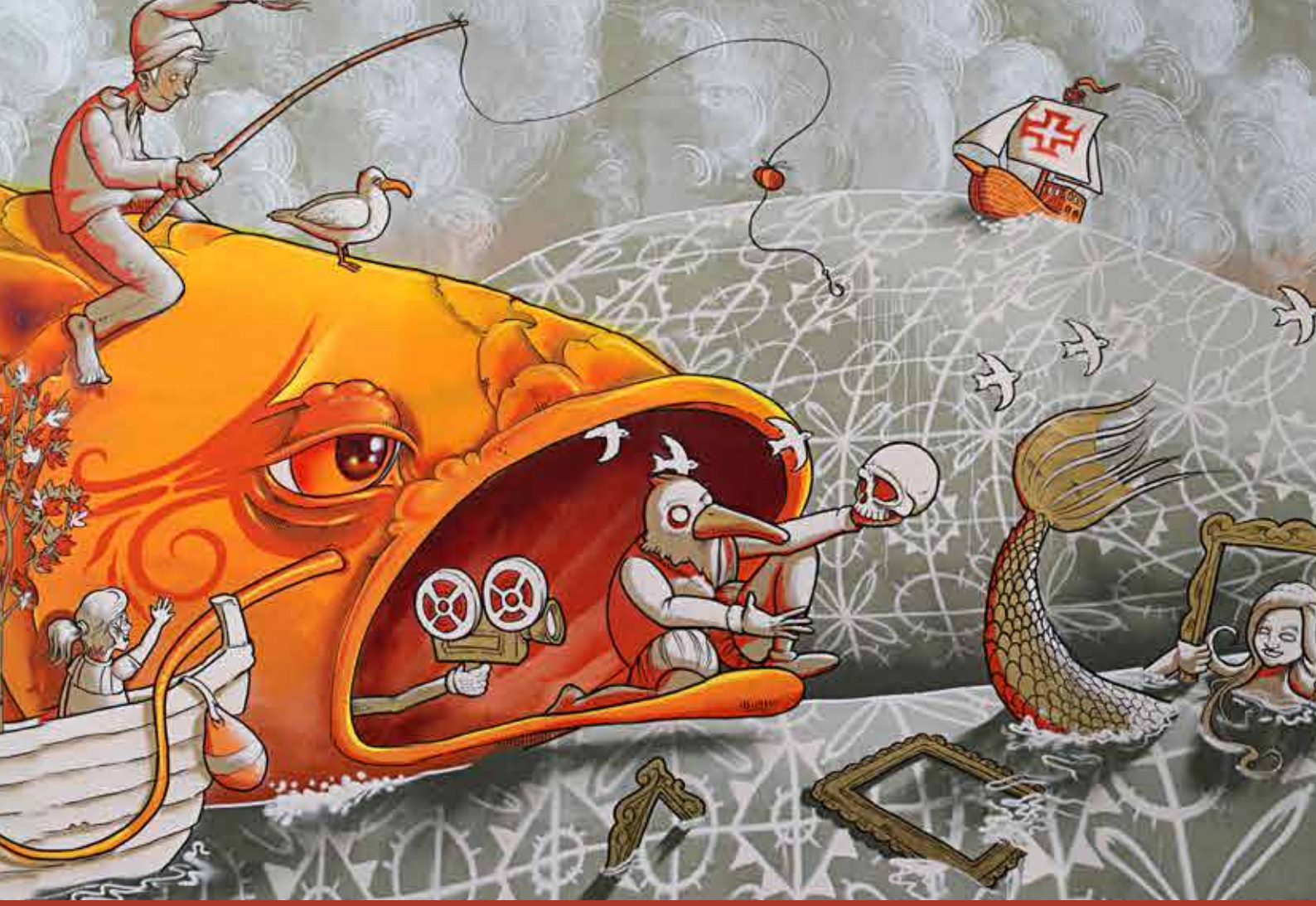
Mafalda Bourbon

There are 2 national studies on familial dyslipidaemias held at the National Institute of Health in Lisbon, both containing a registry. Both studies provide a genetic diagnosis of the different conditions that is free of charge for the patients and the Health Units who refer them, due to having received different fundings during its lifetime, from the Portuguese Science and Technology Foundation, Medical Societies and Pharma Companies. A vast clinical team with approximately 100 clinicians collaborates in these studies. In both studies the genetic diagnosis is performed using a next generation (NGS) panel with 57 genes: 26 dyslipidaemia genes and 31 research lipid genes. The analysis is then divided in different panels: familial hypercholesterolaemia (FH) and phenocopies genes panel, hypertriglyceridaemia panel, low cholesterol panel and low HDL panel. The FH panel also includes the determination of polygenic LDL risk scores and statin intolerance SNPs.

The Portuguese Familial Hypercholesterolaemia Study started in 1999. Since then, more than 3000 families have been studied. The genetic study of FH is performed by the analysis of 8 genes, including 3 FH genes (LDLR, APOB, PCSK9) and 5 phenocopy genes (LIPA; LDLRAP1, APOE, ABCG5/8). Apart from providing the genetic study for patients with a clinical diagnosis of FH, the Portuguese FH Study also continues to investigate other causes of the FH phenotype when the FH genetic study is negative, to improve patient diagnosis. The correct identification of the pathway affected in each patient is important for their management and can improve prognosis. In the scope of the Portuguese FH study functional assays are also performed to determine if the variants found affect the LDLR pathway and how. The latest results show that 41% of all patients with a clinical diagnosis of FH have heterozygous FH, .1% has homozygous FH, 1 % has other monogenic disorders, 20% have hyper lp(a), 12% have a high polygenic score and in 25% a cause for their hypercholesterolaemia has not been found. A new sub-study that will perform the FH patients follow up will start this year. and will bring more information on how these patients are being managed and how to improve patient's prognosis. FH paediatric screening is another study under development.

The Rare Familial Dyslipidaemia Study started in 2017 and provides the elucidation of the underlying genetic cause of dyslipidaemia in patients with a clinical diagnosis of different rare dyslipidaemia, presenting different phenotypes. This study has been divided in 4 different groups concerning 4 distinct phenotypes: hypercholesterolaemia, hypertriglyceridaemia, low LDL cholesterol and low HDL cholesterol. The rare hypercholesterolaemia group comprehends lysosomal acid lipase deficiency (LALD) (LIPA gene), autosomal recessive hypercholesterolaemia (ARH) (LDLRAP1 gene) and sitosterolaemia (ABCG5/8 genes); the hypertriglyceridaemia group comprehends Familial and Multifactorial Chylomicronaemia Syndrome (FCS , MCS) (LPL, APOC2, LMF1, APOA5 and GPIHBL1 genes), infantile transient hypertriglyceridemia (GPD1 gene) and Dunnigan lipodystrophy (LMNA gene); the low LDL group comprehends hypobetalipoproteinaemia (APOB gene), abetalipoproteinaemia (MTTP gene), benign hypocholesterolaemia (PCSK9 gene) and Anderson disease (SAR1B gene); the low HDL comprehends Tangier disease (ABCA1 gene), APOA1 deficiency (APOA1 gene), lecithin cholesterol acyltransferase (LCAT) deficiency and fish eye disease (LCAT gene). Until now, in Portugal, 45 patients have been identified with different rare dyslipidaemia: sitosterolaemia (3), LALD (4), FCS (8), MFC (15), Dunnigan lipodystrophy (8), homozygous hypobetalipoproteinemia (3) heterozygous hypobetalipoproteinemia (2), Tangier (1), Fish Eye Disease (1).

These 2 national studies provide information about these disorders in Portugal and allows the early identification of many patients in order to establish the correct treatment contributing to improve patients prognosis.



SESSION III

ARE WE MOVING FORWARD IN LYSOSOMAL STORAGE DISORDERS?

CHAIRPERSONS

ESMERALDA RODRIGUES,
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LÚCIA LACERDA,
Centro Hospitalar e Universitário de Santo António, Centro de Genética Médica - Unidade de Bioquímica Genética;
ITR- Laboratório para a Investigação Integrativa e Translacional em Saúde Populacional, UMIB - Unidade Multidisciplinar de Investigação Biomédica do ICBAS - Universidade do Porto, Porto, Portugal

SANDRA ALVES,
Research and Development Unit, Departamento de Genética Humana, Instituto Nacional Doutor Ricardo Jorge (INSA); Centro de Estudo da Ciência Animal, CECA-ICETA, Universidade do Porto, Porto, Portugal

THE FUTURE OF ENZYME REPLACEMENT THERAPY

Eugen Mengel

Enzyme replacement therapy (ERT) for the treatment of enzyme deficiencies in lysosomal storage disorders is a 30-year success story. The first to be introduced was placenta-derived alglucerase in 1991, and the last to be approved for ASMD was olipudase alfa in 2022. Treatment is given at regular intervals throughout life.
Due to genetic enzyme defects, patients with lysosomal storage diseases can no longer sufficiently degrade certain macromolecules in some body cells. As a result, the macromolecules that cannot be broken down accumulate in the cell, where they can lead to damage in the cells and various organs built from them. Patients affected by the enzyme defect receive the missing enzyme by means of an infusion. The cells of various organs take up the enzyme in the lysosome via receptor-mediated endocytosis, where they take over the catalytic function of the missing endogenous enzymes. A proportion of patients receiving enzyme replacement therapy develop antibodies to the infused enzyme. Allergic reactions and loss of efficacy are possible.
Enzyme replacement therapy can only treat the non-central nervous disorders of lysosomal storage diseases. The reason for this is that the enzymes applied intravenously cannot cross the blood-brain barrier due to their size and thus cannot reach the brain. For lysosomal storage diseases, in which the brain is affected by the enzyme defect from storing the metabolites that are not broken down, the therapy is ineffective - as far as the cerebral aspects are concerned.
The next generation of ERT aims to overcome the blood-brain barrier. The administration of enzymes directly into the CSF is limited by the fact that many lysosomal enzymes lose their enzyme activity in the non-acidic region of the CSF. Enzyme replacement in the CNS by ex vivo gene therapy and autologous HSCT appears promising in MLD and perhaps other sphingolipidoses. Broader and safer in application is the use of so-called fusion proteins. Here, the enzyme is fused with a second protein. For the second protein there is a transport mechanism across the blood-brain barrier. In MPS II, this therapeutic principle is being tested for the first time in phase 3 trials.

THE PATH TO GENE THERAPY IN LYSOSOMAL STORAGE DISORDERS

Francesca Tucci

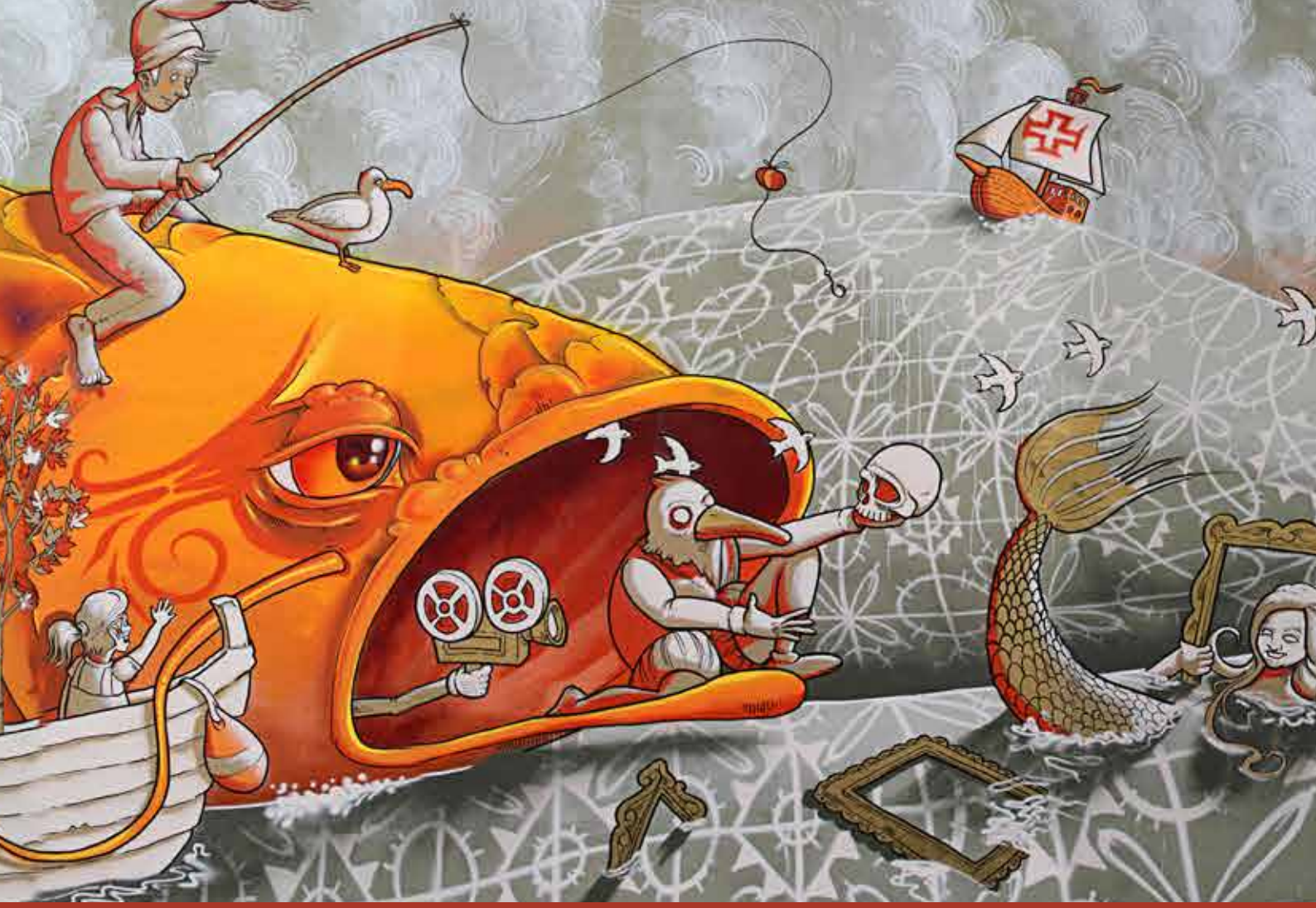
Gene transfer into autologous hematopoietic stem progenitor cells (HSPCs) has the potential to cure monogenic inherited disorders caused by an altered development and/or function of the blood system, such as immune deficiencies and red blood cell and platelet disorders. Gene-corrected HSPCs and their progeny can also be exploited as cell vehicles to deliver molecules into the circulation and tissues, including the central nervous system.
In the past few years, substantial progress has been made in ex-vivo and in-vivo GT for Lysosomal storage diseases (LSDs) to the point that the demonstration of the long-term clinical efficacy of HSPC-GT for metachromatic leukodystrophy (MLD) has led to the marketing authorization in the European Union (EU) of the medicinal product Libmeldy.
Building on this experience and on preclinical works using LV-based HSPC-GT in mucopolysaccharidosis type I (MPSI) mice, which demonstrated correction of MPSI phenotype and long-term safety and efficacy, a first-in-human phase I/II clinical trial (NCT00243023) of HSPC-GT was conducted at SR-TIGET on 8 MPSIH patients. Preliminary results of ex-vivo GT clinical trials in MPS type I, Hurler variant patients have shown a good safety profile together with encouraging biochemical and early clinical outcomes.
Despite these achievements, several challenges remain for HSPC-GT precluding a wider application of this type of gene therapy to a wider set of diseases while gene-editing approaches are entering the clinical arena.

REGISTRIES IN INHERITED METABOLIC DISEASES: HOW TO MOVE FORWARD?

Nadia Belmatoug

A rare disease has a prevalence of less than 1/2000. In 2017, Orphanet registered 6172 rare diseases; 72% are genetic, 70% have an exclusively paediatric onset. Rare diseases share common characteristics: heterogeneity, difficulties in diagnosis; they are chronic, progressive, severe and multisystemic, with repercussions on quality of life and survival. Their care pathway is fragmented and requires the involvement of many specialties, but the scarcity of specialists is necessary to achieve a multidisciplinary approach, especially during the transition from childhood to adulthood. Effective therapies are not always available. Basic and translational research is essential and the role of patient organisations is crucial. For all these reasons, the establishment of registries and databases is a public health policy priority to generate real-world data and knowledge. Their aim is to facilitate access to diagnosis and treatment and to improve epidemiology, research, and the evaluation of innovative therapies and the economic burden of rare diseases.

Different models are presented : the National Database of Rare Diseases (BNDMR), the French Gaucher disease registry, etc. The respective advantages and difficulties of governmental, academic and private registries are analysed as well as their possible complementarity. The importance of good practice recommendations (FAIRification = Findable, Accessible, Interoperable, Reusable), technical compatibility, the use of the same semantics and codes, the rules of the General Data Protection Regulation and data security are highlighted.



SESSION V

NEW APPROACHES IN PORPHYRIAS

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ACUTE HEPATIC PORPHYRIA – THE EXPERIENCE OF A REFERENCE CENTER IN BRAZIL

Charles Marques Lourenço

INTRODUCTION - Acute porphyrias are mostly autosomal dominant inborn metabolic errors, caused by a disturbance in the heme biosynthetic pathway. There are four acute porphyrias and only one is inherited in autosomal recessive manner. Clinical manifestations involve central and peripheral nervous system. The diagnosis is based on the elevated urinary excretion of porphyrins precursors delta-aminolevulinic acid and porphobilinogen.

OBJECTIVE - To evaluate the main clinical and biochemical manifestations of acute porphyrias in Brazilian patients.

METHODS - Retrospective study of medical records from 54 patients with acute porphyrias followed in a reference center in the Southeast region of Brazil

RESULTS/DISCUSSION - Median age of the patients studied ranged from 18 to 47 years old. Usually, female were more severely affected than males. All patient had high levels of delta-aminolevulinic acid and porphobilinogen measured in 24 hours urine collection. The age in which most of the crisis occurred was the third decade. 37 patients presented in the clinics having their first crisis, but 11 of them presented also with chronic manifestations. The commonest clinical presentations were: abdominal pain, change in urine color, motor or sensory-motor deficit, vomiting, alteration of consciousness, convulsions, autonomic cardiovascular signs and psychiatric disorders.

Peripheral motor neuropathy was the initial manifestation in two patients. Six patients died after the initial diagnosis as consequence of complications of the disease. The most commonly used treatments were glucose administration, elevation of carbohydrate intake, and phenothiazines use. Nevertheless, heme (Pan-Hematin®/Normosang®) administration was life-saving for many patients with acute decompensation. Even though the high index of suspicion in some cases, the clinical team usually waited for about a month before ordering the biochemical tests for acute porphyrias.

24 patients (20 females and four males) showed recurrent atacks and "chronic porphyria symptons". Media age of symptons onset in this group was 22 years (range: 12–47 years). All 24 patients reported recurrent porphyria related symptoms, such as pain, neurological and/or psychiatric disorders, nevertheless other systemic complications as hypertension and chronic kidney disease were seen in 10 patients. All patient – but one - had high levels of delta-aminolevulinic acid and porphobilinogen measured in 24 hours urine collection. 10 out of 20 female patients were treated with induced menopause lasting 1-2 years, and 4/24 received the treatment of hematin. All 24 patients had ate least one acute attack in the three months. The median frequency of acute attacks in the last year was 3 times (0–12 times), and the duration of every attack was 8 days (4–20 days). Analgesic dependency to opioid was a problem in 12 patients. Heme therapy was initiated in all patients with remission of the symptoms in most of the patients for more than 6 months in its first use; recurrent attacks followed by repeated heme injections seemed to alleviate symptoms for a shorter period of time. Orthotopic liver transplant was performed in three patients with recurrent attacks (one of the patients passed away one month after liver transplant due to fulminant heart attack , apparently not related to porphyria).

CONCLUSION - Our cohort of patients showed frequent recurrent attacks of acute porphyria (>3 per year) requiring in most of them intravenous heme therapy. Although for patients with recurrent attacks prophylactic heme infusions may be benefic in remitting the symptoms, a subset of patients showed less response to this therapy overtime. Not only facing a debilitating disease state, patients with recurrent attacks can bring a significant burden on health care systems. Acute porphyria patients who suffer from recurrent attacks also report a low quality of life (QoL) and a negative impact on several aspects of everyday life, such as unemployment, personal relationships and long-term disability.

BIOCHEMICAL AND MOLECULAR UPDATE ON PORPHYRIA DIAGNOSIS

Filipa Ferreira & Laura Vilarinho

The porphyrias are a heterogeneous group of rare, (mostly) inherited inborn errors of heme synthesis metabolism. Each porphyria (except X-linked erythropoietic protoporphyria) results from a partial deficiency in one of the eight enzymes of the heme biosynthetic pathway. The porphyrias can be classified as acute and/or cutaneous, depending on their clinical presentation. The Acute Hepatic Porphyria (AHP) are complex, clinically heterogenous disorders affecting multiple organ systems that require a multidisciplinary management approach to reduce significant morbidity and quality of life. AHP should be considered in patients with severe unexplained abdominal pain (which occurs in >90% of acute attacks), particularly if present with pain in other parts of the body, nausea, constipation, mental confusion, change in urine color, muscle weakness, hyponatremia, tachycardia and hypertension.

Porphyrias are diagnosed and differentiated by specific biochemical patterns of elevated porphyrins and porphyrins precursors of heme synthesis, in urine, blood and feces. Once porphyria type is characterized, molecular diagnosis should be performed providing an important method to confirming the biochemical diagnosis, as well as identifying asymptomatic family members (latent heterozygotes) who should be counseled to avoid known precipitating factors that can trigger and acute attack.

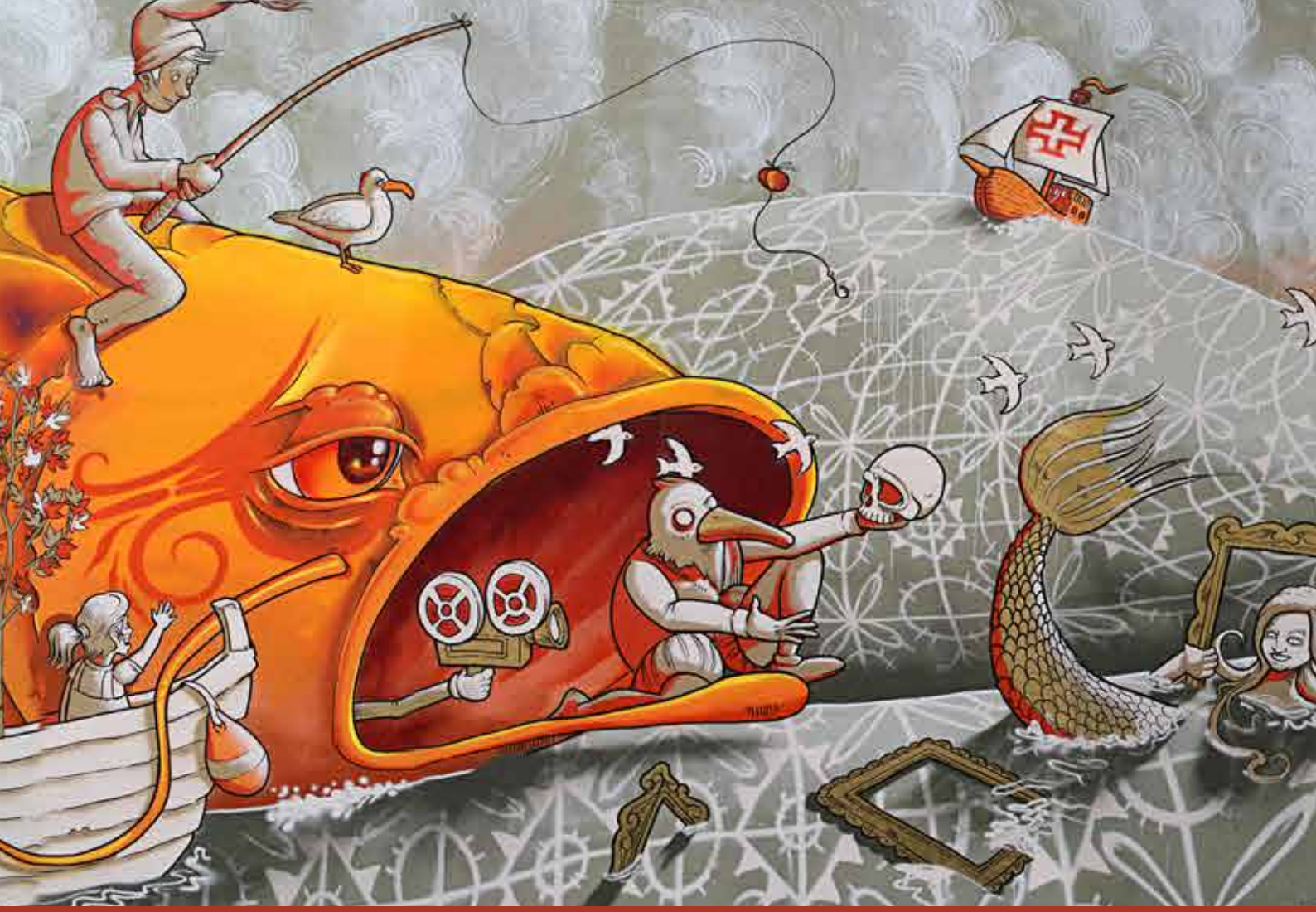
A timely porphyria diagnosis, especially in AHP even being challenging, is crucial as untreated acute attacks can progress, become more severe and potentially lead to permanent neurological damage, or even be life-threatening (Anderson et al., 2005, Stein et al., 2012). Furthermore, undiagnosed patients may therefore unintended be prescribed medications that induce or worsen attacks.

THE RNAi THERAPEUTICS REVOLUTION: FROM BENCH TO BEDSIDE AND BACK AGAIN

Pedro Moreno

RNA therapeutics are a relatively new class of drugs which are rapidly expanding as potential treatment options for a myriad of disease conditions. The development of these new drugs has been spearheaded by research on RNA-silencing oligonucleotides. The pursuit of these new therapeutic modalities was fueled by the option to address disease targets deemed undruggable by small molecules, or the potential to achieve a highly specific and refined mechanism of action towards disease causing genes and proteins.

I will address the basic science path towards achieving the current success, focusing on small interfering RNA drugs and the RNA interference (RNAi) mechanism which have seen major breakthroughs. Here I will highlight the developments on oligonucleotide design, nucleic acids chemistry and delivery technology platforms that have allowed to move these assets from bench to bedside putting a focus on current RNAi therapies for metabolic diseases. A glimpse into the future will be also discussed.



SESSION VI

THINKING BIG AND BOLD IN INHERITED METABOLIC DISEASES

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CHALLENGES AND OPPORTUNITIES FOR USING REAL-WORLD DATA IN METABOLIC MEDICINE

Mário J. Silva

Healthcare practice generates a vast amount of data and that is now available in Electronic Health Records (EHRs). These data provide opportunities for clinical and healthcare effectiveness research, particularly when evidence is difficult to gather through traditional means such as clinical registries and trials. The secondary use of these data can be particularly informative in understanding patient differences among the same disease combinations, their impact on clinical outcomes and healthcare needs. Such data is relevant for addressing rare diseases (e.g., most metabolic diseases), or patients with multimorbidity (i.e., the coexistence of multiple chronic diseases in one individual), which are often subject to conflicting treatment regimens.

We have been addressing the analysis of EHR data in the IntelligentCare project, a CMU-Portugal initiative led by GLSMED Learning Health, in partnership with Hospital da Luz Lisboa (HLL), Priberam and INESC-ID. IntelligentCare is developing a patient centric solution to help manage multimorbidity using analytical methods to explore data from EHRs and the measures reported remotely by the patients, related to outcomes (PROMs) and to life events/ quality of life/physical activity, named as additional value variables (AVVs), using smart sensors and mobile solutions.

The growing amount of data in EHRs led to increased interest in using machine learning ("AI") models to better understand patterns and associations in these data sets. However, learning from data in EHRs is a challenge. There are several important limitations preventing the use of this technology for improving clinical practice. Firstly, the limited availability of clinical data for research due to privacy and security concerns has significantly restricted the application of machine learning methods in this field. There is still much work to be done regarding validation and clinical implementation. Secondly, health data sets pose several challenges such as data multimodality, high dimensionality, sparsity, complex structure, incompleteness, and multiple inherent biases, all of which prevent a straightforward application of machine learning methods. Additionally, although the widespread adoption of EHRs is generating increa sing amounts of clinical data, only a small portion is properly labelled for use in machine learning models. Finally, a major challenge in dealing with clinical data is its temporal nature and the importance of incorporating time into models. Health and disease are dynamic states that change over time, making patient histories, where both the presence or absence of information can carry underlying informative power, hard to process. Time and missing information are essential to accurately capture the dynamics of patient conditions.

In the last decade years, deep learning became the state-of-the-art method in Natural Language Processing (NLP), and inspired researchers to use the technology to analyse data in EHRs, whether they involve text or other data modalities such as medical concept codes, images, vital signs, or laboratory measurements. However, there is currently much debate about the benefits of using machine learning models, including whether they lead to improved outcomes or have a positive economic benefit.

The discussion of the above challenges will be made within the context of the analyses, models, and prediction tools that we have been developing in IntelligentCare. We have access to a large dataset containing the medical histories of 834,529 patients extracted from the HLL EHR, with an observation period spanning between January 2007 and August 2021. Our team developed an information processing pipeline that performs patient phenotyping using not only structured data, but also clinical narrative text and lab test results. Data is normalised under the OMOP Common Data Model, which enables systematic identification of patient cohorts for learning models for predicting clinical outcomes like hospitalisation, and for clustering patients for risk stratification. We will review initial results that we have obtained for a cohort of multimorbidity patients with heart failure and diabetes mellitus.

NEWBORN SCREENING BY WGS: OPPORTUNITIES AND CHALLENGES

David Bick

Newborn screening for treatable disorders has proven effective in preventing or dramatically ameliorating the adverse consequences of these conditions. Screening programs can be found in countries worldwide. In the US, the "Recommended Uniform Screening Panel Conditions" includes 35 disorders.

Ever since screening was first developed for phenylketonuria, additional disorders have been added. New technologies such as tandem mass spectrometry (MSMS) have allowed newborn screening programs to add more disorders at a lower cost and more efficiently. Nevertheless, the current process of "adding" to the current list of disorders occurs one disorder at a time and may eventually be limited by the amount of blood on the newborn screening blood spot card.

As occurred with MSMS, a new technology, genome sequencing offers the promise of screening for more disorders at a lower overall cost per disease. While the screening criteria developed by Wilson and Jungner represent the starting considerations for any screening program in medicine, the use of genome sequencing brings many additional considerations.

In the United Kingdom, Genomics England is initiating The Newborn Genomes Programme. This ethics approved research pilot is embedded in the National Health Service (NHS) to explore the benefits, challenges, and practicalities of offering whole genome sequencing (WGS) to all newborns to accelerate diagnosis and access to treatments for rare genetic conditions.

The programme has three aims: (1) Evaluate the utility, feasibility, and impact on the NHS of screening for a larger number of childhood-onset rare genetic conditions in newborns, including what support they will need. (2) Understand how, with consent, the genomic and health data could be used for research to enable new diagnostic discoveries and treatments to be developed. (3) Explore the potential risks, benefits, and broader implications of storing an individual's genome over their lifetime.

Choosing genes to include is complicated when considering the scope of actions that might follow a diagnosis ranging from treatment (rx-genes.com) to family planning. The problem of positive predictive value when choosing to report a variant in an asymptomatic newborn requires a balancing of sensitivity with specificity. An accepted confirmatory diagnostic test for screen positive cases will be important. Clinical care pathways will be needed for each disorder. Adding the ethical, legal, and psychosocial issues raised by genomic sequencing around consent, discrimination, and data security, represent further challenges to the use of WGS in newborn screening.

Efforts to use genomic testing as a newborn screen are planned or underway in centers worldwide, many of whom are sharing learnings and plans (https://iconseq.org/). The international newborn screening community is starting on a journey to explore the risks and benefits of using genomics in newborn screening. The Genomics England Newborn Genomes Programme along with others around the world will, hopefully, show that genomic testing can improve the lives of newborns everywhere.

AGING IN IMD: UNCOVERING NEW PHENOTYPES

Charles Marques Lourenço

The vast majority of hereditary metabolic disorders are reported in childhood (with onset usually under 16 years of age). In particular, inborn errors of metabolism with neurological manifestations, or hereditary neurometabolic diseases, are a group of heterogeneous genetic disorders that share in common the alteration of specific aspects of the cellular metabolism, ultimately leading to neurological disease.

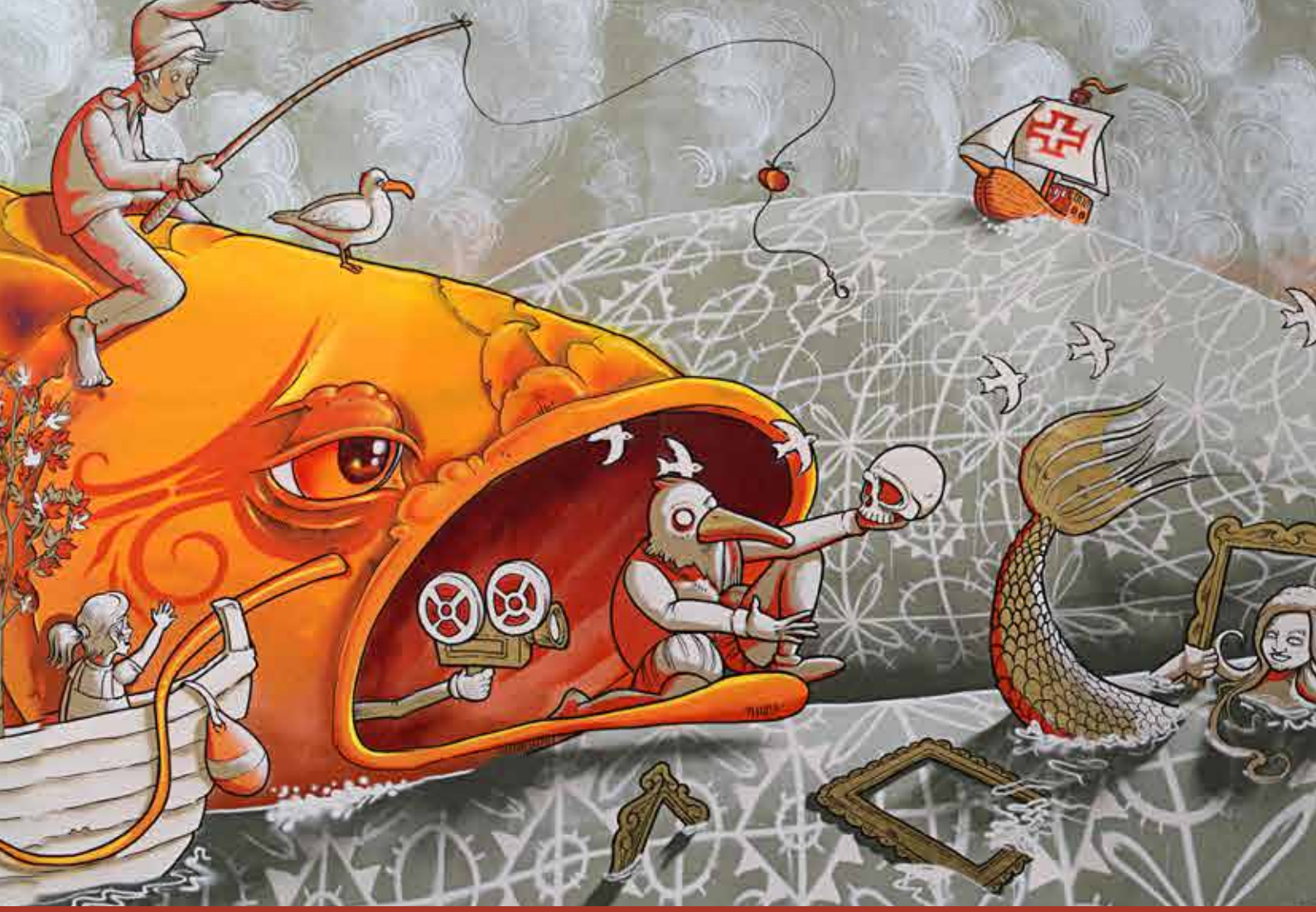
Often first described by pediatricians, this might reflect the fact that the pediatric forms of the disease are more severe and, hence, more easily recognizable. However, in some cases it may be due to a lack of awareness by physicians treating adults of the possibility of inborn errors of metabolism being a cause of adult disease. Nevertheless, even when the patient is diagnosed in childhood, growing with an IEM can bring more challenges in adult life with the outcome of complications not previously reported (since many of those children died in young age with irreversible organ damage or neurological sequelae, without a proper management after a late diagnosis).

The more recently reported adult-onset forms have phenotypes sometimes considerably different from pediatric ones, which may mimic other more common neurological disorders in adults, thus justifying a specific clinical approach and biochemical investigation (combining both traditional metabolic screening and genomic studies).

Although genetic by definition, it is a misconception that IEMs only manifest at young age. There are several factors that can explain this "apparent paradox". Sometimes it can take years before a toxic metabolite accumulates (e.g., lysosomal storage disorder, Wilson's disease) reaching a "non return point" to cause cellular dysfunction. In other neurometabolic disorders, only when an individual is predisposed to extreme environmental stressors (e.g., marathon, pregnancy) , metabolic decompensation (e.g., hyperammonemia, rhabdomyolysis) will develop.

It has been estimated that 45% of the patients at the adult metabolic centers have been diagnosed at adult age. Unfortunately, because of its rare character there is often a delay in the diagnosis of an IEM, which may sometimes lead to irreversible damage or even death. It is, therefore, imperative that a diagnosis is made more rapidly.

In summary, adult patients with IEMs encompass a heterogeneous set of conditions and growing patient population that requires multidisciplinary and specialty approach to provide optimal care (including new treatments and the ability to manage acute decompensation since their management can appear challenging for the adult physician not used to follow patients with hereditary metabolic disorders).



SESSION VIII

UNMET NEEDS IN INHERITED METABOLIC DISEASES

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RUI TATO MARINHO,
Comissão Nacional para os Centros de Referência, Lisboa, Portugal

UNMET NEEDS FOR THE PATIENT AND THE FAMILY

José Vilhena

DOCE - National Association to Disseminate and Guide to Combat and Confront Tay Sachs, Sandhoff and GM1 is a non-profit organization that supports and informs everyone affected by the disease, so that everyone has access to information about studies and clinical trials worldwide and that all children have access to medical support and also equipment for their well-being and quality of life.

DOCE was founded on February 28, 2019, and is an Association of national scope, with its headquarters in Coimbra.

In order to achieve its objective, DOCE proposes to: Make society and State structures aware of the problem of Tay-Sach, Sandhoff and GM1; Sensitize the medical and scientific community to the need for an early diagnosis and the search for a cure; Support families with up-to-date information regarding scientific developments; support families with psychological support during the course of the disease, and through the acquisition of any necessary equipment for patients; support research by channeling grant funds to research centres; sensitize the scientific community to research that is still limited; contribute to the balance of affected families; enter into partnerships with private and public entities in order to meet the objectives of the Association.

DOCE has been working towards the fulfillment of its objectives, however there is still improvement to be done in order to reverse the unmet needs for the patient and their families, namely:

- The diagnostic odyssey;
- The need for a holistic view of the family instead of just focusing on the patient;
- The length of genetic counseling for those who want to have more children
- The importance of caregiver rest
- Exhaustion of health care providers;

All these needs represent an enormous challenge for patients, associations of patients, health professionals and State structures that have to adopt adjustment measures in line with the needs of patients and their families, right after the pandemic period of Covid 19, which represented the highest demand ever from the National Health Service.

THE PHARMACIST AND THE SPECIFICITIES OF IMD

Sara Dias

Inherited Metabolic Diseases (IMD) are a vast and complex group of genetic disorders.

The IMD patient will require life-long follow-up and support from a multidisciplinary team.

Hospital Pharmacists play a key role in this team as they are present through the entire cycle of the drug and its interaction with patient care. Acquisition, stock management, drug prescribing support, pharmaceutical counseling and so on, are activities under the responsibility of Hospital Pharmacists. All the mentioned activities have the main focus on the patient's welfare.

Due to the complex nature of IMD and overall difficulty in tackling these disorders, along with scattered information and lack (or non harmonized) of standard protocols, the discussion on the potential benefits of creating a work group of Hospital Pharmacists to share information, discuss ideas and ultimately contribute to the elaboration of national guidelines must be in order.

REFERENCE CENTRES OF IMD IN PORTUGAL - CHALLENGES AND OPPORTUNITIES

Luísa Diogo

The recognition of rare disease patients' rights across Europe and the need to join efforts to improve healthcare practices led to the implementation of European Reference Networks (ERN), which fostered the recognition of Reference Centres (RC) within the Portuguese National Health Service (NHS). Currently, six RC of IMD (five "generalist" and one "for lysosomal disorders") are official.

The acknowledgement of highly differentiated healthcare teams, dedicated to IMD for a long time, created justified expectations for progress among professionals, patients and families. In fact, it is an opportunity to achieve adequacy of human and material resources and strengthen the NHS. Reinforcing teams' knowledge exchange through networking, both at national and international levels, boosts expertise and quality of care makes patients and families feel safe and confident.

A RC for rare IMD can be a recognizable and prestigious "brand" for Health Care Providers (HCP). Being part of a ERN opens the possibility for cooperative, large scale, clinical investigation and teaching/learning. Otherwise, recognition of a RC (good) results may attract foreign patients.

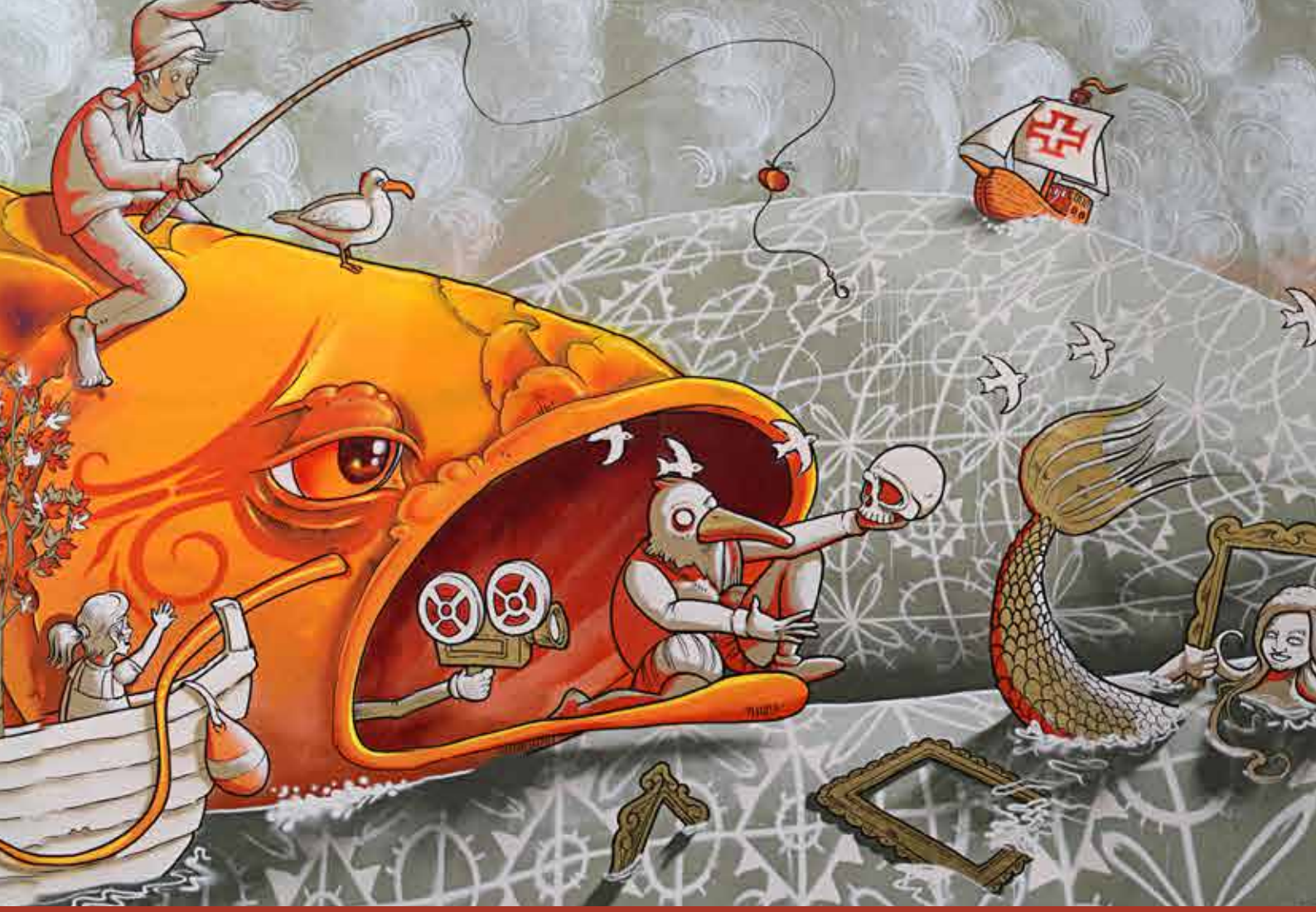
The generalist nature of most IMD RC and the great and growing number of known IMD, most of which are ultra rare disorders, are a huge challenge to professionals. Furthermore, the relatively small area of influence of each IMD RC, with the inherent low numbers of a specific IMD or group of IMD, implies an enormous commitment of the professionals to achieve and maintain expertise.

RC are new in the NHS and their place in HCP structure is still to be regulated. The definition of the RC coordinator's functions and his hierarchical place in the HCP governance is essential. These issues are especially relevant in the case of IMD, since all HCP departments are involved, at paediatric and adult levels.

Counteracting teams' shortage, both in terms of recruiting capacity (including secretariat and project managers) and attracting, motivating and retaining new professionals, is a real challenge. The extension of teams could be self-sustaining in the short or medium term, fostering clinical research and clinical trials and the corresponding funding. The need for exclusive dedication of the core team and designation of the weekly schedule of the element of the RC dedicated to care, clinical research and training activities, in order to achieve the RC objectives, must be understood, accepted and implemented by the HCP Directive Boards.

A clear definition of the objectives for the renewable period of four years in which a IMD RC recognition by the MH takes place, of the human and material resources needed to achieve them and of funding allocation rules is essential to plan activities, gain professional satisfaction and provide better healthcare.

RC of IMD are an unquestionable asset for patients and families. Urgent action is needed to make them function adequately, so that professionals, who are not currently compensated for overtime work associated to the RC and MetabERN extra tasks, including accreditation/certification processes, keep their faith in the project.



SESSION IX

SPOTLIGHT I

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CHANGE IN QUALITY OF DIET AND BURDEN OF CARE IN CHILDREN WITH PHENYLKETONURIA TREATED WITH SAPROPTERIN DIHYDROCHLORIDE: A LONGITUDINAL STUDY

Maria Inês Gama

Introduction: Adjuvant treatments in Phenylketonuria (PKU), such as sapropterin dihydrochloride, aim to increase natural protein tolerance and/or ameliorate blood phenylalanine (Phe) levels in a subset of patients. Changes in feeding patterns and behaviors in sapropterin-responsive populations have not been widely reported in the literature. Our aim was to assess changes in food quality, mental health and burden of care in a PKU sapropterin-responsive cohort.

Methods: In an observational, longitudinal study, questionnaires on food frequency, neophobia, anxiety and depression, impact on family and burden of care were applied to patients at baseline, 3-months and 6-months after saproterin-responsiveness testing.

Results: 17 children (10.83 ± 4.18 years) reached the 6-months follow-up assessment. Patients weight, height and BMI z-scores remained similar after drug initiation ($p = 0.234$; $p=0.169$; $p=0.412$, respectively), while increasing natural protein ($p = <0.001$) and reducing protein substitute intake ($p = 0.002$) significantly ($p<0.05$). Blood Phe control was kept stable throughout the study ($p = 0.731$). Increases in regular milk ($p = 0.001$), meat/fish and eggs ($p = 0.005$), bread ($p = 0.01$) and pasta ($p = 0.011$) were seen, while decreasing intake of low-protein milk ($p = 0.007$), bread ($p = 0.028$) and pasta ($p = <0.001$). Anxiety ($p = 0.016$) and depression ($p = 0.022$) were significantly decreased in caregivers. As for impact on family, differences were seen on the familial-social ($p = 0.002$) and personal strain ($p = 0.001$) subsets. On burden of care, the majority of caregivers considered dietary management to be easier but still restrictive. Before drug treatment more time was spent in PKU related tasks, but this decreased as time went on. Around half of caregivers spent more money on food shopping and the majority went out more for meals more regularly. Fewer caregivers had to deny food choices on a daily basis to their children after 6-months on the drug.

Conclusion: There were significant changes in food patterns, behaviors, and burden of care in children with PKU and their families after 6-months on sapropterin treatment.

NOVEL INSIGHTS INTO TREATMENT STRATEGIES FOR HYPERAMMONEMIA-ASSOCIATED UREA CYCLE DISORDERS AND ORGANIC ACIDURIAS

Margarida Silva

The understanding of pathophysiological processes dependent of nitrogen metabolism is crucial to develop novel pharmacological-based interventions for Urea Cycle Disorders (UCD) and Hyperammonemia (HA)-associated Organic acidurias (OA). Insights into tools and models that contributed to progress towards respective treatment approaches will be presented, where the mitigation and prevention of neurological injury is a major challenge and research aim. Focused on modulation of metabolism, our current research explores the value of mitochondria-targeted small therapeutic molecules for UCD and HA-related OA. Mass spectrometry-based targeted metabolomics was used as primary investigational tool to assess the mechanisms of HA and the connections of proximal or distal UC reactions, in human samples or in cell-based assays. We investigated the mitochondrial metabolome associated with UCD patients' samples, primarily linked with differential diagnosis and management. Using hepatic cell cultures (HepaRG) *in vitro*, the quantification of specific metabolites including orotic acid by stable isotope dilution GC-MS was undertaken in extracellular media. We also addressed the hypothesis that neural stem cells (NSC), the self-renewing multipotent cells that maintain the capacity to neuroregeneration, would present therapeutic potential in HA-induced neurotoxicity. Using NSC cultures under experimental HA conditions we evaluated differences among EGF-responsive NSC-dependent metabolic states. On-going results progress may help to characterize the effects of HA in neurogenesis clarifying the advantages of NSC plasticity in therapy. The refinement of reliable analytical methods for metabolites studies allow to model ammonia effects in cell lines, aiming to assist and contribute for innovation in developing effective therapies for HA-associated inborn errors of metabolism.

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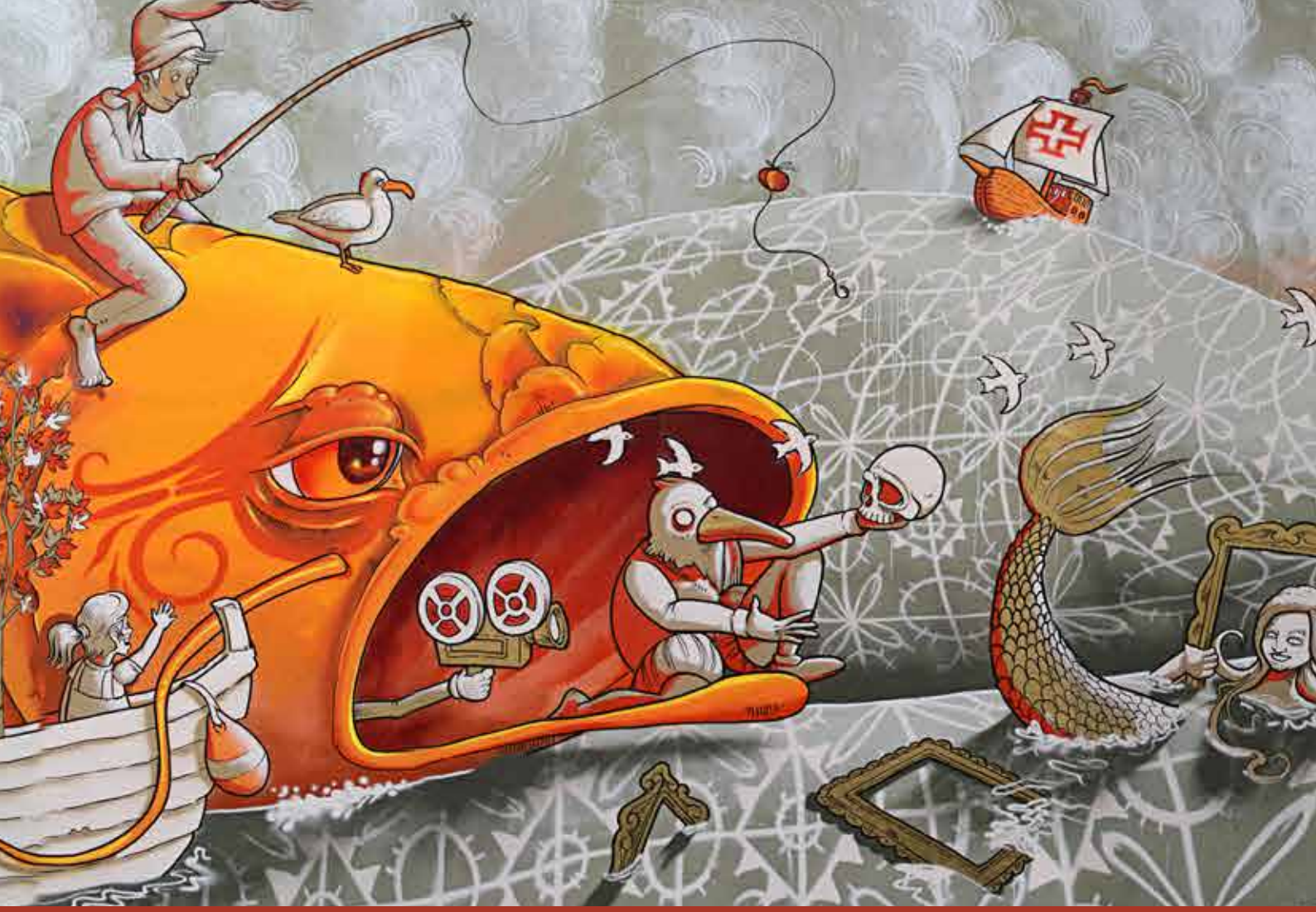

SESSION X

SPOTLIGHT II

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SOMETHING STINKS': IMPAIRED HYDROGEN SULFIDE AND CYSTEINE PERSULFIDE PRODUCTION BY CYSTATHIONINE β-SYNTHASE VARIANTS IDENTIFIED IN CLASSICAL HOMOCYSTINURIA PATIENTS

João B. Vicente, Luís G. Gonçalves, Alessandro Giuffrè and Paula Leandro

Hydrogen sulfide (H_2S) regulates many physiological processes as a pleiotropic signaling molecule. H_2S is produced and detoxified endogenously by specialized enzymes. One of the main H_2S-synthesizing enzymes is cystathionine β-synthase (CBS). While the 'canonical' function of CBS is the condensation of homocysteine and serine in the committing step of the reverse transsulfuration pathway, alternatively it produces H_2S mainly by condensation of homocysteine and cysteine. Disturbed H_2S metabolism due to aberrant CBS expression is growingly established as an etiologic factor of several pathologies, some with clinical presentations common to classical homocystinuria (CHU, CBS deficiency), namely cardiovascular disease and neurological impairment. Given that elevated plasma homocysteine does not fully explain the clinical presentations of CHU patients, disturbed H_2S production is likely to underlie the pathogenicity of various *CBS* mutations.

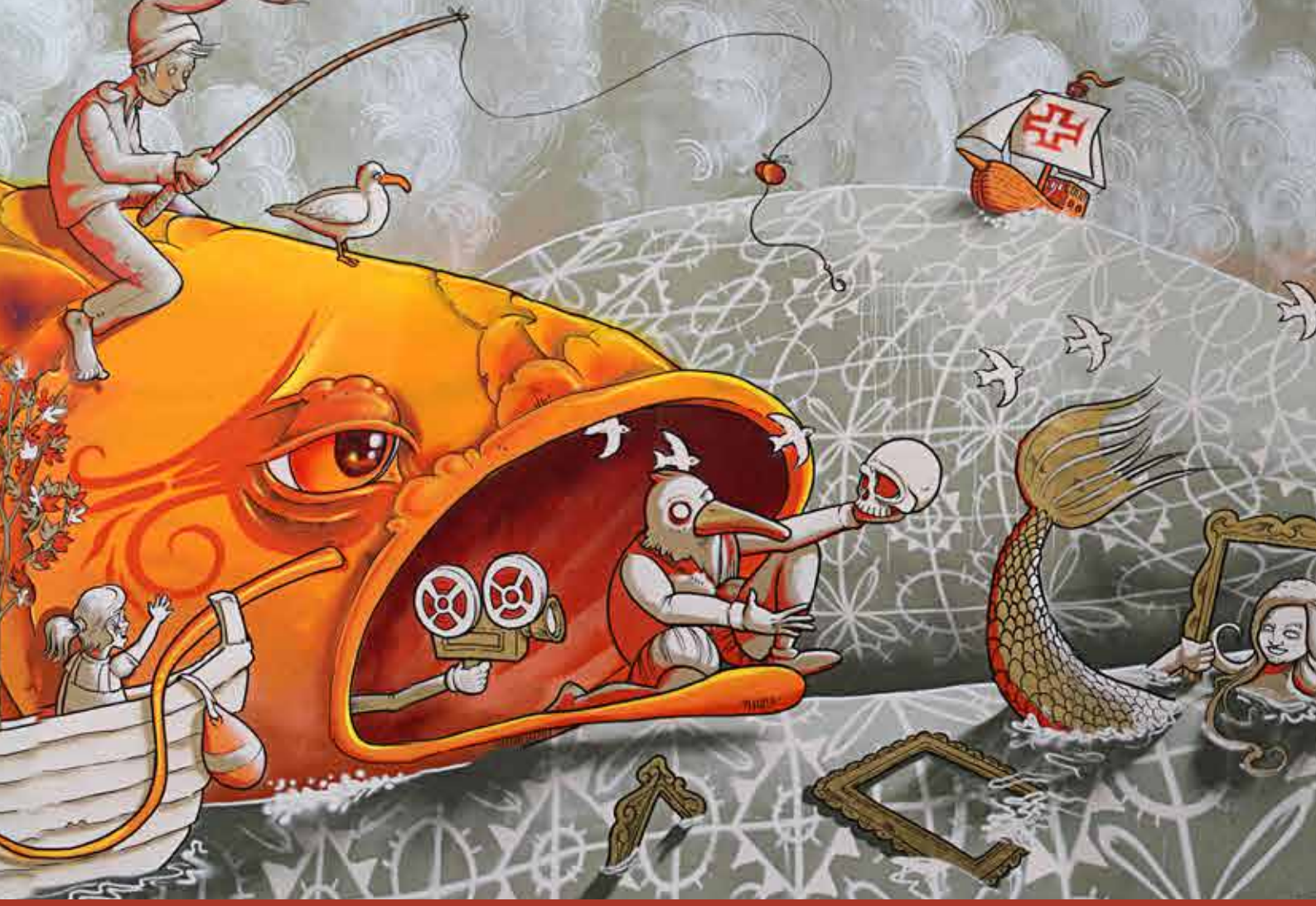
Herein we aim to shed new lights onto the molecular bases of CHU resulting from CBS mutations, by comparatively characterizing wild-type CBS and 13 pathogenic variants with amino acid substitutions spanning its three structural domains. Purified recombinant WT CBS and its pathogenic variants were studied by biochemical and biophysical assays to analyze their thermal and conformational stability, and their functional impairment in terms of the 'canonical' and/or H_2S-producing reactions. To accomplish the latter, a new approach based on ^{1}H nuclear magnetic resonance (^{1}H-NMR) was developed and implemented to measure cystathionine production both through the 'canonical' and H_2S-generating reactions.

The studied pathogenic variants display different profiles of stability and functional impairment depending on the location and nature of the amino acid substitution. The compromised function is reflected on the establishment of a ranking of disturbed H_2S production, from poor to excessive and unregulated. We are currently seeking to correlate these results with the clinical phenotypes associated to these pathogenic variants.

IMPROVE MANAGEMENT OF MADD PATIENTS: A CURATED DATABASE WITH CLINICAL, MOLECULAR AND CELLULAR INFORMATION

Bárbara Henriques

Inborn errors of metabolism comprise a class of genetic diseases which affect genes coding for enzymes involved in different cellular pathways. The expansion of the newborn screening program allows the earlier identification of several new cases associated to these rare diseases. Still clinicians and researchers in the field identified an enormous gap, the lack of a unifying depository for molecular and clinical data on patients, with the majority of cases found disperse in literature, and many not even reported in international journals with full access to all. In this project we propose to contribute to this societal demand, with tremendous impact in the development of new therapeutic approaches, by organizing a curated database with detailed information on mutations associated to Multiple Acyl-CoA dehydrogenase Deficiency (MADD), combining molecular, cellular, and clinical data available in the literature. Further, for mutations that are only reported in clinical case we will take advantage of computational studies to predict and decipher the impact of mutations on protein function using protein stability and conservation analysis. In parallel, experimental studies on MADD-derived fibroblast to evaluate mitochondria morphology and function, and mitometabolome will be performed and analysed, and if possible integrated in the curated database.



ORAL COMMUNICATIONS

OC 01

IMPACT OF STRUCTURAL GLA PROTEIN CHANGES ON PERIPHERAL GLA ACTIVITY AND SUBSTRATE ACCUMULATION IN FABRY DISEASE PATIENTS

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Main category: Translational science study

Disease category: Complex molecule and organelle metabolism

Introduction: Fabry disease is an X-linked lysosomal storage disorder caused by pathogenic variants in the GLA gene, leading to decreased/absent α-galactosidase activity. In clinical practice, enzyme activity and substrate/byproduct accumulation are diagnosis and disease-monitoring biomarkers. However, interpreting biomarker levels is not straightforward and can change according to the underlying GLA protein abnormality. Our goals were to understand how disrupting specific protein regions changes biomarker behaviour and to establish specific patterns for individual variants.

Methods: We analysed data from a Biochemical Genetics Laboratory regarding GLA variants, GLA enzyme activity (in dried blood spots, plasma or white blood cells), plasma LysoGb3 accumulation and urinary Gb3 excretion. We assessed correlations, trends and potential predictor models of biomarker behaviour.

Results/Case report: We assessed 169 hemizygous male and 255 heterozygous female patients. For both groups, substrate accumulation correlates inversely with GLA activity. Variants affecting residues buried within the protein core or the active site were associated with more severe biomarker changes, while those affecting residues that establish disulfide bonds or are glycosylated were similar to other variants. For each non-truncating variant, we also established specific profiles of biomarker behaviour. Finally, we also designed predictor models of biomarker behaviour based on structural variant information. This study provides the groundwork for the impact of GLA protein variation on GLA activity and substrate accumulation.

Conclusion: This knowledge is of extreme relevance for diagnostic labs and clinicians, as some genetic variants are challenging to interpret regarding pathogenicity: assessing whether biomarker changes are in the expected range for a specific variant may help diagnostic evaluation. This study also contributes to recognising not disease-causing variants, considering their overall biochemical impact, and to provide a comparative reference for biomarker discovery studies. In the future, correlation of these findings with disease severity may be of great relevance for diagnosis and monitoring progression.

OC 02

MCADD PATIENTS: HOW TO FACE CARDIAC FUNCTION BIOMARKERS DURING ACUTE EPISODES?

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Main category: Case series

Disease category: Lipid metabolism and transport

Introduction: Medium-chain acyl-CoA dehydrogenase deficiency (MCADD) is the most common fatty acid oxidation disorder (FAO). The great majority of patients remain clinically asymptomatic, although it has been increasing the number of reports describing life-threatening symptoms including encephalopathy, rhabdomyolysis, and cardiac manifestations such as ventricular tachycardia and cardiac arrest. To investigate this possibility, heart function biomarkers namely NT-proBNP, was added to the protocol in use in our IEM Reference Centre for MCADD follow-up. We present our first set of results.

Methods: We reviewed the clinical charts of 84 MCADD patients diagnosed by NBS, and selected 7 patients (5 male) with high levels of NT-proBNP above the reference value. Clinical symptoms recorded at the time of NT-proBNP elevation were considered. Complete heart evaluation was performed at follow-up.

Results/Case report: All cases were asymptomatic at screening time. High levels of cardiac markers, especially NT-proBNP (406-3314 pg/mL; RV<300 pg/mL) were recorded in 7 MCADD patients. NT-proBNP was elevated in 14 episodes (1-5 episodes/ patient). At the time of the episode of NT-proBNP elevation patient´s age ranged from 1month to 4years of life. Clinical symptoms reported at the time were: fever (8), vomiting (7), feeding refusal (7), nasal obstruction (5), cough (4), diarrhea (3), prostration (3), prolonged fasting (2), otitis (2), respiratory distress (1). Cardiac ultrasound (n=5) performed, at the acute event, revealed left ventricular dilatation in 2 patients. All patients recovered completely at follow-up with normalization of the heart abnormalities.

Conclusion: Cardiac involvement is rarely recognized in MCADD patients, and it is mainly manifested by arrhythmia that may be life-threatening. Cardiac ventricular myocytes release pro-BNP in response to pressure overload, volume expansion, myocardial wall stress (1). Our MCADD patients had high NT-proBNP levels during acute decompensation. Increased NT-pro-BNP level has been correlated with clinical signs of inadequate cardiac output/ cardiogenic shock, such as tachycardia. May this biomarker be valuable in MCADD patients for early detection of risk for developing lethal arrhythmias and/or heart failure?

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OC 03

HELP COMES FROM UNEXPECTED PLACES: HOW A TINY FAIRY AND A TROPICAL FISH MAY HELP US MODEL MUCOPOLYSACCHARIDOSES

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Main category: Basic science study

Disease category: Complex molecule and organelle metabolism

Introduction: When it comes to disease modeling, countless models are available for Lysosomal Storage Diseases (LSD). Historically, two major approaches are well-established: in vitro assessments are performed in patient fibroblasts, while in vivo pre-clinical studies are performed in mouse models. Still, both platforms have a series of drawbacks. Thus, we implemented two alternative and innovative protocols to mimic a particular sub-group of LSDs, the Mucopolysaccharidoses both in vitro and in vivo.

Methods: The first one relies on a non-invasive approach using dental pulp stem cells from deciduous teeth (SHEDs). SHEDs are multipotent neuronal precursors that can easily be collected. The second, uses a state-of-the-art gene editing technology (CRISPR/Cas9) to generate zebrafish disease models.

Results/Case report: Even though this is an ongoing project, we have already established and characterized two MPS II and one MPS VI SHED cell models. These cells self-maintain through several passages and can give rise to a variety of cells including neurons. Furthermore, all MPS-associated sub-cellular phenotypes we have assessed so far are easily observable in these cells.

Regarding our zebrafish models, we have successfully knocked down both naglu and hgsnat and the first results we got from the behavioral analysis are promising ones, as we can observe some hyperactivity patters in the genetically modified fish. For this particular approach we chose MPS III forms as our target disorders, since their neurological features (hyperactivity, seizures and motor impairment) and lifespan decrease would be easily recognizable in zebrafish.

Conclusion: Now that these methods are well-established in our lab, their potential is immense. On one hand, the newly developed models will be of ultimate value to understand the mechanisms underlying MPS sub-cellular pathology, which have to be further elucidated. On the other hand, they will constitute an optimal platform for drug testing in house. Also noteworthy, our models will be published as lab resources and made available for the whole LSD community.

OC 04

CLINICAL AND LABORATORY FINDINGS IN GLYCOGEN STORAGE DISEASE TYPE V: RESULTS FROM A RETROSPECTIVE OBSERVATIONAL STUDY IN A TERTIARY HOSPITAL

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Main category: Case series

Disease category: Several disease categories

Introduction: Glycogen storage disease type V (GSDV, MIM #232600) is an autosomal recessive metabolic myopathy caused by pathogenic variants in the PYGM gene. The characteristic symptoms of exercise intolerance, myalgia and cramps, which improve after a few minutes of rest, are frequently unrecognized in affected children. When there is clinical suspicion, the initial approach with a forearm exercise test has diagnostic value by detecting low post-exercise plasma lactate-to-ammonia ratio values. The diagnostic algorithm is followed by genetic testing if the results suggest myophosphorylase deficiency.

Methods: Retrospective observational study based on reviewing medical records of patients with GSDV in a tertiary hospital. We assessed demographic variables, including the timing of onset and diagnosis, relevant clinical characteristics and whether genetic testing was performed, including its results.

Results/Case report: Our goal was to review the GSDV cases in our center, to assess our cohort's diagnostic timing and clinical and genetic characteristics. We identified 28 patients from 24 families, three with consanguinity. The mean age at the time of the study was 43 years. While most (26/28; 93%) recalled their first symptoms in childhood/adolescence, only 25% (7/28) were diagnosed then. All patients had exercise intolerance and CK elevation, while about half reported the second wind phenomenon. Genetic testing was performed in 22 patients, revealing biallelic PYGM variants (9 homozygous, 13 compound heterozygous), the most common being p.R50*.

Conclusion: GSDV is rare and presents in the pediatric age, with subtle manifestations often underestimated for decades. A late diagnosis may negatively impact the psychosocial development of affected children. It is essential to recognize some unique features that facilitate diagnosis: history of exercise intolerance, the second wind sign and high resting serum CK levels. Identifying the disease-causing variants in PYGM is currently the gold standard for diagnosis as it is less invasive than performing a muscle biopsy, and may promptly diagnose the condition and avoid wrongful labelling of patients.

OC 05

GLUTARIC ACIDEMIA TYPE 1: DIAGNOSIS, CLINICAL FEATURES, AND OUTCOME IN A PORTUGUESE COHORT

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Main category: Case series

Disease category: Several disease categories

Introduction: Glutaric acidemia type 1 (GA1) is a rare autosomal recessive disorder characterized by a deficiency of glutaryl-CoA dehydrogenase, resulting in the accumulation of glutaric acid (GA), 3-hydroxyglutaric acid, and glutarylcarnitine, especially in the brain (1). GA1-affected children are clinically characterized by macrocephaly. Neurological abnormalities usually appear between 6 and 18 months of age (2), often triggered by a catabolic event. On the other hand, several biochemically affected individuals may remain asymptomatic or experience an insidious onset of mild neurological abnormalities.

Methods: Retrospective study of GA1 patients followed at a Portuguese Hereditary Metabolic Disease Center, to characterize the phenotypic and genotypic variations associated with GA1. Therefore, we analyzed the clinical, neuroradiological, biochemical, and genetic information from 14 patients.

Results/Case report: 14 patients (four months-27 years old) were identified in the last 26 years, 9 were male, 1 from a consanguineous family. 11 were diagnosed by newborn screening (NBS) and 3 identified following clinical symptoms (later diagnosed, LD). There were 3 phenotypic presentations: 6 asymptomatic, 3 with motor disability after encephalopathic crisis (EC) and 5 with insidious onset. Acute EC occurred in 1/3 of the LD patients, and in 2/11 NBS-identified patients. About urinary GA concentrations: 5 were low excretors (LE), 9 high excretors (HE). All LE showed symptoms, and 2 had EC. Concerning HE, 3 showed symptoms and 1 had EC. GCDH analysis showed: 6 compound heterozygotes and 8 homozygotes. most frequent variant was c.1204C>T (p.R402W). All of them received appropriate therapy from the time of diagnosis, with a mean age of 23,3 months in LD patients and 13,3 days in NBS-identified patients.

Conclusion: The outcomes were different between the two groups: all the LD patients presented motor dysfunction however in the NBS-identified patients only 5 developed this symptom. Patients identified by NBS had better outcome showing that NBS enables an early diagnosis, and treatment, and consequently improves the clinical outcomes for these patients. No correlation was observed with clinical phenotype between LE and HE, as both groups can suffer the most severe neurological manifestations. These conclusions are in agreement with previous cohorts described in the literature (3).

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OC 06

FORTY-THREE YEARS AFTER THE START OF NEONATAL SCREENING IN PORTUGAL: THE RESULTS OF A RETROSPECTIVE COHORT STUDY WITH 113 ADULT PKU PATIENTS

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Main category: Translational science study

Disease category: Intermediary metabolism: others

Introduction: Phenylketonuria (PKU) is the most common inborn error of protein metabolism in Europe whose consequences are preventable. The year of 1993 marks, in our Reference Centre, a paradigm shift in the follow up of these patients: the definition of safety Phe levels ≤ 6 mg/dL up to the age of 12 years, more diversity of special low protein foods freely available and a more regular follow up by a multidisciplinary team, are changes whose results on quality of dietetic control (QDC) and cognitive outcomes we intended to evaluate in the long-term follow up of these patients.

Methods: We carried out a retrospective cohort study with 113 adult PKU patients early diagnosed, without additional disorders, characterizing them in terms of QDC and mental health. Software Statistical Package for the Social Sciences® (SPSS®) version 20.0 was used for data analysis

Results/Case report: We observed significant differences between the three groups of PKU patients considered, hyperphenylalaninemias (HPA), mild and classical, on their last global IQ values, with classical PKU patients having the lower mean IQ global values, the worse QDC, the higher percentage of individuals with adapted curriculum or special education and more severe comorbidities. However, classical PKU patients seemed to deal as well as other groups with tasks such as parenting. Patients with HPA were the only ones showing a good QDC throughout life in all groups of age considered, with annual medians of Phe ≤ 8 mg/dL. After 1993 we observed a clear improvement in the lifelong QDC in mild and classical PKU patients, with an impact on their cognitive performance and quality of life.

Conclusion: These results point to the need for a regular psychological follow-up in the mild and classical forms of the disease to optimize their QDC and cognitive outcomes. Being born after 1993 marks a paradigm shift in the performance of PKU patients in their quality of metabolic control. We hypothesized that the definition of safety Phe levels ≤ 6 mg/dL up to the age of 12 years, with a more diversity of special low protein foods, available for free, and the establishment of a more proactive and regular follow-up by the multidisciplinary team of these patients, contributed to this improvement.

OC 07

THE HOLE IN THE WHOLE: MITOCHONDRIAL DNA DELETIONS SCREENING

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Main category: Translational science study

Disease category: Several disease categories

Introduction: OXPHOS diseases are heterogeneous and multisystemic, affecting mainly organs with high energy needs[1,2].The classical ("biopsy first") diagnostic approach was based in deep clinical phenotyping and OXPHOS activity in tissues, targeting gene analysis. Recently, Next Generation Sequencing (NGS) became widely available, leading to a "genetics first" approach[3]. Still, tissue biopsy value in diagnosis should be kept in mind, considering the tissue specificity of OXPHOS.

We present the screening results of large mtDNA deletions in 305 patients, in blood and muscle and/or liver biopsy.

Methods: Total DNA was extracted from blood, muscle, and liver biopsies by standard methods. To screen deletions, a flanking PCR was performed in six regions (3150–14704, 3150–16192, 3150–16406, 7241–14704, 8222–13727, 8222–16192), followed by electrophoresis. Confirmation/location were done by sequencing.

Results/Case report: From the 305 patients studied, mitochondrial DNA (mtDNA) deletion(s) were identified in 132 patients (43%) in at least one of the tissues analyzed. In 115 of these patients (87%), the mtDNA deletions were detected in muscle and/or liver biopsies, but not in the blood sample. Only 16 patients (12%) had mtDNA deletions in blood and muscle and/or liver biopsies. In one patient the mtDNA deletion was detected in the blood sample, but not in other tissue biopsy.

Deletions are most likely to be found in tissue biopsies, rather than in blood, as we have observed, except for one case. This reinforces the idea that the choice of the best specimen for testing is critical and increases the probability of mtDNA molecular diagnosis[2].

Conclusion: The NGS approach can be a breakthrough in diagnosis of OXPHOS diseases, especially if used correctly. Our approach is based on enrichment of entire mtDNA by a single amplicon long-range PCR and only then followed by NGS, to detect pathogenic sequence variants and deletions simultaneously[1], allowing high specificity. Evaluation of family history, clinical and biochemical findings, and imaging and/or histopathological data, and the availability of different tissues for functional and genetic analysis is still mandatory for the pursuit of a correct diagnosis[2], instead of NGS in blood for all.

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OC 08

RESTORING CHOLESTEROL HOMEOSTASIS IN NEURONS BY AAV-MEDIATED CYP46A1 DELIVERY IS NOT SUFFICIENT TO STALL THE PROGRESSION OF NIEMANN-PICK TYPE C DISEASE

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Main category: Translational science study

Disease category: Lipid metabolism and transport

Introduction: Cholesterol 24-hydroxylase (CYP46A1) is a neuronal-specific cytochrome P450, which catalyzes the major elimination pathway of brain cholesterol, through its conversion into 24S-hydroxycholesterol. We and others have shown that besides leading to cholesterol reduction, targeting CYP46A1 has a positive effect on cognition. Therefore, we hypothesized that CYP46A1 could be a potential therapeutic target in Niemann-Pick type C disease (NPC) disease, which is a rare and fatal neurodegenerative disorder, characterized by cholesterol accumulation in endolysosomal compartments.

Methods: Herein, we show that CYP46A1 ectopic expression, in cellular models of NPC, and in vivo by adeno-associated virus-mediated gene therapy in the Npc1tm(I1061T) mouse, improves NPC disease phenotype.

Results/Case report: In vivo CYP46A1 expression partially prevented weight loss and hepatomegaly, corrected the expression levels of genes involved in cholesterol homeostasis, and promoted a redistribution of brain cholesterol accumulated in late endosomes/lysosomes. Moreover, concomitant with the correction of cholesterol metabolism dyeregulation, CYP46A1 attenuates microgliosis and lysosomal dysfunction in mice cerebellum, favoring a pro-resolving phenotype. Nevertheless, the correction of cholesterol homeostasis is not sufficient to impair Purkinje neuronal death in the cerebellum,

Conclusion: Unesterified cholesterol accumulation has frequently been indicated as the main cause of neuronal cell death in NPC and most developed drug screenings have been directed to late cholesterol storage and modulation of cholesterol regulation. Nevertheless, our results suggest that cholesterol accumulation in neurons may not be the primary culprit of neurodegeneration in this human lipidosis.

OC 09

PALLIATIVE CARE IN CHILDREN WITH INHERITED METABOLIC DISEASES: WHY DOES IT MATTER?

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Main category: Basic science study

Disease category: Several disease categories

Introduction: Inherited metabolic diseases (IMD) bring considerable burden on the child and family. Challenging areas for health care include identification of distressing symptoms, prognostic uncertainty and bereavement. Literature regarding the impact of paediatric palliative care (PPC) is scarce.

This study aims to evaluate children with IMD referred to a PPC team (PPCT) and to analyse its impact on home care, decision to limit treatment (DLT), use of hospital resources(emergency department admissions - EDA, hospital admissions – HA, intensive care admissions – ICA) and end of life support.

Methods: Retrospective cohort study of children with IMD referred to a specialized PPCT (2016-2022). We assessed clinical data: symptoms control, time of referral and length of follow-up period, DLT, device dependency, use of hospital resources prior and after referral, place of death and end of life support.

Results/Case report: Fifteen children with IMD were referred to PPCT (8% of total referrals), with median age of 7 years (4 months – 17 years); 53% female. All children were non or pre-verbal. Most prevalent symptoms were neurologic and motor impairment (100%), respiratory and gastrointestinal (75%). 80% had tube feeding, 90% had some respiratory device (non-invasive ventilation in 23%).

All children had multidrug use, with a mean of 6 drugs per child (2-9). 73% had home PPC and 80% had DLT planned. Nine children died (78% in hospital), after a mean of 17 months of follow-up (2 months to 4 years), all with DLT planned. 67% had support from PPCT at the end of life. All these families received emotional support.

Decrease in EDA (10 vs 2) was noticed before and after PPCT. No impact was seen in HA and ICA (6 vs 5 and 1 vs 1, respectively) and there was a longer mean of hospitalisation stay (15 vs 32 days).

Conclusion: Our cohort includes a group of children with severe, complex and neurodegenerative IMD. They need multiple medications for symptoms control, are highly dependent on medical devices and consume significant healthcare resources. Communication impairment adds complexity being a major barrier to symptom assessment.

PCT referral allowed home support, anticipated care plans development with end of life and bereavement support, as well as a tendency towards a reduction in EDA.

These findings reinforce the need for holistic approach to identify and address the PPC needs of children with IMD.

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OC 10

BOOSTING INSIGHTS ON THE IMMUNOPATHOLOGY OF PMM2-CDG

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Main category: Basic science study

Disease category: Several disease categories

Introduction: PMM2-CDG is the most frequent congenital disorder of glycosylation - a group of ~170 rare genetic metabolic diseases.(1) It is caused by deficiencies in phosphomanomutase 2 impairing the conversion of Man-6-P to Man-1-P which translates in defects in N-glycosylation. The occurrence of recurrent and severe infections with fatal outcomes in 20% of the child cases is therefore not surprising given the importance of glycosylation to the good functioning of the immune system.(2,3) However, the compromised cellular and molecular mechanisms behind this immunopathology have not yet been deciphered.

Methods: To unveil this immune dysfunction, fibroblasts from 3 PMM2-CDG patients and matched apparently healthy individuals were stimulated with the inflammatory TNF-α cytokine and the RNA was sequenced. The differences in the molecular response to the stimulus were identified and validated in vitro.

Results/Case report: We identified gene expression alterations in our PMM2-CDG cohort upon stimulus. Specifically, in the PMM2-CDG fibroblasts, 161 genes failed to respond normally to TNF-α. Some of these are genes that codify cytokines (e.g., IL-6, IL-15, IL-34). A functional analysis of these genes further reveals immunological alterations between PMM2-CDG and healthy samples. Interestingly, differences in the MAPK, ERK1/2 and JNK signaling cascades downstream to the TNF-α receptor were identified, as well as the IL-6 cytokine production and regulation. An in vitro analysis confirmed the lower levels of the JNK-2 protein in PMM2-CDG as well as the impairment of the secretion of the IL-6 - an important effector cytokine to fight infections - and RANTES - a chemokine that recruits leukocytes into inflammatory sites.

Conclusion: Our study identified defects in biological pathways and highlighted deregulated immune players in PMM2-CDG. Not only does it help describe immunopathology in PMM2-CDG, but also identifies potential therapeutic targets to ameliorate immune-related symptoms in PMM2-CDG patients

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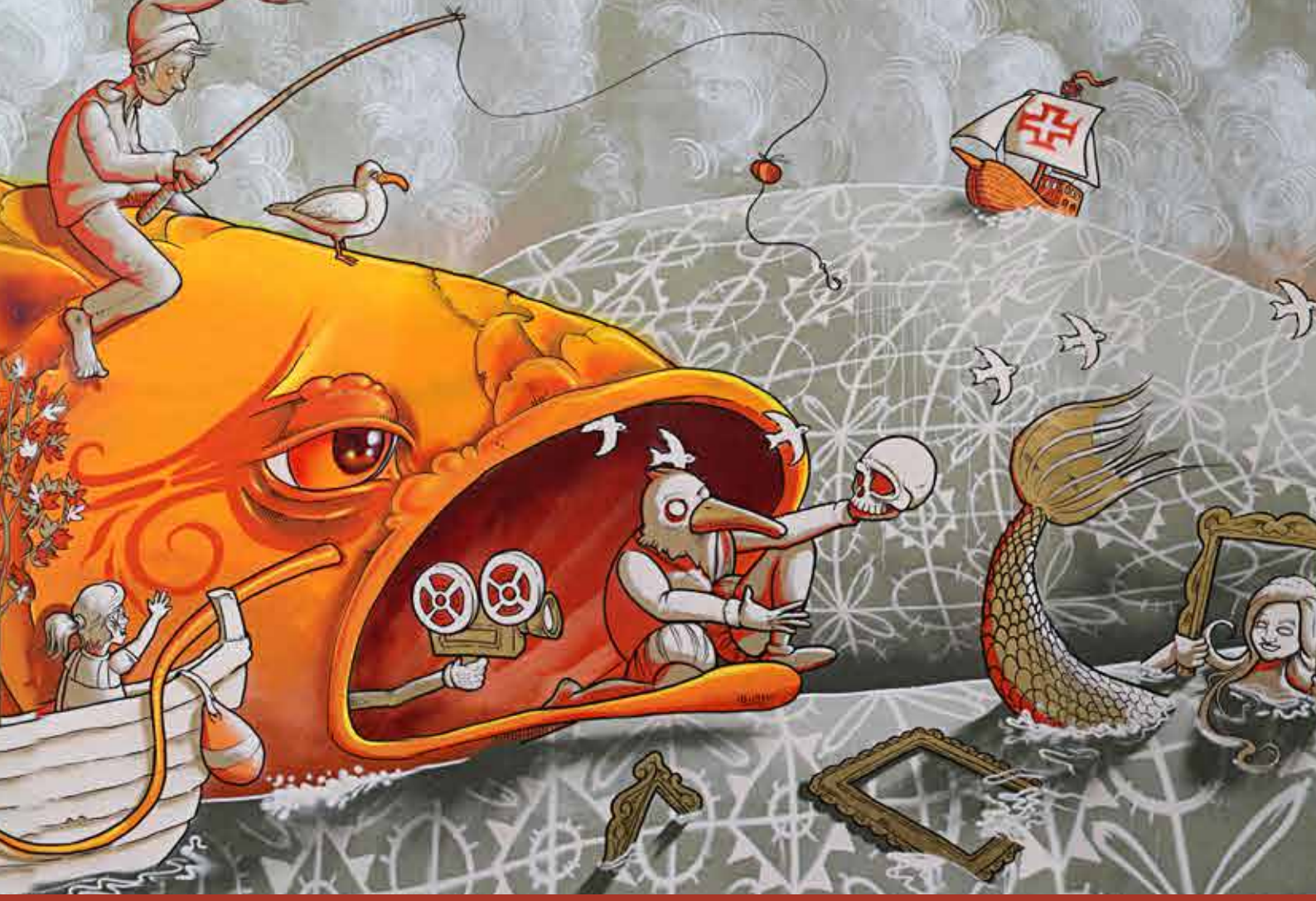

POSTERS COMMUNICATIONS

PO 01

18 MONTHS OF TREATMENT WITH TRIHEPTANOIN IN 2 PATIENTS WITH LONG CHAIN FATTY ACID OXIDATION DISORDERS

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Main category: Case series

Disease category: Intermediary metabolism: energy

Introduction: Long chain fatty acid oxidation disorders (LC-FAOD) are inborn errors of metabolism, also identified in newborn screening in Portugal. They interfere with adequate energy utilization, namely by muscles, heart and liver. Treatment aims to maintain patients in an anabolic state, with increase caloric intake, using carbohydrates and medium chain fatty acids (1).

Treatment with triheptanoin (THP), a synthetic seven-carbon fatty acid triglyceride compound with an anaplerotic effect that increases energy availability to the cell, has been advocated as an efficacious and safe therapy in LC-FAOD.

Methods: Retrospective revision of clinical records of 2 LC-FAOD patients comparing number, severity and admissions for rhabdomyolysis crises, maximum CK values and weight gain in a period of 18 months before and after treatment with THP.

Results/Case report: Patient 1 is a 12 year old male with VLCADD, with main manifestation being rhabdomyolysis crises. After he started THP we found a decrease in admissions (6 to 2), less rhabdomyolysis crises treated at home(5 to 3), and lower maximum CK values (72352 U/Lto 13.000U/L). He had a large increase in weight - 13kg in 18 months. He was able to start pool exercises with no rhabdomyolysis associated.

Patient 2 is an 8 year old male with LCAHDD, with main manifestations being rhabdomyolysis crises and retinopathy. After he started THP we found a decrease in admissions (4 to 1), no rhabdomyolysis crises treated at home and lower maximum CK values (100.000U/L to 19848 U/L). He also increased is weight - 7kg in 18 months. He plays football in school and swims with no rhabdomyolysis associated.

In both patients no major side effects were observed.

Conclusion: In our patients we could observe a reduction in the number of admissions, and less severe rhabdomyolysis crises after THP use. The weight gain was significative. There were no major side effects.

Despite regarding only two patients, our finding are in line with latest literature on THP and LC-FAOD (2,3), reinforcing the utility THP as one more tool in the treatment of these disorders with rhabdomyolysis as main manifestation. The weight increase is an issue to be aware and to address from the start of the treatment.

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PO 02

METABOLIC MYOPATHIES: EXPERIENCE OF A REFERENCE CENTRE OF INHERITED METABOLIC DISEASES

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Main category: Case series

Disease category: Intermediary metabolism: energy

Introduction: Metabolic myopathies (MM) are a heterogenous group of genetic disorders affecting metabolic pathways involved in energy production during rest, exercise, and physiologic stress (illness, fasting). Impairments in the pathways of glycolysis/glycogenolysis, fatty acid transport/oxidation or in mitochondrial respiratory chain present primarily with exercise intolerance, myalgias, weakness, cramps, or rhabdomyolysis. Depending on aetiology, the diagnosis can be made through neonatal screening, pre-symptomatic or in set of clinical manifestations, for which a high level of suspicion is important.

Methods: Retrospective descriptive study of the clinical, biochemical, and molecular features of patients with a confirmed diagnosis of MM followed by the multidisciplinary team of the Reference Centre of Inherited Metabolic Diseases of Centro Hospitalar Universitário de Lisboa Central, from 2009 to 2022.

Results/Case report: Twenty-three patients with MM were included: 9 (39%) glycogen storage diseases (7 McArdle and 2 Pompe), 7 (30%) fatty acid oxidation disorders (3 CPT2, 3 LCHAD and 1 MAD deficiencies), 6 (26%) mitochondrial disease with significant muscle involvement (2 Pearson, 1 Kearns Sayre, 1 VARS2, 1 SUCLA2 and 1 MT-TL1 deficiencies), and 1 myoadenylate deaminase deficiency. Ages varied from 15 months to 35 years. Eighteen (78%) patients were diagnosed by clinical symptoms, 3 by newborn screening (LCHAD) and 2 were asymptomatic (1 Pompe and 1 McArdle). Frequent symptoms were rhabdomyolysis triggered by illness or exercise 12 (52%), fatigue 11 (48%), exercise intolerance 10 (43%), and myalgia 9 (43%). Eight (35%) patients (LCHAD and mitochondrial) had multisystemic involvement. In 20 (87%) patients the diagnosis was confirmed by biochemical and/or genetic analysis and 3 (McArdle) by muscle biopsy.

Conclusion: MM are a heterogenous set of disorders but a careful history may guide the differential diagnosis among biochemical pathways and other aetiologies. Nowadays molecular testing has become a powerful tool for diagnosis confirmation, surpassing muscular biopsy in most cases. Accurate diagnosis is important to identify who may benefit from specific therapeutic options such as enzyme replacement therapy, restricted diets, emergency regime and cofactors. All patients benefit from adequate lifestyle modifications, individualized exercise prescription, nutritional intervention, and genetic counselling.

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PO 03

DIHYDROPTERIDINE REDUCTASE DEFICIENCY – A RARE AND POTENCIALY TREATABLE CAUSE MICKING CEREBRAL PALSY

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Main category: Case report

Disease category: Intermediary metabolism: others

Introduction: Dihydropteridine reductase deficiency (DHPRD) is a rare genetic disorder of tetrahydrobiopterin (BH4) regeneration, a cofactor for several enzymes, including phenylalanine hydroxylase. Due to hyperphenylalaninemia (HPA), patients can be detected by the newborn metabolic screening, when available. The most common symptoms of DHPRD may mimic cerebral palsy: developmental/cognitive impairment, hypotonia, peripheral hypertonia, dystonia, feeding difficulties, epilepsy and microcephaly. The long-term neurodevelopmental outcome is strongly influenced by the early initiation of effective treatment.

Results/Case report: A 2-year-old boy, born in Guinea, was evaluated in our center with the diagnosis of "cerebral palsy". He was born after a prolonged labor, had feeding difficulties and severe developmental delay. On examination presented microcephaly, axial hypotonia and dyskinetic movements without hypertonia. No seizures or oculogyric crisis were reported. Brain MRI showed slight brain atrophy and hyperintensity T2/FLAIR in basal ganglia. The diagnosis of cerebral palsy was questioned, and further investigation was carried out. HPA raised the possibility of BH4 deficiency, supported by increased biopterin in urine, decreased neurotransmitters in CSF and low DHPR enzyme activity. A variant (128_130del (p.(Val43del)) in apparent homozygosity was later detected in the QPDR gene. At 4 years old, he started L-dopa/carbidopa, oxitriptan and a phenylalanine restrictive diet with moderate clinical improvement.

Conclusion: When the diagnosis of "cerebral palsy" is questionable, other etiologies should be investigated, in particularly disorders that have specific disease-modifying treatment. In our patient the atypical constellation of neurological signs, brain MRI findings and nonexistence of newborn metabolic screening in the country of origin, supported additional investigation The presence of dystonia associated with HPA oriented the investigation, confirmed latter on to be DHPRD. Unfortunately, at this stage, the reversibility of the neurological damage in response to treatment is doubtful.

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PO 04

CHALLENGES IN GENETIC DIAGNOSIS OF MITOCHONDRIAL DISEASES: WHAT CAN FUNCTIONAL GENOMICS' STUDIES DO?

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Main category: Translational science study

Disease category: Intermediary metabolism: energy

Introduction: Mitochondrial oxidative phosphorylation (OXPHOS) diseases are challenging both from clinical and therapeutic perspectives. The advent of next generation sequencing (NGS) boosted discovery of new genetic defects affecting OXPHOS, with pathogenic variants identified in >350 genes to date[1]. However, in many patients, novel variants of unknown clinical significance are found. Subsequent functional studies may clarify its pathogenic consequences and modify variant's classification, establishing a genetic diagnosis[2,3].

Methods: Analysis of data obtained from patients (P1-P5) with novel genetic causes and functional genomics' studies performed, namely OXPHOS respiratory/glycolytic rates (Seahorse XF), enzymatic activity and assembly (BN-page), protein levels (SDS-WB), single muscle fiber assay, NGS and bioinformatics.

Results/Case report: P1-Leigh syndrome (40y, male); Complex IV activity deficiency (full assembly absent), homozygous deletion (c.-11_13del, SURF1), not detected by NGS[2]. P2-Epileptic encephalopathy (8y, male); homozygous c.882-1G>A, FASTKD2; OXPHOS decrease; reduced FASTKD2 expression and abnormal respiratory/glycolytic rates. P3-Cardiomyopathy/nephropathy (39y, male); c.29G>C, FASTKD2; OXPHOS decrease; reduced FASTKD2 levels. P4-CPEO (62y, female); multiple OXPHOS deficiency; mtDNA alterations (m.7486G>A, MT-TS1; 4,977bp del); higher levels of mutant mtDNA alterations in COX-deficient fibers[3]. P5-Polyneuropathy (15y, female); heterozygous c.1437C>A, POLG; combined def. or normal OXPHOS activity/respiratory capacity (tissue variable), raised CI assembly; normal POLG levels. Also, proteins' expression levels were reduced (P1-4), confirming pathogenicity. In P5, data do not support pathogenicity.

Conclusion: If specific functional results are similar to controls, one might inquire about the pathogenicity of the studied variant and more genetic or bioinformatics analyses and family investigations are needed. There are also limitations of NGS in mutation detection that Sanger sequencing can overcome (P1). When performed first, the OXPHOS activity may guide to genetic screening or interpretation, concordant to later assembly results. All cases were solved and data may be crucial for genetic counseling.

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PO 05

CLINICAL, BIOCHEMICAL AND MOLECULAR FEATURES OF A COHORT OF 8 PATIENTS WITH INHERITED DISORDERS OF VITAMIN B12 METABOLISM IN A METABOLIC REFERENCE CENTER

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Main category: Case series

Disease category: Cofactor and mineral metabolism

Introduction: Vitamin B12 or cobalamin (Cbl), undergoes a complex series of absorptive and intracellular processing steps before serving as cofactor for the enzymes methylmalonyl-CoA mutase and methionine synthase (1). Disorders of intracellular cobalamin metabolism have variable phenotype and age of onset related to the location of the defect in the metabolic pathway leading to a combined methylmalonic acidemia and homocystinuria (cblC, cblD, cblF and cblJ), Isolated methylmalonic acidemia (cblA, cblB and cblDv2) and isolated homocystinuria (cblDv1, cblE and cblG). (2)

Methods: We conducted a retrospective study of the clinical biochemical and molecular features of a cohort of patients with disorders of intracellular Cbl metabolism followed in the our Reference Centre of Inherited Metabolic Diseases (CR-IMD) for the last 23 years (2000-2023)

Results/Case report: - CblC: P1 and P2, pré-newborn screening (NBS), had an early and severe presentation evolving to multiorgan failure and death. P3 was asymptomatic at NBS with an excellent evolution except for nystagmus and retinitis pigmentosa. P4 presented at 19Y with an atypical hemolytic uremic syndrome and is presently on hemodialysis.

- CblD: P5 had developmental delay (DD) and hypotonia and presented at 14m with seizures

- CblDv2: P6 had DD and failure to thrive (FTT) and presented at 4Y with acute metabolic acidosis

- CblDv1: P7 had DD, FTT, and hypotonia and presented at 16m with seizures and anemia,

- CblG: P8 had DD and FTT and presented at 15m with macrocytic anemia.

In all, characteristic biochemical profile guided the diagnosis, afterwards confirmed by genetic analysis (4 MMACHC, 3 MMADHC, 1 MTR). All patients received either betaine, hydroxycobalamin, or both(P3 is on very high dosage).

Conclusion: Our cohort of patients has similar clinical and biochemical characteristics with the ones described in the literature. Outcomes of patients reinforce the importance of newborn screening and the need for consensus guidelines for optimal doses of parenteral hydroxocobalamin.

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PO 06

EFFECT OF SHORT-PEPTIDES ON THE STABILITY AND ACTIVITY OF HUMAN PHENYLALANINE HYDROXYLASE

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Main category: Basic science study

Disease category: Intermediary metabolism: nutrients

Introduction: Molecular chaperones Hsp90 and Hsp70, assisted by co-chaperones, are among the Proteostasis Network (PN) elements involved in the cytosolic folding and conformational maintenance of proteins. Recently, DNAJC12 was identified as the co-chaperone on Hsp70-assisted folding of human phenylalanine hydroxylase (hPAH), both wild-type and variants causing phenylketonuria, directly interacting with hPAH. We posited that the specific DNAJC12 amino acid sequences interacting with hPAH may contribute to protein stabilization promoting the folding of hPAH variants and rescuing their biological function.

Methods: In silico tools were used to map DNAJC12/hPAH interacting regions contributing for hPAH stabilization/folding. Short-peptides (PEPs) were synthesized based on the retrieved sequences and their effect on hPAH activity and structure were studied by DSF and ITDF.

Results/Case report: Four putative DNAJC12/hPAH interacting regions were identified by computational methods. Disclosed DNAJC12 sequences were optimized (relative free-energies of binding, solvent-accessible surface area, residue's contact frequencies, and hydrogen bonding/salt bridging formation) and four short-peptides were synthesized (PEP1, PEP2, PEP3 and PEP4). Their effect on the activity and stability of recombinant hPAH was studied. None of the designed peptides promoted an increase in hPAH thermostability (Tm), as monitored by DSF.

However, kinetics of thermal denaturation (ITDF), showed that at 42 °C PEP2, PEP3, PEP4 promoted a decreased hPAH thermal denaturation, which was also observed at 52 °C for PEP4. Additional studies on the time-dependent thermal enzymatic inactivation profile of hPAH, at 42 °C, showed that the protective effect detected by ITDF was also observed on the hPAH activity.

Conclusion: Obtained data indicates that among the designed 4 peptides, 3 (PEP2, PEP3 and PEP4, are putative stabilizers of hPAH wild-type. Importantly, in the presence of PEP3 the hPAH wild-type activity was ~20% higher than in the absence of peptides during 90 min of incubation at 42 °C. These studies will be extended to hPAH variants, in particular to those that are non-responsive to BH4 therapy. In addition, by establishing the proof-of-concept the designed strategy will have a great potential to be applied to other inherited metabolic disorders for which PN pathways are already identified.

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PO 07

CITRULLINEMIA AND WHAT ELSE?

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Main category: Case report

Disease category: Intermediary metabolism: nutrients

Introduction: Citrullinemia type I (CTLN1) is a rare autosomal recessive metabolic disorder. Symptoms typically include vomiting, lethargy, seizures and coma. In neonatal presentation, death occurs in days, if untreated. Survivors may evolve with neurocognitive dysfunction.

Results/Case report: Two 10 YO, non-identical, twin sisters (S1; S2) with citrullinemia type I were born after a 36W gestation: S1 by eutocic delivery and S2 by cesarean section with nuchal cord (Apgar score 5/10). On day four, S2 presented hyperammonemia with coma. S1 had no complications. Diagnosis followed that of S2.

Neurocognitive development was monitored 3 months - 4 years of age with Griffiths Scales (1): global development quotient kept within the average, but S2 had a deficit in language and eye and hand coordination.

At 5 years, the neurocognitive abilities were evaluated using WPPSI-R (2). S2 revealed difficulties in verbal area (vocabulary, comprehension and memorizing sentences), with a lower average verbal intelligence quotient (IQ). S1 had high average IQ. Due to learning difficulties, S2 was reassessment at 8 YO with WISC-III: full-scale IQ -"extremely low".

Conclusion: These non-identical twin sisters share the same citrullinemia type 1 causing variants in the ASS1 gene. Nevertheless, their clinical presentation and neurocognitive evolution are diverse. Other factors, like the different genetic background and perinatal issues such as the type of delivery and its circumstances and the neonatal coma episode of S2 may explain the dissimilar evolution. Maximum ammonium levels (and its duration) are critical for the patients' neurodevelopment: 131 in S1 and 546 umol/l in S2.

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PO 08

PATIENT PREFERENCE INFORMATION (PPI): A QUALITATIVE STUDY TO INFORM SYMPTOM PRIORITIZATION IN CONGENITAL DISORDERS OF GLYCOSYLATION (CDG)

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Main category: Translational science study

Disease category: Several disease categories

Introduction: Congenital Disorders of Glycosylation (CDG) are a large group of rare metabolic diseases that usually have a multi-systemic involvement, making it difficult to develop therapies[1]. Despite this challenge, there are few ongoing clinical trials for CDG, but it is important to define clear clinical endpoints. Patient Preference Information(PPI) is an essential tool, as it helps regulators assess the risks and benefits of potential treatments [2, 3]. This study aims to identify the main signs and symptoms CDG patients and families consider most important for improving their quality of life

Methods: The SPQCDG questionnaire was created to assess how patients and their families prioritize different signs and symptoms. In order to increase the number of people who respond, a multi-channel approach was used to disseminate the questionnaire, and it was translated into seven different languages.

Results/Case report: A total of 164 individuals participated in the study, consisting of 4 patients (2.4%) and 160 family relatives (97.6%), comprising 34 different CDG. The majority of respondents live with PMM2-CDG (n=91, 55.5%), the most prevalent CDG in the world. Other CDG represented in this study were PIGN-CDG (13, 7.9%), PIGA- and ALG1-CDG (6, 3.7%), and ALG13- and ALG6- CDG (5, 3.0%). The most commonly reported signs and symptoms were neurological (146, 89.6%), ophthalmologic (124, 75.6%), and problems related to the gastrointestinal system (92, 56.1%).

The results indicated that respondents prioritize intellectual development delay (105, 63.6%), gross motor disability (105, 63.6%), and seizures (83, 50.3%) as the most important symptoms to treat. Signs and symptoms related to the reproductive system, like infertility (91, 55.2%), and ophthalmologic conditions like strabismus (72, 43.6%) were the

Conclusion: CDG patients and families prioritized the treatment of signs and symptoms associated with the central nervous system, as they cause neuronal impairment and lack of neuromuscular balance and coordination. To the best of our knowledge, this is the first PPI study giving the CDG community a voice to express their unmet needs related to the prioritization of symptoms. These findings provide valuable insights for decisions-makers involved in the design of clinical trials aimed at developing targeted therapies to improve the quality of life of CDG patients.

PO 09

LINCE PROJECT: A RAPID DIAGNOSIS OF NEURONAL CEROID LIPOFUSCINOSES 1 AND 2

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Main category: Basic science study

Disease category: Intermediary metabolism: nutrients

Introduction: The Neuronal Ceroid Lipofuscinosis (NCL) are a heterogeneous group of neurodegenerative lysosomal storage disorders with onset essentially in childhood. Recently, in Portugal the LINCE Project emerged with the aim of making clinicians aware of the importance of an early diagnosis for NCLs. This project is a scientific partnership of the Portuguese Society of Neuropediatrics and the Portuguese League Against Epilepsy with the laboratory partnership of the National Institute of Health Dr. Ricardo Jorge.

Methods: This project is a diagnostic tool for NCL1 and NCL2. The activity of the lysosomal enzymes palmitoyl protein thioesterase 1 (PPT1) and tripeptidyl peptidase 1 (TPP1), respectively, were determined in dried blood spots (DBS).

Results/Case report: The preliminary results of this project will be presented, with regard to the number of samples studied, phenotypic presentation, age range and identified patients.

Conclusion: The LINCE project allows, in an easy and simple way, to identify and characterize cases of NCLs existing in paediatric age allowing an early intervention.

PO 10

MIT.ONOFF – SCIENCE COMMUNICATION FOR PUBLIC AWARENESS ABOUT MITOCHONDRIAL CYTOPATHIES

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Main category: Other

Disease category: Intermediary metabolism: energy

Introduction: Mitochondrial diseases are rare, heterogeneous, incurable and complex to diagnose. Probably due to its rareness, there is still a lack of literacy in this area, especially in society, but also in schools and in general health care services. Accordingly, tools that may bring light to science and health literacy are needed. Mit.OnOff is a science communication project, based on a bilateral partnership between the University of Coimbra (Portugal) and the University of Bergen (Norway). It aims to inform society about rare diseases -mitochondrial cytopathies - with emphasis on LHON.

Methods: The initiative focuses on the creation of an illustrated book explaining the diseases caused by the failure of energy production in simple and accessible language. The aim is to raise awareness (particularly in Portugal and Norway) and give greater visibility to people suffering from these diseases.

Results/Case report: This project involves expert scientists in the field of mitochondrial disease, science communicators and artists, in alignment with the United Nations SDGs, agenda 2030. Mit.OnOff is a bilateral partnership (Portugal and Norway) established to address the lack of science and health literacy on the subject of mitochondrial disease. The book will be distributed in both countries, creating a sense of inclusion and visibility and influencing decisions regarding these diseases. It is a relevant educational medium (e.g. schools, health care provision). The distribution of the book is complemented with other communication materials. Oral communications are made, together with public involvement in which special glasses will be distributed to simulate a mitochondrial disease that leads to blindness (LHON), for the public to experience what it is like living with a rare disease.

Conclusion: It is hoped that the production of this book will give patients a sense of inclusion and representation in the media. This, in turn, will contribute to achieving the SDG targets (3,4,5,8,10,12), i.e. ensuring people live healthy lives, reducing child mortality and increasing life expectancy; ensuring access to inclusive, equitable and quality education for all; ensuring gender equality; contributing to a peaceful and prosperous world.

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PO 11

POMPE DISEASE: PHENOTYPE, GENOTYPE AND GLC4 BIOMARKER

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Main category: Case series

Disease category: Complex molecule and organelle metabolism

Introduction: Pompe disease (PD, MIM 232300) is an autosomal recessive lysosomal storage disorder caused by pathogenic variants in the GAA gene (MIM 606800) that encodes the lysosomal acid alpha-1,4-glucosidase (GAA). GAA deficiency leads to glycogen accumulation, especially in cardiac and skeletal muscles. PD classification includes infantile onset and late-onset (IOPD and LOPD).
Complete characterization of patients involves quantification of GAA enzymatic activity in leucocytes, dried blood spots or cultured skin fibroblasts, Glc4 tetrasaccharide urinary excretion and confirmation by gene analisys.

Methods: Authors collected data from 12 PD patients, including GAA enzyme activity, genotype and urinary Glc4, aiming to establish a correlation between laboratory parameters to define prognosis and specific treatments. Urinary Glc4 quantification was performed through an in-house LC-MS/MS method.

Results/Case report: The retrospective study of the PD patients (3 IOPD and 9 LOPD) included GAA enzyme activity determination in leukocytes and GAA sequencing prior to Glc4 quantification. In our cohort, IOPD patients' age was below two years old, and the mean urine Glc4 concentration was 56 mmol/mol of creatinine, five times higher than the upper limit of the age-matched reference range. More importantly, Glc4 urinary concentration revealed an inversely proportional correlation between the patient's age and urinary tetrasaccharide excretion. Regarding the nine LOPD patients aged 7 to 53, Glc4 excretion had a mean concentration of 4.6 mmol/mol of creatinine, within the age-matched reference range. Six patients were homozygous or compound heterozygous for the IVS1-13T>G pathogenic variant, the most common in the Portuguese population, accounting for 36% of the pathogenic alleles.

Conclusion: With 80% of LOPD from a total of 65 patients diagnosed in our laboratory, period prevalence of PD in Portugal is 2,7787 per 100000 live births. Current work supports evidence that Glc4 is a valuable biomarker as a non-invasive method to screen IOPD patients before a second-tier test. It is also valuable in the case of pseudodeficiencies, independently of the variant classification, given the normal excretion of Glc4. Early diagnosis is essential to anticipate treatment and reduce irreversible organ damage associated with PD progression; moreover mandatory for genetic counseling.

PO 12

EXPERIENCE OF MIGLUSTAT THERAPY IN PEDIATRIC PATIENTS WITH NIEMANN-PICK TYPE C DISEASE

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Main category: Case series

Disease category: Complex molecule and organelle metabolism

Introduction: Niemann-Pick disease type C (NP-C) is an inherited neurovisceral lysosomal lipid storage disease characterized by progressive neurological deterioration, an estimated incidence of 1/100.000. Different clinical forms have been defined based on patient age at onset: perinatal, early infantile (EI), late-infantile (Li), juvenile and adult. Approximately 95% of patients harbour mutations in NPC1, the remainder in NPC2. To date, miglustat is the only treatment specifically approved in the European Union (EU) for the treatment of progressive neurological manifestations in patients with NP-C. [1,2,3]

Methods: We have carried out a retrospective, descriptive study by reviewing the clinical histories of all NP-C patients treated with miglustat followed in the Hereditary Metabolism Diseases Unit of Centro Materno Infantil do Norte – CHUdSA.

Results/Case report: Six patients (4 male; 2 female) were included: 1 EI, 3 Li (case 2-4) and 2 juvenile forms (case 5-6). All had NPC1 pathogenic variants. Li manifestations included slow motor function, ataxia, speech delay, dystonia. Cases 1-5 required a gastrostomy for dysphagia and feeding difficulties. Juvenile form presentation included praxis disorders, cerebello-dystonic syndrome, cognitive decline, and swallowing disorder. Vertical gaze palsy was universal. Patient 1 (EI) began therapy 14 months after disease onset was treated for 12 months (stop therapy because of no clinical improvement). The median interval between onset and treatment was 3 years in Li, with a mean duration of 38.7 months and a current mean 5-domain NPC score of 20. Case 5 has died. Case 6 was diagnosed after her sister and began therapy with an NPC score of 2 She is under miglustat for 30 months with a current NPC score 3

Conclusion: NP-C diagnosis is often delayed due to the heterogeneous presentation and early non-specific symptoms. Miglustat affects the disease hystory by stabilizing or delaying the neurological progression. The progression of the disease is faster in the early presentations, potentially with a minor impact of miglustat, particularly when treatment is started in a more advanced phase of the disease. Accordingly, our patients with later presentations and smaller interval between onset and treatment had a better response to therapy.

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PO 13

MMA AND PA: DIETARY INTAKE IMPACT IN ANTHROPOMETRIC EVOLUTION

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Main category: Basic science study

Disease category: Intermediary metabolism: nutrients

Introduction: Methylmalonic acidemia (MMA) and propionic acidemia (PA) are inborn errors of metabolism caused by deficiencies of enzymes or cofactors that contribute to the breakdown of the branched-chain amino acids (BCAA) L-isoleucine and L-valine.1 In both diseases, dietary treatment consists of a protein-restricted diet. However, current guidelines advise an intake of 100% of the safe levels of protein defined by the World Health Organization (WHO).2

Methods: Case series study of 4 pediatric patients with organic acidurias followed at a Metabolic Disease Reference Center. Authors evaluated patient´s growth evolution and dietary intake during the acute crisis and follow-up, for one year, according to the most recent treatment guidelines in the literature.

Results/Case report: Two patients were diagnosed with MMA and 2 with PA. All the patients were identified by newborn screening. Three patients were male, one female, and current age between 5 and 15 years. Regarding the observational study period, the weight z-score ranged between -4.555 and 0.634; the heigh z-score ranged between -3.617 and 1.062 and the Body Mass Index (BMI) ranged between -4.682 and 0.48. Three patients had 2 decompensation episodes. During decompensations, a partial urgent or urgent regimen was instituted, in which protein intake was reduced between 50-94%. As expected, the patient without decompensations had the higher anthropometric z-scores.

Conclusion: Three out of four patients showed growth below the z-score percentiles, most evident for the youngest patient. During the follow-up, protein intake met the WHO safe levels for all patients and the protein-energy ratio remained between 2-2.5g/100kcal/day, agreeing with the latest recommendations1. Although, during the acute episodes, a major protein reduction was necessary, with a negative impact in patient´s growth. Consequently, even when reaching the recommended intakes, these diseases seem to have a negative impact on growth.

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PO 14

CALCIUM, VITAMIN D, AND BONE MINERAL DENSITY STATUS IN PATIENTS WITH CLASSIC GALACTOSEMIA

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Main category: Basic science study

Disease category: Intermediary metabolism: nutrients

Introduction: Classic galactosemia is a rare inherited disorder of galactose metabolism. Although good adherence to a lifelong galactose-restricted diet leads to a good physical development, cognitive and performance parameters often become subnormal. The objective was to describe the calcium (Ca), vitamin D (Vit D) and bone mineral density status of patients with classic galactosemia followed at the Reference Centre for Inherited Metabolic Diseases of the Centro Hospitalar Universitário de Santo António (Porto, Portugal).

Methods: Retrospective observational study resorting to digital clinical records since 2009. Anthropometric data, Vit D and Ca intake were collected from Nutrition appointments. Blood samples were taken regularly. Bone mineral density was assessed by DEXA (lumbar spine).

Results/Case report: Nine patients currently aged between 15-41y were included (3 females; 2 asymptomatic diagnosis). All patients adhered well to a galactose-restricted diet since diagnosis. Only 2 of 62 total erythrocyte galactose measurements were ≥5 mg/dL (mean±sd: 3.2±1.1mg/dL). In the last assessment, BMI was within normal range in adult patients (mean±sd: 20.4±2.67kg/m2), the youngest was underweight. Mean dietary Ca and Vit D intake was 809±471.1mg/d and 8±6.7ug/d, respectively. Mean±sd serum Ca and Vit D levels were 2.40±0.12mmol/L and 70±28.2 nmol/L, respectively. The mean±sd z-score in the last DEXA was -1.5±0.72, within the expected range for age according to ISCD, however the mean over time correspond to osteopenia in 3 patients. Five patients (56%) had mean serum Vit D<75nmol/L but none had mean Ca<2.15mmol/L. In the low serum Vit D group, the prevalence of osteopenia was higher (40% vs. 25%).

Conclusion: Although adherence to dietary treatment and compliance with the supplementation on Ca and Vit D appears to be good, cases of osteopenia have occurred. Deficits of serum Vit D, as opposed to Ca, have been observed. We therefore suggest a greater focus on nutritional consultation, evaluating the frequency of consumption of foods that provide Vit D and promoting their ingestion. It would also be useful to reflect on the pharmaceutical form and frequency of supplements that have been prescribed, since in some cases it may affect the patient adherence and therapeutic efficacy.

PO 15

SEIZURES AND CEREBRAL HAEMORRHAGIC CYSTS IN A THREE-DAY OLD NEWBORN – AN UNUSUAL AETIOLOGY

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Main category: Case report

Disease category: Cofactor and mineral metabolism

Introduction: Neonatal seizures and neurologic dysfunction are most commonly associated with hypoxic-ischemic encephalopathy, ischemic or haemorrhagic injuries, electrolyte imbalance, hypoglycaemia, congenital abnormalities, and infection. A high index of suspicion for a metabolic disease should be present when there is an early onset or inadequate response to anti-seizure therapy. Findings in electroencephalogram and brain imaging are usually nonspecific but can be highly suggestive.
Multidisciplinary discussions and comprehensive laboratory studies are essential to achieve a correct diagnosis.

Results/Case report: Term female newborn with an unremarkable prenatal and birth history, presented with feeding difficulties, hypertonia, and progressive epileptic encephalopathy since 3rd day of life. Sepsis workout was negative. MRI (5thday) revealed cerebral edema, T2 hyperintensity in basal ganglia and multiple haemorrhagic cystic and punctiform lesions. Serial electroencephalograms showed a burst-suppression pattern with multifocal seizures. Initially, uric acid and Sulfitest® were normal, but later, absent blood uric acid, blood taurine increase, cystine decrease and urinary sulphocysteine and thiosulfate increase were found. A homozygous pathogenic variant in the MCOS1 gene was found, confirming Molybdenum cofactor deficiency (MoCD) type A. She was discharged at 7 weeks of life, feeding autonomously and with a triple anti-epileptic regimen. Typical dysmorphic features were already evident.

Conclusion: This report summarizes an early-onset neurometabolic syndrome caused by MoCD type A, an extremely rare autosomal recessive disease that leads to sulphite intoxication and irreversible brain injury in the first few days of life. A high level of suspicion and investigation by an experienced multidisciplinary team is essential to achieve early diagnosis. This should allow the team to proper inform parents of the prognosis as well as provide adequate genetic counselling for future gestations. Therapy with cyclic pyranopterin monophosphate can change the prognosis only if used pre-symptomatically.

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PO 16

THE ODYSSEY JOURNEY OF CONGENITAL DISORDER OF GLYCOSYLATION (CDG): A COMMUNITY-CENTRIC APPROACH

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Main category: Other

Disease category: Several disease categories

Introduction: Congenital disorders of glycosylation (CDG) are a group of rare genetic metabolic diseases that result from defects in the glycosylation pathways. CDG has an overall prevalence of 0.1-0.5/100,000 in Europe. The large and increasing number of potentially affected genes and associated clinical phenotypes make CDG diagnosis a challenge which results in many CDG cases remaining underdiagnosed and undertreated[1,2]. Hence, there is a need to identify the current gaps in the healthcare system along the patient's journey, from symptoms onset to definitive diagnosis and following that.

Methods: The CDG Journey Mapping questionnaire was developed to overcome this need and adapted to both professionals and families/patients. The questionnaire encompasses the first signs and symptoms and families' informational needs.

Results/Case report: A total of 160 families and 35 professionals completed the questionnaire. From the family group, PMM2-CDG (MIM: 212065) was the most common CDG (n = 89; 55.6 %). Therefore, due to underrepresentation of other CDGs, two groups were formed -PMM2-CDG and Non-PMM2-CDG- with the goal to gain a thorough understanding of their journey. Concerning symptom onset, hypotonia and developmental delays are the main symptoms identified in both groups. Some signs and symptoms can be recognized as unique clinical features in one group and not the other, namely strabismus (adj-p = 4.56e-7, Cramer's V = 0.40) and seizures (adj-p = 1.52e-9,C'V = 0.50) for the PMM2-CDG and Non-PMM2-CDG groups, respectively. Concerning informational needs, interestingly, a mere 65.6% (n=105) of individuals who were diagnosed received the information orally, emphasizing the need for diverse methods to convey crucial info.

Conclusion: Understanding the CDG patient journey will enable stakeholders to address the needs of the community. For example, CDG professionals and families may contribute towards improving standards of care and mitigating the current needs of the different CDG populations as well as help establish or improve clinical management guidelines.

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PO 17

A DIAGNOSTIC CHALLENGE IN A RARE CASE OF PAROXYSMAL DYSKINESIA ASSOCIATED WITH GLUCOSE TRANSPORTER DEFICIENCY SYNDROME

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Main category: Case report

Disease category: Intermediary metabolism: energy

Introduction: Classic GLUT1 deficiency syndrome (GLUT1DS) presents as an epileptic encephalopathy, with epilepsy developing within the 1st year of life, followed by global developmental delay, a complex movement disorder, and secondary microcephaly. Nonclassical GLUT1DS cases are rare and present as a complex movement disorder without epilepsy, characterized by ataxic-spastic gait, limb dystonia, chorea, tremor, myoclonus, dyspraxia, and nonkinesigenic dyskinesias. Nonepileptic paroxysmal events may be triggered by fasting and stress states. Milder disease has also been described in some adults.

Methods: We performed a retrospective review of our patient's medical records.

Results/Case report: We report a teenage girl born to nonconsanguineous parents presenting with paroxysmal dyskinesias since age 2. Her family history was unremarkable. Paroxysmal events occurred twice a year and consisted of erratic limb and facial movements, mostly limited to one or few body segments and alternating hemiplegia. Ictal EEG showed generalized paroxysmal brain activity. Brain MRI was normal. Initially, the clinical picture suggested a focal form of epilepsy, and valproic acid was initiated, but with poor response. Cerebrospinal fluid (CSF) analysis revealed hypoglycorrhachia and a CSF-to-blood glucose ratio of 0.48. Genetic testing via a next-generation sequencing multigene panel including 7 genes associated with paroxysmal dyskinesias detected a heterozygous missense variant in SLCA1: c.388G>A, p.(Gly130Ser), classified as pathogenic and confirmed to be the novo after parental studies.

Conclusion: Our patient represents a rare phenotype of GLUT1DS, accounting for only 10% of cases. CSF analysis is a diagnostic clue, even in nonclassical presentations. Establishing the diagnosis of GLUT1DS was essential to this patient's management since the ketogenic diet is the most successful treatment for this syndrome and valproic acid should be avoided. This case supports the genotype-phenotype correlations that have been established since missense variants are thought to occur in association with milder phenotypes. Parental molecular testing confirmed the couple has a low recurrence risk.

PO 18

UNIPARENTAL DISOMY AS A MECHANISM FOR COMBINED OXIDATIVE PHOSPHORYLATION DEFICIENCY ASSOCIATED WITH MRPS34 GENE

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Main category: Case report

Disease category: Intermediary metabolism: energy

Introduction: Mitochondrial oxidative phosphorylation (OXPHOS) is a cellular process that generates most of the cellular energy required by the body. Disorders affecting OXPHOS are multisystem diseases caused by pathogenic variants in more than 50 genes. In 2017, biallelic variants in the MRPS34 gene were shown to cause combined oxidative phosphorylation deficiency type 32 (COPD32) (OMIM#617664), with only seven patients reported in the literature to this moment. COPD32 is characterized mainly by a severe Leigh-like syndrome.

Methods: Whole-exome sequencing identified a homozygous pathogenic variant in the MRPS34 gene: c.322-10G>A (p.?). Only the mother was heterozygous for this variant. SNP-array analysis revealed a region of an absence of heterozygosity in 16q with 9.8Mb, compatible with maternal uniparental disomy.

Results/Case report: We report an 18-year-old female with unremarkable family history. The pregnancy was complicated by oligohydramnios, and the neonatal period was unremarkable. She evolved with low weight, mild-moderate developmental delay/intellectual disability, and hypogonadotropic hypogonadism. On examination, she had slender habitus, joint laxity, and kyphoscoliosis. The cardiac evaluation was normal, and the head MRI showed bilateral olivary nucleus degeneration that was not subsequently confirmed. Extensive metabolic studies documented only mild lactate and pyruvate and alanine elevation, and the chromosomal microarray was normal.

Conclusion: We report the first patient with COPD32 due to partial maternal uniparental disomy of chromosome 16, who is the first in Portugal and only the seventh in the literature. Contrarily to previous patients, who died in the first months of life or survived with severe DD/ID and had a Leigh-like syndrome, this case is significantly milder, contributing to a better characterization of the phenotypic spectrum. The recurrence risk is unexpectedly low in this instance. This case illustrates the importance of segregation analysis in patients with homozygous recessive mutations.

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PO 19

BIOCHEMICAL AND ANTHROPOMETRIC OUTCOMES IN PAEDIATRIC PATIENTS WITH HETEROZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA AFTER COVID-19 PANDEMIC LOCKDOWNS: AN EXPLORATORY ANALYSIS

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Main category: Other

Disease category: Lipid metabolism and transport

Introduction: The COVID-19 pandemic lockdowns caused difficulties in access to healthcare services and affected the eating habits and physical activity of children and adolescents, leading to a surge in childhood obesity. Patients with familial hypercholesterolemia (FH) may be more vulnerable to the lockdown effects given their high risk of cardiovascular disease. Despite limited evidence of lipid profile deterioration in adults with FH, data is lacking in paediatric ages. We investigated the impact of lockdowns on lipid profile and anthropometry in paediatric patients with FH in an exploratory analysis.

Methods: Blood lipids and anthropometry were measured once in September 2021 – April 2022 on paediatric patients with FH at our Reference Centre and retrospectively compared with pre-pandemic values. The study was designed and approved by the Ethics Committee post-lockdowns. Informed consent was given.

Results/Case report: The study included 30 participants aged 1 to 16 years, with a median of 11 years (57% female) at baseline. At baseline, 8 participants were on lipid-lowering drugs vs. 9 post-pandemic. Half of the participants had zero or one consultation with the Reference Centre paediatricians from March 2020 to August 2021. No significant changes were found in lipid profiles from baseline to post-pandemic. The median [P25-P75] blood LDL-C concentration was 125 [112-150] mg/dL pre-pandemic vs. 125 [100-147] mg/dL post-pandemic (p=0.89); HDL-C was 58 [52, 65] mg/dL vs. 56 [51, 61] mg/dL (p=0.11); triglycerides were 64 [44, 86] mg/dL vs. 59 [42, 86] mg/dL (p=0.18); and total cholesterol (available in 10 participants) was 197 [178, 228] mg/dL vs. 211 [157, 244] mg/dL (p=0.92). Change in BMI z-score was not significant (0.19 [-0.58, 0.89] pre-pandemic vs. 0.30 [-0.48, 1.10] post-pandemic, p=0.52).

Conclusion: Non-deterioration of lipid and anthropometric profiles during the COVID-19 pandemic may be seen as a positive outcome since some worsening was expected. We speculate that the Reference Centre clinical team was successful in educating patients and families on the health risks of FH, making them more prone to uphold healthy habits during lockdowns. However, these findings must be interpreted with caution given the small and heterogeneous study sample. Further research using a multicentric approach would be crucial to gain a better understanding of the impact of lockdowns in this population.

PO 20

NEONATAL GLYCOGEN STORAGE DISEASE TYPE IA: A RARE PRESENTATION

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Main category: Case report

Disease category: Intermediary metabolism: nutrients

Introduction: Glucose homeostasis is essential to energy production and function of the central nervous system, depending on glycogen metabolism. Glycogen storage diseases (GSD) are caused by enzymatic defects of the glycogen degradation and involve mainly the liver since the inhibition of hepatic glycogen breakdown results in its excessive storage and hepatomegaly. Other findings are hypoglycemia and hyperlactatemia and consequent neurological symptoms. GSD Type Ia is a severe disease with clinical manifestations usually occurring in the first months. Morbidity and mortality are high, when not treated.

Results/Case report: Term male newborn, of a non-consanguineous couple, born by eutocic delivery and weight 3760g. Day 2, weight loss >10%, jaundice were noticed, and physical examination as normal. The investigation showed low glucose that only respond to iv glucose, metabolic acidosis, hyperlactatemia and elevated liver enzymes. Considering a inherited metabolic disease he was transfer to the Reference Center. Complementary tests showed hypertriglyceridemia and absence of ketone bodies. Abdominal US revealed a liver in the upper limit of normal. Most likely clinical diagnosis was GSD type Ia, confirmed by genetic test. He needed iv glucose, but then stabilized with formula without galactose, supplemented with dextrin every 2 hours. He is now 7 months old, has flash glucose self-monitoring system, maintaining frequent feedings, with sporadic hypoglycemia. Normal physical development and no hepatomegaly.

Conclusion: Hypoglycemia and early weight loss in newborns are red flags for metabolic diseases or other conditions. When accompanied by other metabolic findings, as hyperlactatemia and metabolic acidosis, associated with short fasting periods, glycogen metabolism disorders must be considered. Patients with GSD Type Ia generally appear normal at birth and it is not frequent such an early presentation, within the first hours after birth. Avoiding fasting and hypoglycemia are of vital importance, for better cognitive outcome, global prognosis and prevention of other metabolic abnormalities.

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PO 21

SERAC1 DEFICIENCY, A NEW PHENOTYPE?

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Main category: Case report

Disease category: Intermediary metabolism: energy

Introduction: SERAC1 deficiency phenotype range from MEGD(H)EL syndrome, the most severe, to juvenile complicated spastic paraplegia, to adult onset dystonic features (in only one patient). The MEGD(H)EL syndrome is characterized by (3-methylglutaconic aciduria with deafness-dystonia, [hepatopathy], encephalopathy, and Leigh-like syndrome). Biochemical abnormalities: elevated urinary 3 – metilglutaconic and 3-metilglutaric acids, high lactate and alanine in serum. Diagnosis is confirmed when biallelic pathogenic variants in SERAC1 gene are found. Brain MRI: basal ganglia lesions and generalised atrophy.

Results/Case report: A 30 years old patient with a moderate intellectual disability, developed, since the age of 25, a progressive loss of previous capacities (hand dexterity, oral language), and later subacute generalized dystonic features. Currently he has spastic tetraparesis, dystonia, scoliosis and autistic behavior, with bilateral basal ganglia lesions on brain MRI. Genetic study revealed biallelic pathogenic variants in SERAC1 gene, confirm MEGD(H)EL. A 73 years old patient with cognitive impairment and progressive spastic tetraparesis had multiple periventricular T2 hyperintense lesions. She has a homozigotic SERAC1 variant NM_032861: exon4:c.T139A: p.F471 (rs112780453), considered benign. Bicohemical study revealed elevater plasmatic alanine and urinary3-metilglutaconic and 3-metilglutaric acid. This profile is concordant with mitochondrial dysfunction and SERAC1 Deficit.

Conclusion: The first patient has the clinical symptoms associated to the MEGD(H)EL syndrome, and the biochemical and genetic confirmation of the diagnosis, without reservations.
However, in the second patient, the progressive paraparesis and cognitive impairment did not appear to be caused by multiple sclerosis nor subcortical vascular leukoencephalopathy (without vascular risk factors). The abnormal biochemical profile is suggestive of SERAC1 Deficiency, even without genetic confirmation. In what should we believe?

PO 22

IT'S NEVER TOO LATE FOR A DIAGNOSIS

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Main category: Case report

Disease category: Complex molecule and organelle metabolism

Introduction: Zellweger spectrum disorder (ZSD) (OMIM#214100) is a phenotypic continuum ranging from severe to mild presentations. ZSD is now used in all individuals with a defect in one of the 13 ZSD-PEX genes, regardless of phenotype. Diagnosis can be suggested by abnormal levels of very-long-chain fatty acids, phytanic acid, pristanic acid, plasmalogens, pipecolic acid or bile acids. However, false negatives are frequent, mostlyin older patients. Definite diagnosis is established in a proband with suggestive clinical findings by identification of biallelic pathogenic variants in one of the 13 ZSD-PEX gene

Results/Case report: A 39-year-old female patient had a global development delay since her first year of life. Never have oral language, but had sphincter control and was able to walk and laugh. At 8 years old she had a first seizure and loost sphincter control at 20 y. At 28 y she had an episode of status epilepticus, with severe prostration and became bedridden. She is currently mute, without capacity for communication or motor control. She has no consanguineous parents, has a 35 years old brother with global developmental delay and their mother had a history of an abortion. Brain MRI of the patient revealed severe leukodystrophy mainly periventricular, bilateral and symmetric, and less prominent in the cerebellar white matter, with severe cerebral and corpus callosum atrophy. Molecular study: homozygotic patogénico variant on PEX 1 gene (NM_000466.3) – c.2528G>A (p.(Gly843Asp)), confirming the ZSD.

Conclusion: Homozygosity for PEX1 p.Gly843Asp seems to be associated with an intermediate/milder ZSD phenotype,with survival until adulthood. Some patients develop progressive degeneration of CNS myelin, a leukodystrophy pattern, like this patient, which may lead to regression. This girl with ZSD had a rapid and severe loss of previous skills after a seizure. Even though there is no specific treatment for this disease, a correct diagnosis was very important for the parents and for family genetic counselling.

PO 23

FOLLOW-UP OF PATIENTS WITH HEREDITARY METABOLIC DISEASES DURING THE 3 YEARS OF THE PANDEMIC IN THE REFERENCE CENTER FOR HEREDITARY METABOLISM DISEASES OF THE CENTRO HOSPITALAR UNIVERSITÁRIO LISBOA NORTE

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Main category: Other

Disease category: Several disease categories

Introduction: The adult unit of the Reference Center for Hereditary Metabolism Diseases of the Centro Hospitalar Universitário Lisboa Norte was created in 2002. The team that supports this unit is made up of several specialists, including 2 Internal Medicine Doctors and 2 Nutritionists. The unit carries out its activity mainly in an outpatient clinic, on fridays. Between March 2020 and December 2022, the team adapted the support given to this unit, transforming some external appointment into non-face-to-face appointment in order to maintain contact with patients, and reduce the deslocation to the CHULN

Methods: The analysis reported below reflects the activity in face-to-face and non-face-to-face appointment of the medical team and nutrition team in the critical period.

Results/Case report: A total of 220 patients were evaluated, 56.4% female and 43.6% male. Regarding the evaluated pathologies, these were divided into 3 groups: aminoacidopathies – 40%, organic aciduria – 6.5% and other metabolic diseases – 53.5%. During these three years a total of 580 nutrition appointments were scheduled, 457 face-to-face and 123 non-face-to-face. 32% of patients scheduled did not attend the appointments or it was not possible to make telephone contact.
This percentage is divided into 90% face-to-face appointments and 10% non-face-to-face appointments. Regarding medical appointments, the total was 797, 667 of which were face-to-face and 130 non-face-to-face. 16.8% of absences were registered in face-to-face and non-face-to-face appointments. 98.5% Of absences concern non-face-to-face appointments.

Conclusion: Despite the troubled period worldwide, support for these patients was always ensured, both by the Medical team and by the Nutrition team. Despite the solutions found to keep patients safe, in this specific period, the % of absences from the outpatient clinic is quite high, and one of the main justifications presented by the patients is related to the fact that they are afraid to go to the hospital. With regard to absences recorded in non-face-to-face appointments, there were several situations in which patients reported not being able to answer the phone during their working hours.

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PO 24

PAEDIATRIC PALLIATIVE CARE IN A REFERENCE CENTRE OF INHERITED METABOLIC DISEASES

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Main category: Case series

Disease category: Several disease categories

Introduction: Paediatric palliative care (PPC) has a significant role in improving quality of life of children with life-limiting or life-threatening illnesses, diminishing symptom burden and providing holistic support to patients and families. (1) Inherited metabolic diseases (IMD) are a group of heterogeneous diseases that often present with severe neurologic impairment needing lifelong care and challenging symptom management.(2) Our aim was to characterize the cohort of patients with IMD followed by the paediatric palliative care team (PPCT) and to describe the provision of care provided.

Methods: Descriptive analysis of demographic, clinical and care delivery data of a cohort of paediatric patients with a confirmed diagnosis of IMD, followed in a Reference Centre, in the care of PPCT between 2018 and 2023.

Results/Case report: Thirteen (10%) of a total of 134 patients in care of PPCT had a confirmed diagnosis of an IMD: 6 mitochondrial, 3 peroxisomal, 3 lysosomal and 1 pterin metabolism disorder. Median age at referral was 9 years (0-18), median duration of care was 2 years [2-4], median number of home visits in the last year was 2 [1-4] and median number of outpatient consults was 4 [2 -8].Twelve patients (92%) had no autonomy in their activities of daily living. Neurologic (100%), gastrointestinal (92%) and respiratory (69%) symptoms were the main focus of care. All patients were polymedicated (5 or more different drugs). Nine (69%) had percutaneous gastrostomy and 2 (15%) noninvasive ventilation. Median hospital admissions before and after starting care by PPCT was 4 and 1. Three patients have died, one at home.

Conclusion: Mitochondrial, lysosomal and peroxisomal disorders are complex multisystemic diseases that very often have no treatment intended to cure. These patients have a heavy symptom burden and frequent intercurrences. Addressing these symptoms is challenging but has proven that reduces hospital admissions with consequent improvement of quality of life. In future, PPC should be available for all children and families with life-threatening conditions.

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PO 25

PHARMACOGENETIC VARIANTS CAN INFLUENCE OPTICAL MEDICATION USE

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Main category: Basic science study

Disease category: Several disease categories

Introduction: Single Nucleotide Polymorphisms (SNPs) are used as drug susceptibility biomarkers in metabolic diseases. Alterations in the gene encoding the enzyme flavin monooxygenase 3 (FMO3), involved in the Sulindac metabolization, are responsible also for the inherited metabolic disorder Trimethylaminuria (TMAu, OMIM: 602079). DPYD gene variants are associated with the enzyme dihydropyrimidine dehydrogenase deficiency (DPD; OMIM: 274270). This autosomal recessive metabolic disorder leads to the inability to metabolize fluoropyrimidines, causing severe toxicity in individuals treated with these drugs.

Methods: Variants in genes responsible for the expression of enzymes that encode transporters or receptors involved in the metabolization pathways of certain drugs may condition the individual response to certain drugs, compromising the therapeutic response and clinical prognosis. The sequencing and identification of variants become relevant, not only for the knowledge of these variants' effects on disease causality but also in terms of side effects resulting from the coding enzymes responsible for drug metabolization.

Results/Case report: It was found that patients with the c.472G>A (p.Glu158Lys) and c.923A>G (p.Glu308Gly) polymorphisms, in homozygosity, in FMO3 gene did not develop polyps, thus have a protective effect in the treatment of Familial Adenomatous Polyposis (PAF). However, in the case of the DPYD gene, c.1905+1G>A (IVS14+1G>A), c.1679T>G (p.Ile560Ser), c.2846A>T (p.Asp949Val) e c.1236G>A/HapB3 variants can be lethal in cancer patients indicated for fluoropyrimidine-based chemotherapy.

Conclusion: Knowledge of these mechanisms will affect the therapeutic response of patients treated with a given drug. In this way, pharmacogenetics is an essential tool in personalized medicine, since molecular studies allow the clinician to predict the probability of efficacy and toxicity of certain drugs, thus individualizing treatment and improving patient safety. Through the characteristics of the drug and its metabolization site, the study of the genes involved in the encoding of enzymes responsible for its metabolization will be of great interest from a personalized medicine perspective.

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PO 26

PORTUGUESE NEONATAL SCREENING PROGRAMME: A RETROSPECTIVE COHORT STUDY OF 18 YEARS OF MS/MS

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Main category: Case report

Disease category: Several disease categories

Introduction: The Portuguese Neonatal Screening Programme (PNSP) identifies patients with rare diseases through nationwide screening. Currently, 27 diseases are diagnosed, amongst which are 24 Inborn Errors of Metabolism (IEM), covering of approximately 100% of neonates (1). In 2004, the national laboratory implemented a new screening method, tandem mass spectrometry (MS/MS) to test for amino acids and acylcarnitines. This new protocol revolutionized the PNSP and allowed for the analysis of an increased number of IEM, with clear improvements of treatment timings and clinical outcomes (2).

Methods: From 2004 to 2022, 1 764 830 neonates were screened with MS/MS technology. Those who displayed biochemical profiles indicating an IEM were subjected to molecular characterization via genomic DNA extraction, PCR amplification, and direct Sanger sequencing method, of dried blood spot samples.

Results/Case report: A cohort of 681 newborns were diagnosed with an IEM. MCAD deficiency is the most frequent, with 233 confirmed diagnoses, shows predominantly c.985A>G (p.K329E) mutation of the ACADM gene in homozygosity. Approximately 1/3 of the 33 confirmed cases of Glutaric Aciduria type I, present homozygous for the c.1204C>T (p.Arg402Trp) mutation in GCDH. Around 60% of cases of MAT II/III deficiency display the dominant mutation of the MAT1A gene, c.791G>A (p.Arg264His). These genetic profiles and others were determined as diagnostic confirmation for 24 the IEM screened.

Conclusion: This data shows the molecular epidemiology of patients with confirmed IEM diagnosis identified by neonatal screening. Some diseases out of the scope of the PNSP were also detected as a differential diagnosis after biochemical suspicion in the dried blood spot sample. The retrospective analysis of the PNSP allows for an overview of 18 years of achievements accomplished by the national screening for IEM since MS/MS was implemented. For some pathologies with low incidence, it's difficult to trace a discernible pattern. However, presenting de novo mutations for these diseases might provide insights on how to approach different phenotypes. The aim of this work is to establish the molecular epidemiology of metabolic diseases screened.

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PO 27

INCREASING SANFILIPPO SYNDROME AWARENESS THROUGH CHILDREN'S LITERATURE AND MUSIC

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Main category: Other

Disease category: Several disease categories

Introduction: There is an ongoing effort to increase rare disease awareness amongst healthcare providers. This front is important and can help to address several challenges faced by rare disease patients, such as lengthy diagnosis times, difficulty in finding adequate providers of medical services and experts, and adequate treatment, if one exists.

Methods: On another front there is the need for awareness among citizens and their support in the advocacy for public policies towards rare disease patients and families. Awareness campaigns are prevalent in social networks and fundraising events.

Results/Case report: In this poster we present a complementary approach to engage the society and promote rare disease awareness through children's literature and music. A Portuguese teenager wrote a book ('My life with my sister'), describing simple and daily moments spent with her teenage sister affected by Sanfilippo syndrome. A professional illustrator designed and illustrated the book. The book is bilingual in Portuguese and English. The author, with the assistance of her music teacher, also composed a song which was recorded with the participation of professional musicians.

Conclusion: The book and song promote the inclusion and love for people affected with rare diseases and their families. To increase outreach, sister organizations translated the book, adapted the song and published/recorded the material in Brazilian Portuguese and French. The proceeds from the sales go towards the Sanfilippo foundations in their respective countries to fund common research projects. The material is being advertised on social media, television, interviews, newspapers, podcasts, libraries, schools, bookshops, book fairs and others. To date, more than eight hundred books have been sold to individuals and companies. The interviews and videoclips add to more than twelve hundred views. The target audience is children, parents, teachers but also companies and their employees.

PO 28

PRE-IMPLANTATION GENETIC TESTING IN INHERITED METABOLIC DISEASES? STATE-OF-THE-ART AND CURRENT CHALLENGES

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Main category: Other

Disease category: Several disease categories

Introduction: Inborn errors of metabolism (IEM) are genetic diseases involving congenital disorders of enzyme activities. Most follow Mendelian autosomal recessive inheritance and few follow mitochondrial inheritance. In many cases, parents discover they are carriers for a condition after the birth of an affected child and worry about the risk of recurrence in future offspring. Preimplantation genetic testing (PGT) can analyze embryos before their transfer to the uterus and prevent the transmission of hereditary conditions to descendants, however, this procedure is of limited value in mtDNA conditions.

Methods: Review of the list of diseases currently approved for PGT, and the process for eligibility, from the Comissão Nacional Procriação Medicamente Assistida (CNPMA), from Portugal (PT). Review of international practices for Assisted Reproductive Techniques (ART) in IEM.

Results/Case report: As of 07.2022, 23 IEM diseases associated with deleterious variants in nDNA were approved for PGT in PT. Couples at risk for conditions not included in the list can solicit an evaluation from an expert committee, after a medical genetics consultation. To qualify for approval, diseases must cause significant suffering and/or premature death. Across the world, many more IEM conditions have been approved for PGT due to a greater number of solicitations. ART for mtDNA is not available in PT. International expert centers include PGT for specific well-documented variants and mitochondrial donation.

Conclusion: PGT is a reliable approach to reduce the risk of transmission of a genetic condition to the offspring. The list of IEM disorders currently accepted for this technique in Portugal is small, but expanding, as many more diseases fit the necessary criteria. While appealing in theory, low success rates coupled with limited availability can be discouraging for patients. Genetic counseling is of paramount importance after the diagnosis of IEM diseases. It is important for both clinicians and patients to be made aware of the available reproductive options and their limitations.

PO 29

COBALAMIN A/C DEFICIENCY, SUBCUTANEOUS HYDROXOCOBALAMIN USE WITH I-PORT ADVANCE®: A CASE STUDY

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Main category: Case report

Disease category: Intermediary metabolism: others

Introduction: Cobalamin A/C deficiency is a hereditary metabolic disease affecting the remethylation of homocysteine to methionine due to a disturbance in the synthesis of adenosylcobalamin, which primarily affects the nervous system and bone marrow. Based on guidelines treatment with IM hydroxocobalamin is crucial to prevent cardiovascular, neurological, and megaloblastic anemia manifestations associated with the disease by reducing homocysteine levels.Daily administration through the IM route is often associated with painful procedures and is a source of anxiety for the child and caretakers,

Methods: Clinical case report of a child with 11months old with Cobalamin C deficiency, where the therapeutic intervention proposal was created for the use of the i-Port Advance® device as a SC administration vehicle for the 1mg/ml HOCbl formulation, to minimise the discomfort associated with administration.

Results/Case report: The child was admitted to start HOCbl IM and respective administration were taught to the mother, since then an improvement in homocysteine was observed (97.5 µmol/l). Due to the pain and anxiety associated with IM administration, at 3 months of age, the nursing team taught and empowered the parents regarding the use of i-Port Advance® for SC administration, at that time homocysteine was 30.4 µmol/l. Good adaptation to the device by the parents was observed, with no adverse reactions or changes in laboratory control of the disease (homocysteine at 30 µmol/l).

Conclusion: Based on this case study, we see, as mentioned in the literature, that changing the administration route from intramuscular to subcutaneous HOCbl allows for continued treatment without risks or associated complications and without affecting homocysteine measurements. In addition to improving the quality of life of the patient and their caregivers, it also facilitates adherence to treatment. More studies will be required with a higher number of patients to validate these results.

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PO 30

EVALUATION OF MITOCHONDRIAL FUNCTION ON PYRUVATE DEHYDROGENASE COMPLEX DEFICIENT PATIENT-DERIVED CELL LINES

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Main category: Basic science study

Disease category: Intermediary metabolism: energy

Introduction: Pyruvate Dehydrogenase Complex (PDC) is a pivotal gatekeeper between cytosolic glycolysis and mitochondrial oxidative phosphorylation, playing important role in aerobic energy metabolism. PDC deficiency, most cases being caused by mutations in PDHA1 encoding the α subunit of the rate-limiting E1 enzyme, is characterized by abnormal phenotypes caused by energy deprivation at peripheral/central nervous systems and muscular tissues. This study aims to evaluate the potential therapeutic effect of arginine and thiamine in ameliorating mitochondrial function in patient-derived cultured cells.

Methods: PDC-deficient cell lines, carrying three different PDHA1 variants, were cultured in the absence and presence of arginine and/or thiamine at therapeutical levels, 4 mM and 100 µM, respectively. Mitochondrial bioenergetics profile was evaluated using the Seahorse extracellular flux analyzer.

Results/Case report: In physiological conditions, control cells presented standard values for all parameters evaluating the mitochondrial function, no differences being observed after supplementation of culture medium with therapeutic levels of arginine and/or thiamine. However, PDC-PDHA1 deficient cell lines consumed less oxygen than the control cells, but arginine and thiamine supplementation increased the basal respiration for values similar or higher than the control cell line. Moreover, arginine and thiamine treatment highlighted an inefficient oxidative phosphorylation carried out by PDC-deficient cell lines. Finally, this treatment showed an increased oxygen consumption by enzymes other than those in the respiratory chain, thus proving the dependence of these mutant cell lines on cytosolic sources for ATP production, namely glycolysis.

Conclusion: This study showed that arginine and thiamine, at therapeutical levels, increase the basal oxygen consumption rate of PDC-deficient cell lines, as well as their ATP-linked respiration. This parameter measures the capacity of the cell to meet its energetic demands and, therefore, its increase reveals a higher electron flow through the respiratory chain, which is coupled to elevated oxidative phosphorylation, thus indicating an overall increased robustness in mitochondrial-related bioenergetics.

PO 31

ALLOW NATURAL DEATH (AND) IN INBORN ERRORS OF METABOLISM

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Main category: Case series

Disease category: Several disease categories

Introduction: Healthcare providers must help families to make important end-of-life care decisions after a child's neurodegenerative disorder diagnosis. Care option discussion can benefit from the use of terminology such as "allow natural death" (AND) or "continuing care" and avoid negative statements such as "there is nothing more we can do" or "do not resuscitate" (DNR). The term AND allows the creation of a dialogue between families and doctors focusing on the quality of life for the last few days, embodying the hope that death will occur as peacefully and naturally as possible, surrounded by loved ones.

Methods: The authors performed a retrospective review of the end-of-life care of four neurodegenerative disease patients, provided by a team of professionals working together to reach the family`s wishes.

Results/Case report: Case 1 - DGOUK mitochondrial disease diagnose at 2 months. The mother had "the feeling" that her child would die very young, and so she was not surprised by diagnosis. Death occurred at hospital, in the presence of the three doctors responsible for his care, as was the mother`s wish.
Case 2 - Menkes disease diagnosed by two months old. He started treatment with copper histidinate with no improvement in the outcome, dying at the age of 4. He was discharged from the hospital and died at home the following day, as was the mother`s wish.
Case 3 – PMM2-CDG diagnosed in the neonatal period, with severe cardiac and neurologic manifestations. He died at hospital, in a serene enviroment, with both parents.
Case 4 – Leigh syndrome, diagnosed at 3months, deceased at home in the arms of the mother, who later phoned the doctor to inform them of the peaceful death.

Conclusion: The change in terminology has been difficult to implement and the question regarding "the signed DNR" tends to prevail. The more frequent use of the term AND facilitates a positive end-of-life care discussion and may help families focus on reducing suffering and promoting comfort, quality, and dignity for all involved: family, caregivers, and professionals. Effective end-of-life care planning may also lead to more families choosing their child to die at home. The authors suggest that basic training in palliative care should be offered to inborn errors of metabolism professionals.

PO 32

DIVERSITIES IN LEIGH SYNDROME ASSOCIATED TO MT-ATP6 GENE VARIANTS

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Main category: Case series

Disease category: Intermediary metabolism: others

Introduction: Leigh syndrome (LS) is clinically and genetically heterogeneous and presents defective mitochondrial bioenergetics. Patients present neurological symptoms and imagiological features that may result in early death [1]. The LS has been associated to mitochondrial DNA (mtDNA) variants, e.g., m.8993T>G (L156R) and m.8993T>C (L156P), in the MT-ATP6 gene. They lead to substitution of a highly conserved aminoacid in subunit 6 of ATP synthase, affecting the F0 domain and ATP synthesis [1-3]. We present five cases with m.8993T>G and a family harbouring m.8993T>C+m.1555A>G (proband and four relatives).

Methods: Our laboratory received 48 samples from LS-suspected patients. The samples (various tissues) were assessed for bioenergetics (activity of mitochondrial respiratory chain (MRC) complexes, ubiquinone content) and genetic analyses (mtDNA copy number, Sequencing and PCR-RFLP), by established protocols.

Results/Case report: Bioenergetics were assessed in 5 patients (various tissues), with varying levels of MRC/ATP synthase impairment. Six cases had a mtDNA pathogenic variant in the 8993 nucleotide, associated with LS. Five cases presented the m.8993T>G variant, one of which (P5) possibly de novo. This variant was in homoplasmy (P1-3) or very high heteroplasmy (P4/5, 90-95%). Of the four patients with bioenergetics assessment, three (P1/3/4) had deficiencies of MRC complexes and P5 had small deficits. The other case (familial, proband and 4 relatives) presented a combination of m.1555A>G (homoplasmy) and m.8993T>C (heteroplasmy) variants. The proband presents m.8993T>C in 95% heteroplasmy and 85-35% in three relatives. All have m.1555A>G in homoplasmy, including the fourth relative without m.8993T>C. For proband, a deficiency (31%) was found in complex V activity in muscle.

Conclusion: We present a case series of patients harbouring pathogenic variants in the 8993 nucleotide of mtDNA, which have been associated with LS and impairment of MRC's complex V. These cases highlight the variability in clinical symptoms and their severity, as well as genetic heterogeneity within LS. Many patients will not present a classic pathogenic variant and there are many cases of asymptomatic relatives (carriers). It is important to get a broader view of the cases - classical methods and multiple tissue analysis are still valuable tools for the comprehensive characterization of patients.

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PO 33

TARGETING THE STABILITY AND ACTIVITY OF MEDIUM CHAIN ACYL-COA DEHYDROGENASE P.K329E VARIANT WITH PENTA- AND HEXAPEPTIDES

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Main category: Basic science study

Disease category: Intermediary metabolism: energy

Introduction: ACADM gene mutations lead to medium chain acyl-CoA dehydrogenase (MCAD) deficiency (MCADD), with the c.985A>G ACADM mutation (p.K329E variant) affecting ~80% of MCADD patients. Upon dehydrogenation of MCAD substrates, electrons accepted by the MCAD cofactor (FAD) move to the electron transferring flavoprotein (ETF), creating an electron flux towards the respiratory chain. MCAD/ETF contact take place via MCAD α-helices C and D and ETFβ recognition loop (RL). As protein ligands may promote protein stability, we posited that peptide sequences derived from ETFβ-RL may rescue p.K329E stability.

Methods: In this work using computational tools amino acid sequences derived from the ETFβ-RL were optimized regarding free-energies of binding and ligand efficiency towards MCAD. Short-peptides (SPep) were characterized for their effect on the activity and stability of wild-type MCAD and p.K329E variant.

Results/Case report: Three short-peptides (SPep) with 5 to 6 amino acid residues (<660 Da) were identified and synthesized. Differential scanning fluorimetry showed that the stability of the p.K329E variant increased in the presence of SPep2 (ΔTm = 3.9 °C) and SPep3 (ΔTm = 3.1 °C). SPep2 also decreased the denaturation rate of p.K329E at 37 °C as monitored by isothermal denaturation fluorimetry. Together with the increase in the protein Tm, SPep2 and SPep3 also exerted a protective effect towards enzyme inactivation of p.K329E, as upon 10 min incubation, at 37 °C, SPep2 and SPep3 lead to an increase in the activity of the p.K329E, when compared to time zero, of 210% and 154%, respectively. Importantly, when the enzymatic assays were performed in the presence of the natural electron acceptor (ETF) and SPep2 or SPep3 obtained data indicate that the SPep did not compete for ETF binding.

Conclusion: From the designed and optimized peptide sequences SPep2 (hexapeptide) and SPep3 (pentapeptide) proved to increase the stability and protect the catalytic activity of the most common variant identified in MCADD patients (p.K329E) from thermal inactivation. To overcome the constraints associated to the use of peptides as therapeutic agents SPep2 and SPep3 structures were already utilized to develop a new fingerprinting function to score a virtual screening campaign for small non-peptide molecules constituting hit compounds for development of a pharmacological therapy for MCADD.

PO 34

C26:0-LYSOPC: HOW A NOVEL METHOD IMPROVES X-ALD FEMALE CARRIERS SCREENING

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Main category: Translational science study

Disease category: Complex molecule and organelle metabolism

Introduction: X-linked adrenoleukodystrophy (x-ALD) is the most prevalent leukodystrophy. Very long-chain fatty acid (VLCFA) accumulation is a hallmark of the condition, due to mutations in ABCD1. Recent studies regarding cerebral x-ALD treatment emphasize the importance of its early diagnosis (1). Around 15–25% of x-ALD women, plasma VLCFA analysis yields a false negative result. According to previous authors, women with ALD, even those who had normal plasma C26:0 levels, had higher amounts 26:0 lysophosphatidylcholine (LysoPC). Altogether, this turns it into the elective biomarker for X-ALD screening (2)

Methods: Testing the robustness of and underivatized high-performance liquid chromatography with tandem mass spectrometry (HPLC MS/MS) for x-ALD screening, establishing the reference ranges using 76 plasma samples, and making a retrospective comparison of VLCFA and C26:0-lysoPC were the main goals.

Results/Case report: The developed underivatized method proven robust besides the benefit is the reduced sample preparation time, volume and cost. The analysed cohort included 18 x-ALD patients, 9 carriers and 49 normal individuals. x-ALD patients revealed a C26:0-lysoPC median concentration of 0,564 µmol/L (reference range 0,226 – 0,902 µmol/L), carriers 0,454 µmol/L (reference range 0,260 – 0,648 µmol/L) and the control group 0,039 µmol/L (reference range 0,000 – 0,084 µmol/L). The results obtained proved the stability of the C26:0-lysoPC and its usefulness in retrospective studies. C26:0-lysoPC plasma levels establish a clear distinction between the reference range of patients and female carriers and controls, respectively. Overall, our results show that in all patient categories, C26:0-LPC analysis outperforms VLCFA analysis (C26:0 and C26:0/C22:0 ratio) in terms of diagnostic performance.

Conclusion: These results corroborate that plasma C26:0-lysoPC levels are a better and more reliable biomarker for ALD carrier testing than VLCFA. Moreover, being a reliable biochemical biomarker, C26:0-lysoPC can be used as a first tier, facilitating extended family screening. Based on our findings, we advise adding C26:0-LPC analysis in plasma during the peroxisomal diseases diagnostic work-up (3, 4). A future goal of this work is to extend this retrospective comparison of VLCFA and C26:0-lysoPC as biomarker for Zellweger spectrum disorders.

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PO 35

RMND1 – RELATED MITOCHONDRIAL DISEASE, AN ULTRA-RARE MITOCHONDRIAL DISORDER

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Main category: Case report

Disease category: Intermediary metabolism: energy

Introduction: Biallelic mutations in RMND1 (Required for Meiotic Nuclear Division Protein 1) gene have recently been linked to mitochondrial disease (in 2012), namely combined oxidative phosphorylation deficiency 11 (OMIM #614922). The main clinical phenotypes raging from fatal, infantile encephalomyopathy with lactic acidosis and early death, to a less severe phenotype characterized mainly by developmental delay, sensorineural deafness, hypotonia, lactic acidemia and renal disease. Ragged-red fibers, COX-negative fibers and multiple complex deficits (I-IV) are find in the muscle.

Results/Case report: Two brothers born prematurely at 36 and 34 weeks, presented with global developmental delay since first months of live (never talk, sit or walk alone). The 24 years old sister, had congenital neurosensorial deafness, epilepsy (West syndrome phenotype), anemia, slight renal insufficiency. The main problem is severe auto and hetero aggressive behavioral who compromise all family. The 20 years old brother has neurosensorial deafness, spastic tetraparesis, spastic blade, muscular atrophy, hyperCK, hypertension, hyperuricemia, cardiomyopathy with mitral and aortic insufficiency and renal insufficiency. He have very friendly and kind behavioral. WES identified a homozygous pathogenic variant c.731A>G p.(Asn238Ser) in RMND1 gene, responsible for the phenotype of two siblings, confirmed the diagnosis of OXPHO defect 11.

Conclusion: Those brothers present with the less severe phenotype with adult survivor, also associated to the homozygous p.(Asn238Ser) variant in RMND1 gene, and have the main clinical symptoms already described. However the sister have a more severe intellectual disability with severe auto and hetero-aggressive behavioral not previous described. The WES analysis increase the diagnostic rate of those rarer phenotype associated to disorder, reducing the necessity of biochemical and functional studies, in mitochondrial diseases, who are difficult to interpret.

PO 36

LATE ONSET POMPE DISEASE: A LIMITATIVE MOTOR DISORDER WITH A REWARDING TREATMENT

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Main category: Case report

Disease category: Complex molecule and organelle metabolism

Introduction: The late onset form of Pompe disease (LOPD), (OMIM #232300) is characterized by a progressive proximal and axial muscular weakness, and respiratory distress, mainly due to diaphragmatic weakness. LOPD patients seem to benefit from enzyme replacement therapy (ERT), significant in walking distance, a reduced effect on muscle strength or respiratory capacity. (Sara B and all). Due to costly therapy, this treatment has been considered questionable in case of adult patients presenting mild phenotypes.

Results/Case report: A 56 years old female presented with dyspnea, orthopnea and fragmented sleep. She had global respiratory insufficiency (PaCO2: 70 mmHg), severe obstructive sleep apnea (IAH: 66, 3/H) and hypoventilation (SatO2<90%: 310 m. SatO2 medium: 65,4%). With a severe restrictive ventilator syndrome, she required non-invasive nocturnal ventilation. DBS: alfa-glucosidase activity 0.95 pmol/h/puntion (4.51-32.7), blood leucocytes alfa-glucosidase activity 4.2 nmol/h/mg prot. (44.1 - 144) and has a compound heterozygosity c.-32-13T>G and c.1912G>T (p.G638W) GLA gene variants, confirming Pompe Disease. She started ERT with MyozimeR, with 20 mg / Kg every other week. One year later the patient recovered quality of live, is able to walk 10 Km/day, recovered from sleep apnea and no report daily somnolence. Moreover, daily gasometry became normal, and nocturnal oximetry and capnography has also normalize.

Conclusion: Our results showed that this patient benefit of enzymatic treatment on LOPD not only in walking distance but with respect to ventilator problems. This is an example of personalized medicine. In this patient ERT positively affects muscle strength, pulmonary function, and of at most importance, the daily life activities.

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PO 37

MUSCLE QUALITY AND RISK OF METABOLIC SYNDROME IN ADULT PATIENTS WITH INHERITED METABOLIC DISEASES

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Main category: Basic science study

Disease category: Intermediary metabolism: nutrients

Introduction: Adult patients with several inherited metabolic diseases (IMD) follow diets controlled in proteins, rich in carbohydrates, and free amino acids formulae, which cause hyperinsulinism and ectopic fat. Previous studies showed IMD adult patients having higher prevalence of metabolic syndrome and their complications.(1) Recently, ultrasound (US) is being validated for malnutrition, assessing muscle quality subjectively. (2) Higher echo intensity (EI) is associated with poorer muscle quality and functional results in ageing (3) and other clinical settings, but it has never been evaluted in IMD.

Methods: US to measure EI with Image J (rectus femoris, x3), anthropometry, bioimpedance and biochemistry were made in 19 IMD patients and 6 healthy controls (only US) from Hospital Universitario de Badajoz (HUB). HUB ethic committee approved protocol and informed consent. Statistics was made with Jamovi.

Results/Case report: Mean age was 29.9 (range 18-47) in IMD patients vs. 33.7 (26-47) in controls. Distribution of IMD is shown in Figure 2. Mean EI in IMD was 56.9 (60.9 in PKU) vs. 54.4 in controls, NOT being the differences statistically significant (t-Student p=0.633; in PKU, p=0.246). Box plot is shown in Figure 3. IMD patients had excess of body fat in a variable degree depending on the method (Figure 4): anthropometry, BIA, preperitoneal fat or myosteatosis. 40% had insulin resistance by HOMA, 20% prediabetes by HbA1c, 58.8% had low HDL-cholesterol levels, and 29.4% has hypertriglyceridemia. Insulin resistance status is shown in Figure 5. Obesity by anthropometry was significantly correlated with subcutaneous abdominal and preperitoneal fat by ultrasound and fat mass by BIA. Fat mass by BIA was correlated preperitoneal fat, and fat-free mass by BIA with HOMA and degree of metabolic control of IMD.

Conclusion: Muscle quality, by an objective tool such as echo intensity, is worse in patients with IMD than in controls, reflecting poorer muscle metabolic condition and higher risk of metabolic syndrome. It is not statistically significant probably due to the small sample size. Prevalence of obesity and other metabolic syndrome components are higher in IMD patients than in general population of the same age. Body composition analysis by BIA and nutritional ultrasound can help to identify patients in risk of metabolic syndrome before biochemical markers show.

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PO 38

SULPHUR AMINO ACIDS: HOW IMPORTANT IS IT TO SET REFERENCE RANGES FOR EACH POPULATION?

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Main category: Translational science study

Disease category: Intermediary metabolism: nutrients

Introduction: Metabolism of sulfur amino acids requires an optimal interplay between nutritional demand, enzymes, transporters, and adequate dietary intake of B vitamins. Insufficient intake and excess are detrimental, and concentrations depend on health status. However, plasma aminothiol concentrations, previously reported in healthy subjects using highly sensitive methods, vary considerably, and age- and gender differences were observed. Therefore, defining age- and gender-specific ranges for each population is crucial to evaluate the meaning of plasma thiol redox state in health and disease.

Methods: A healthy Portuguese pediatric population (n=90), aged 9- (n=38) and 17-year-old (n=52), was evaluated. Plasma aminothiols, total homocysteine (tHcy), cysteine (tCys), glutathione (tGSH) and γ-glutamylcysteine (tγ-Glu-Cys), were analysed as SBD-F derivatives by HPLC with fluorescence detection.

Results/Case report: Mean plasma concentrations (SD), respectively for the 9- and the 17-year-old groups, were as following: tHcy = 4.58 (0.98); 8.13 (3.27) μM, $p < 0.001$; tCys = 207.34 (32.07); 198.59 (21.24) μM, $p = 0.274$; tGSH = 4.54 (1.08); 5.20 (1.84) μM, $p = 0.123$ and tγ-Glu-Cys = 1.47 (0.30); 1.06 (0.28) μM, $p < 0.001$. No statistically significant differences were found between males and females in the 9- years-old group. However, in the 17-year-old group, significant differences between gender were observed for tHcys ($p < 0.001$) and for tγ-Glu-Cys ($p = 0.039$), with males presenting the highest concentrations. When correlating the four thiols' plasma concentrations, only the precursors of glutathione, tγ-Glu-Cys and tCys, were positively correlated ($r = 0.450$, $p < 0.001$).

Conclusion: Our results showed significant differences in tHcy and tγ-Glu-Cys levels across both age groups, which increased and decreased with age, respectively. It is interesting to highlight that in the 17-year-old group, tHcy and tγ-Glu-Cys levels were higher in males than in females. These observations showed that age and gender influence plasma levels of thiols, which may impact cellular oxidative status. In conclusion, setting age and gender distinct ranges for each specific population is of utmost importance for understanding disease mechanisms and the effectiveness of therapeutic interventions.

PO 39

PILOT STUDY OF NEWBORN SCREENING FOR SPINAL MUSCULAR ATROPHY

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Main category: Other

Disease category: Several disease categories

Introduction: Newborn screening (NBS) in Portugal is a significant public health measure to provide early detection for specifc disorders when early treatment is both possib SMA is an autosomal recessive neuromuscular disorder that causes degeneration of anterior horn cells in the human spinal cord and subsequent loss of motor neurons. Its incidence is estimated in 1.6000-11.800 live births. The pilot study of 100.000 newborns is being carried in the neonatal screening laboratory with the aim of determining the specificity, sensitivity and feasibility of the SMA screening at the NBS laboratory in Portugal.

Methods: The study presented here was based upon data obtained from neonatal screening, through the analysis of 25.000 newborns.SMA screening is performed by a qualitative detection of exon 7 of the SMN1 gene. The assay was performed using a commercially available real-time PCR, the Eonis SMN1, TREC, KREC ki

Results/Case report: A total of 25.000 dried blood spots were tested, among these newborns, two were diagnosed as having SMA with survival motor neuron 1 (SMN1) deletion. This two SMA -positive were sent to a specialized clinical centre and a peripheral blood sample as sent to the reference laboratory for confirmation of the exon 7 deletion and for determination SMN2 copy number.

Conclusion: Early diagnosis and intervention is important for therapy to be effective, the treatments should be started at the pre-symptomatic stage of SMA. Thus, newborn screening for SMA is strongly recommended. Now the targeted therapies for SMA are available, attempts are being made wordwide to include screening for SMA in general newborn screening.

PO 40

RAPIDLY PROGRESSIVE LATE NEURODEGENERATIVE DETERIORATION IN L-2-HIDROXIGLUTARIC ACIDURIA

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Main category: Case report

Disease category: Intermediary metabolism: energy

Introduction: L-2-hydroxyglutaric aciduria (L2OHGA, OMIM #236792) is a rare autosomal recessive encephalopathy caused by mutations in the L-2-hydroxyglutarate dehydrogenase gene. Affected patients have a slowly progressive neurodegenerative symptoms with intellectual disability, pyramidal and extrapyramidal envolvement, epilepsy and behavioral problems. Elevated levels of L-2- hydroxyglutaric acid (L2HG) in urine and subcortical leukoencephalopathy suggest the diagnosis.

Results/Case report: A female patient with mild intellectual disability, had stable deficits until she was 38 years old. She could walk, talk, and collaborate actively in daily activities. At that age, after a fall with head trauma, she rapidly lost capacity to swallow and walk, with urinary and fecal incontinence. At 40 years old she had dysphagia for liquids, ataxia, spastic tetraparesis and needs a wheelchair. Brain MRI showed severe diffuse subcortical leukoencephalopathy, bilateral and symmetric, with severe cortico-subcortical atrophy, mainly supratentorial, and mild dentate nuclei T2 hyperintensity. Spine MRI was normal. Molecular analysis of L2HGDH gene revealed the c.293A>G (p.His98Arg) mutation in homozygosity and confirmed the diagnosis of L2HGA. Abnormal plasma aminoacids profile identified an elevated lisina, ornitina, alanine, glicina and organic acids in the urine were not available.

Conclusion: L2OHGA clinical presentation is usually a slowly progressive neurodegenerative disease. However a different milder phenotype could delay the diagnosis many years and the rapidly progressive loss of capacities could suggest a different diagnosis. The characteristic diffuse subcortical, bilateral and symmetric, leukoencephalopathy, with no periventricular involvement, is very helpful for the correct diagnosis. This case highlights the need for brain MRI study and metabolic screening in all patients with intellectual disability for a higher rate of diagnosis and better individual care.

PO 41

PHOSPHATIDYLSERINE FLIPPASE DEFICIENCY DIAGNOSED BY WHOLE EXOME SEQUENCING – A CASE REPORT

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Main category: Case report

Disease category: Lipid metabolism and transport

Introduction: Phosphatidylserine flippase deficiency, also referred as cerebellar ataxia, mental retardation, and disequilibrium syndrome type 4 (CAMRQ4, MIM:615268; ORPHA: ORPHA:1766), is a rare autosomal recessive disorder of glycerophospholipid metabolism caused by biallelic pathogenic variants in the ATP8A2 gene. Loss of function variants are described to cause encephalopathy, intellectual disability, severe hypotonia, chorea and optic atrophy. There are only 35 reported cases.

Methods: Etiological investigation included electromyography, brain and vertebromedullar MRI, metabolic analysis, muscle biopsy and genetic testing (SMN1 analysis, mitochondrial genome analysis, CGH-array and disease exome), all of them inconclusive. , Additionally, WES and segregation studies were perform.

Results/Case report: A. is a 12-year old boy, 2nd child of a non-consanguineous Portuguese couple, with severe intellectual deficiency, generalized hypotonia and dystonia (never acquired gait or speech). Perinatal period was normal. He presented in the second month of life with hypotonia and dystonia, development delay, failure to thrive and hyperlactacidemia. Subsequently muscular atrophy with severe low weight, myogenic ptosis, ophthalmoplegia, and bilateral optic atrophy were noticed. WES identified a probably pathogenic variant c.1761dup p.(Arg588Serfs*5) in homozygosity in the ATP8A2 gene, leading to the diagnosis of CAMRQ4.

Conclusion: Phosphatidylserine flippase deficiency is a rare neuromotor disorder with non-progressive symptoms, which may difficult the distinction from dyskinetic cerebral palsy. Involuntary movements and visual and auditory impairment may lead to the suspicion of CAMRQ4. This case report illustrates the importance of a correct diagnosis and adequate genetic counselling to achieve a good family planning, reduce unnecessary medical exams and explore effective rehabilitation techniques. To our knowledge, this is the first case of CAMRQ4 reported in the Portuguese population.

PO 42

"NON CLASSICAL" METHYLMALONIC ACIDURIA – TWO CASES

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Main category: Case report

Disease category: Intermediary metabolism: nutrients

Introduction: Isolated methylmalonic aciduria (MMA) is an autosomal recessive disorder of propionate degradation, which usually presents with ketoacidosis and hyperammonemia, leading to encephalopathy and coma. The condition is usually caused by methylmalonyl-CoA mutase (MUT) deficiency. Methylmalonil-CoA epimerase (MCE) deficiency is a rarer cause of MMA, with a broad clinical spectrum.

Methods: Two male brothers, 5 and 11 years-old, from a refugee's family recently in Portugal, were referred to our Centre with the scarce information of "methylmalonic acidemia". Parents were third-degree consanguineous.

Results/Case report: Both had had three decompensation events with coma, associated with febrile infections and seizures in the first years of life. They were on a protein-restricted diet and medicated with carnitine, metronidazole, vitamin B12 and antiepileptic drugs. The older brother has a severe intellectual disability, does not speak and is wheelchair ridden. The younger presents a neurodevelopment delay, is not able to talk and has an ataxic gait. The investigation revealed, in both, methylmalonic acidemia with normal homocysteine and vitamin B12 levels, methylmalonic and methylcitric aciduria and elevation of propionylcarnitine. A genetic panel for inherited metabolic diseases, which included the MUT gene, was performed, with inconclusive results. The subsequent analysis of MCEE gene, which codes for MCE, disclosed a pathogenic mutation (p.Arg47*) in homozygosity in both patients.

Conclusion: MCE deficiency was first described in 2006, with few reported cases. It presents with diverse clinical severity, from mild symptoms to life-threatening metabolic decompensation with coma, as apparently occurred with our patients in infancy. Neurological outcome is variable, and may be severe, as in these brothers. Genetic testing is indispensable for diagnosis, since both MUT and MCE may have a similar biochemical profile. In the present cases, the correct diagnosis allowed discontinuation of vitamin B12 supplement and an adequate genetic counseling for the family.

PO 43

PHENYLKETONURIA METABOLIC CONTROL AND NEUROCOGNITIVE OUTCOMES

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Main category: Basic science study

Disease category: Intermediary metabolism: nutrients

Introduction: Phenylketonuria (PKU) causes a defective hydroxylation of phenylalanine (Phe). The disrupt reaction compromises brain white matter and Phe conversion to tyrosine, a precursor of catecholaminergic neurotransmitters. Higher Phe levels have been negatively associated with intellectual and behavioural disability.[4] Due to a pronounced burden of diet, insufficient treatment adherence is observed.(1) A worldwide consensus regarding optimal Phe levels to minimize the cognitive and behavioural effects is lacking, so the Phe target therapeutic range for adolescents varies between countries.(2)

Methods: We aimed to assess the neuropsychological profile of a cohort of adolescents with PKU followed since the neonatal period. We evaluated the association between mean ($\bar{x}$) Phe levels, intelligence quotient and executive functions through Weschler Intelligent Scale (WISC-III) and D2 tests (Brickenkamp).

Results/Case report: We investigated 15 early-treated PKU patients aged 12–17 years, diagnosed through NBS (median age at diagnosis 7 days; dietary treatment 11 days). Phe levels ranged from 176.8–487.2μM (n=1471; $\bar{x}$ =316.9μM; SD=210.7) until 12 years age and from 220.7–843.6μM (n=333; $\bar{x}$ =425.9μM; SD=259.8) above. The results of the WISC III Scale varied between 51 and 111 points ($\bar{x}$=85). Patients with mean Phe level >360μM throughout life, had significant lower IQ scores (Total, Verbal, Performance) and lower verbal comprehension index, abstract reasoning and perceptual organization. Moreover, younger patients (<12 years) with mean Phe levels >360μM correlated to poor IQ performance and older patients (> 12 years) with mean Phe levels >600μM correlated to poorer performance in the D2 test (processing speed, concentration performance, accuracy index, attention and inhibitory control and fluctuation rate).

Conclusion: According to the European Guidelines (7), our population had mean Phe levels within the recommended target range. Nevertheless, impairments in neurocognitive evaluation were noted. Interestingly, higher Phe levels (>360μM) below 12 years of age were negatively correlated to lower IQ scores, while Phe levels >600μM later on, had a negative impact in higher intellectual functions. These results underscore the need to monitor intellectual performance, executive and attention functions as children age. Multicentre studies are needed to better understand the physiopathology in PKU neurodevelopment.

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PO 44

COMBINED OXIDATIVE PHOSPHORYLATION DEFICIENCY TYPE 13 WITH PERINATAL PRESENTATION: A CASE REPORT.

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Main category: Case report

Disease category: Intermediary metabolism: energy

Introduction: Polynucleotide phosphorylase is involved in RNA processing in mitochondria. Biallelic variants in PNPT1 cause mitochondrial RNA import protein deficiency and heterogeneous clinical manifestations. (1)

Methods: A, born at 35 weeks by caesarean section due to fetal growth restriction, the first child of remote consanguineous parents. Apgar index was 9/10/10. Birth weight, length and head circumference were at 3rd, <3rd and 10th percentiles, respectively.

Results/Case report: In the first hours of live,respiratory distress, hypoglycaemia and seizures ensued. She started invasive mechanic ventilation, phenobarbital and was transferred to ICU. Physical examination:minor facial dysmorphisms, brief eye opening, hypotonia and hyporeflexia. Electroencephalogram:immature pattern; multifocal paroxysmal activity. MRI D8 of life: severe reduced brain volume. CSF:slight increase in protein; normal aminoacid screen. Expanded newborn screening:negative.Mitochondrial organic aciduria.WES: A homozygosity likely pathogenic variant in the PNPT1 gene.MRI 6-months:brain atrophy, thin corpus callosum, reduced brainstem volume.Bilateral and symmetrical lesions in globi pallidi,compatible with Leigh syndrome. Currently, 14 months:no neurodevelopment progress,dystonia,visual deficit,sensorineural deafness,hypertrophic cardiomyopathy, microcephaly and failure to thrive.

Conclusion: The early and severe Leigh-like presentation of our patient expands the phenotype spectrum of this disease. As far as we know, this is the first reported case of PNPT1 mutation with onset in the perinatal period. Moreover, hypertrophic cardiomyopathy had not yet been described in association with mutation of the PNPT1 gene. WES was the key for early diagnosis in this patient. It should be done in all children with severe clinical presentation of unknown origin.

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PO 45

REVIEW OF CARDIOVASCULAR RISK IN MCARDLE PATIENTS

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Main category: Basic science study

Disease category: Intermediary metabolism: nutrients

Introduction: The glycogenosis type V or McArdle disease (OMIM# 232600) is a common metabolic myopathy related to muscle glycogen metabolism, with mutation on PYGM (11q13) and consequent myophosphorylase deficit. The clinicals manifestations despite with some typical signs, are difficult to recognise in the regular clinic, leading to a delayed diagnosis, many times performed in adult life. Unfortunately, no specific and effective treatment are currently available.

Methods: The follow up of several patients in this reference centre showed a potential increase in cardiovascular risk. The authors reviewed all the patients that was diagnosed through the years, with active follow up and made an evaluation of the risk factors and calculate cardiovascular risk.

Results/Case report: We find a frequent diagnosis of excess of weight, hyperuricemia, dyslipidaemia and diabetes in this cohort of patients. Many factors may contribute for this like diet rich in carbohydrates, limited exercise and probably some uncovered pathophysiology mechanism related with the disorder and aging.

Conclusion: There are some challenges in the management of the cardiovascular risk in patients with McArdle's disorder, but a correct assessment is crucial to a personalized approach. We anticipate that this will be an important problem for the aging patients of our clinic. Further studies in this subject are important to improve survival and quality of life.

References: https://www.omim.org/entry/232600

HTTPS://SIMPOSIO.SPDM.ORG.PT/

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