spdm
SOCIEDADE PORTUGUESA
DE DOENÇAS METABÓLICAS

14th March 2019

FIRST SPDM NATIONAL TREATMENT PROTOCOL GROUP MEETING
FIFTH SPDM NUTRITION MEETING (SPDM-GN)

16th March 2019

SATELLITE MEETING | *Managing PKU during Life*

Secretariat:

it's Comunicação
Susana Pires | 914315258
spdm@its-comunicacao.pt

Welcome address

On behalf of the Organizing and Scientific Committees, it is a great pleasure to welcome all the participants for the **15th International SPDM Symposium** in Coimbra, an old city full of tradition, known for its historic University, a UNESCO World Heritage Site, as well as for its dynamic academic life.

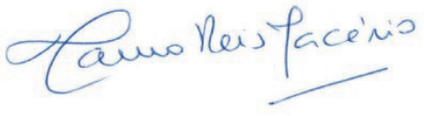
The concept of Inborn Errors of Metabolism (IEM) is becoming broader, urging our community to crossover classic boundaries. Recent and growing impact of new genetic tools and other omics technologies in IEM are undeniable. They contribute to a much better understanding of IEM pathophysiology, leading to the discovery of new disorders and to the rethinking of treatment decision making. Therefore, the Scientific programme is focused on how this new emerging information affects diagnosis, therapeutic approaches and financial concerns. We worked hard to set up a challenging but useful programme and hope to have succeeded.

This International SPDM Symposium gathers national and international professionals, from very different backgrounds, with an interest in IEM. We are proud to have some of the leading experts in this field as invited speakers, who will contribute with their experience and surely promote fruitful discussions of the latest research results. We believe that the Symposium will be an excellent opportunity to encourage networking between prominent and promising researchers in this field. Considerable time is allocated to short oral communications and to oral poster presentation, that will certainly contribute to the success of this meeting with exciting new findings.

The **15th International SPDM Symposium** will take place at the Hotel Vila Galé - Coimbra, a venue that provides excellent facilities to accommodate the delegates and the industry exhibitions. The Symposium includes the First SPDM National Treatment Protocol Group Meeting and the Fifth SPDM Nutrition meeting. A satellite meeting dedicated to Phenylketonuria (PKU) – "Management of PKU during life" – will take place on the 16th of March, at the same venue.

The Organizing Committee is looking forward to a very successful meeting.

Maria Carmo Macário



Symposium Chairperson
2019 SPDM Annual Symposium Meeting

15th INTERNATIONAL SYMPOSIUM OF THE PORTUGUESE SOCIETY FOR METABOLIC DISORDERS

OLD DISEASES, NEW TREATMENTS

VENUE: COIMBRA | HOTEL VILA GALÉ
14th – 16th MARCH 2019

Event management:

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Programme

Scientific Programme

Thursday, 14th March

08:00 - Registration Opening

08:45 - Symposium Opening - Welcome Address on behalf of the SPDM
Local organization representatives

09:00 - 10:15 - Session I – The moving targets of expanded newborn screening for Inborn Errors of Metabolism
Chairpersons: Helena Santos, Lisboa, PT / Laura Vilarinho, Porto, PT

09:00 - The experience in the United Kingdom
Rachel Carling | London, UK

09:20 - Newborn Screening of Lysosomal Storage Disorders
Alberto Burlina | Padova, IT

09:40 - Expanded newborn screening in Portugal
Ana Marcão | Porto, PT

10:00 - Discussion

10:15 - 10:30 - Coffee Break

10:30 - 11:45 - Session II – Politics and economics in the treatment of Inborn Errors of Metabolism
Chairpersons: José Manuel Silva, Coimbra, PT / António Freire Gonçalves, Coimbra, PT

10:30 - Economic perspective
Nadim Habib | Lisboa, PT

10:50 - Regulatory perspective
Carlos Fontes Ribeiro | Coimbra, PT

11:10 - Clinical perspective
Teresa Cardoso | Porto, PT

11:30 - Discussion

11:45 - 13:30 - Session III – Inborn Errors of Metabolism I: an update
Chairpersons: Sílvia Sequeira, Lisboa, PT / Isabel Rivera, Lisboa, PT

11: 45 - Therapeutic goals in Gaucher Disease: the best definition of treatment response
Deborah Elstein | Jerusalem, IL

12: 05 - Neuronal Ceroid Lipofuscinoses: assessment and treatment
Paul Gissen | London, UK

12:25 - Expanding treatment options for Methylmalonic aciduria
Stephanie Grünewald | London, UK

12: 45 - CYP46A1 as a new therapeutic target in Niemann-Pick type C disease (2018 SPDM research grant winner)
Elsa Rodrigues | Lisboa, PT

13:05 - Discussion

13:30 - 14:45 - Poster View / Lunch

14:45 - 16:00 - Session IV – Metabolic pathways and subcellular organelles: new connections
Chairpersons: Catarina R. Oliveira, Coimbra, PT / Isabel Santana, Coimbra, PT

14:45 - Endoplasmic reticulum stress: new insights in Inborn Errors of Metabolism
Cláudia Pereira | Coimbra, PT

15:05 - Hypothalamic dysfunction and neurodegeneration
Cláudia Cavadas| Coimbra, PT

15:25 - Intercellular communication in Inborn Errors of Metabolism
Henrique Girão | Coimbra, PT

15:45 - Discussion

16:00 - 16:30 - Coffee Break

16:30 - 18:00 - Session V – Selected Free Communications
Chairpersons: Esmeralda Rodrigues, Porto, PT / Patrícia Janeiro, Lisboa, PT

18:10 - First SPDM National Treatment Protocol Group Meeting
Chairpersons: Teresa Cardoso, SPDM President*, Porto, PT*

18:10 - Fifth SPDM Nutrition meeting (SPDM-GN)
Chairperson: Manuela Ferreira de Almeida, Porto, PT

19:30 - Departure from the hotel (Meeting point at the Hotel Lobby)

20:00 - Symposium Dinner

Friday, 15th March

08:00 - 09:00 - Session VI – Selected Free Communications
Chairpersons: Anabela Oliveira, Lisboa, PT / Hugo Rocha, Porto, PT

09:00 - 10:20 - Session VII – Nutritional paradigms in Inborn Errors of Metabolism
Chairpersons: Ana Faria, Coimbra, PT / Júlio César Rocha, Porto, PT

09:00 - Micronutrients: speculations in Inborn Errors of Metabolism
Peter Clayton | London, UK

09:20 - Nutritional Intervention after hepatic transplant in Inborn Errors of Protein Metabolism
Anne Daly | Birmingham, UK

09:40 - The effect of the nitrogen source on metabolism in Phenylketonuria (2018 SPDM/Orphan Europe research grant winner)
Maria João Pena | Porto, PT

10:00 - Discussion

10:20 - 10:40 - Coffee break

10:40 - 11:45 - Session VIII – Mitochondrial diseases: from clinics to basic research and back
Chairpersons: Célia Nogueira, Porto, PT / Sandra Jacinto, Lisboa, PT

10:40 - The challenges in the clinical evaluation of mitochondrial diseases
Shamima Rahman | London, UK

11:00 - Current role of functional mitochondrial study in the genomic era
Manuela Grazina | Coimbra, PT

11:20 - What is new in the treatment of mitochondrial disorders?
Mirian Janssen | Nijmegen, NL

11:40 - Discussion

12:00 - 13:15 - Session IX – Selected Free Communications
Chairpersons: Ana Cristina Ferreira, Lisboa, PT/ Hélder Esperto, Coimbra, PT

13:15 - 14:15 - Poster View | Lunch

14:15 - 15:10 - Session X – Inborn Errors of Metabolism II: an update
Chairpersons: Dulce Quelhas, Porto, PT / Anabela Bandeira, Porto, PT

14:15 - Urea Cycle Disorders: what is old, what is new, what can we change?
Amaya Bélanger-Quintana | Madrid, ES

14:35 - Riboflavin-Responsive Disorders
Manuel Schiff | Paris, FR

14:55 - Discussion

15:10 - 16:00 - Session XI – Treating Inborn Errors of Metabolism: future directions
Chairpersons: Elisa Leão Teles, Porto, PT / Isabel Tavares de Almeida, Lisboa, PT

15:10 - The development of new enzyme replacement therapies: the example of Hypophosphatasia
Sérgio Sousa | Coimbra, PT

15:30 - The possibilities of gene therapy for Inborn Errors of Metabolism
Paul Gissen | London, UK

15:50 - Oral treatment for Fabry Disease: the evolution in chaperone therapies
Patrício Aguiar | Lisboa, PT

16:10 - Discussion

16:30 - 16:50 Coffee Break

16:50 - 17:50 - Session XII – Selected Poster Communications
Chairpersons: Paula Leandro, Lisboa, PT / João Durães, Coimbra, PT

18:00 - Awards / Closing Remarks
Teresa Cardoso, SPDM President

18:30 - SPDM General Assembly

Selected Free Communications

14th MARCH 2019

Session I – 16h30 – 18h00

OC 01 – **Transcriptomics profiling of niemann-pick type c patients – activation of the unfold protein response in a specific case**
Marisa Alexandra Rego da Encarnação, Instituto Nacional de Saúde Dr. Ricardo Jorge, Porto, Portugal.

OC 02 – **Glutaric aciduria type i – functional and structural characterization of two glutaryl-coa dehydrogenase disease-associated variants**
Ribeiro JV, Faculdade de Ciências, Universidade de Lisboa, Lisboa, Portugal.

OC 03 – **Design of small molecules that increase human phenylalanine hydroxylase thermosatbility** -
Lopes, R., Faculdade de Farmácia da universidade de Lisboa, Lisboa Portugal.

OC 04 – **The constraints of the treatment in a pediatric population: a parental survey**
Teresa Campos, Centro Hospitalar e Universitário de São João, Porto, Portugal.

OC 05 – **Pediatric liver transplantation in portuguese Wilson's disease patients**
Susana Nobre, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal.

OC 06 – **Overview of glycine encephalopathy in a metabolic reference center**
Filipa Rodrigues, Hospital Pediátrico, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal.

15th MARCH 2019

Session II – 08h00 – 09h00

OC 07 – **Effect of arginine and thiamine on pyruvate dehydrogenase complex deficient patient-derived cell lines**
Hana Pavlů-Pereira, Faculdade de Farmácia, Universidade de Lisboa, Lisboa, Portugal

OC 08 – **SCARB2 mutations as modifiers in Gaucher disease: the wrong enzyme at the wrong place?**
Maria Francisca Coutinho, Centro de Genética Médica Dr. Jacinto Magalhães, Centro Hospitalar do Porto, Porto, Portugal

OC 09 – **Neuronal ceroid-lipofuscinoses: from clinical to molecular bases**
Rita Jotta de Oliveira, Centro Hospitalar e Universitário de Lisboa Norte, Lisboa, Portugal

OC 10 – **The diagnostic paradigm shift: mitochondria are innocent untill proven guilty**
Margarida Paiva Coelho, Centro Hospitalar Universitário do Porto, Porto, Portugal.

Session IX - 12:00 – 13:15

OC 11 – **Nutritional management of maternal pku in chup (NMMPKU): retrospective study and offspring outcome**
Élia Joana Rodrigues Pinto, Centro Hospitalar e Universitário do Porto, Porto, Portugal.

OC 12 – **Biopsychosocial profile of pku patients throughout life: challenges in psychological support**
Rocha JR, Centro Hospitalar e Universitário do Porto, Porto, Portugal.

OC 13 – **Pyruvate dehydrogenase deficiency – review of 6 clinical cases**
Ana Luísa Rodrigues, Hospital Divino Espírito Santo de Ponta Delgada, Açores, Portugal.

OC 14 – **Congenital disorders of glycosilation – retrospective analysis of a cohort with n-glycosilation defects**
Sofia Freire Fernandes, Hospital Pediátrico, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal.

OC 15 – **Fish odor syndrome genetic investigation: how far can we go?**
Teresa Loução de Almeida, Hospital do Espírito Santo de Évora, Évora, Portugal.

Selected Poster Communications

Session XII - 16:50 – 17:50

PC 01 – **CTNS molecular genetics profile in a portuguese cystinosis population**
Filipa Ferreira, Instituto Nacional de Saúde Dr. Ricardo Jorge, Porto, Portugal.

PC 02 – **Transition from paediatric to adult care in phenylketonuria (TRANS-PAC-PKU): the 2 year's impact on metabolic control and adherence**
Maria de Campos Paiva Peres, Centro Hospitalar e Universitário do Porto, Porto, Portugal.

PC 03 – **Molecular diagnosis of mitochondrial disease with targeted next generation sequencing: a cohort of 250 patients**
Célia Nogueira, Instituto Nacional de Saúde Dr. Ricardo Jorge, Porto, Portugal.

PC 04 – **Prolidase deficiency: report of three patients**
Ana Rita Soares, Centro de Genética Médica Dr. Jacinto Magalhães, Centro Hospitalar Universitário do Porto, Porto, Portugal.

PC 05 – **Mitochondrial protein import genes involvement in leber's hereditary optic neuropathy (LHON)**
Márcia Teixeira, Centro de Neurociências e Biologia Celular, Laboratório de Biomedicina Mitocondrial e Teranóstica, Universidade de Coimbra, Coimbra, Portugal

PC 06 – **Genetic studies – a usefull tool for diagnosis of heterogeneous mitochondrial disorders**
Andreia Forno, Hospital do Espírito Santo de Évora, Évora, Portugal.

PC 07 – **Assembly of oxphos system in patients with respiratory chain disease**
Marta Simões, Centro de Neurociências e Biologia Celular – Laboratório de Biomedicina Mitocondrial e Teranóstica, Universidade de Coimbra, Portugal.

PC 08 – **Brain magnetic resonance imaging findings in chronic progressive external ophthalmoplegia**
Daniela Vieira, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal.

PC 09 – **ARNT2 mutations: expanding the spectrum of mitochondrial disorders**
Helena Santos, Centro Hospitalar de Vila Nova de Gaia/Espinho, Vila Nova de Gaia, Portugal.

PC 10 – **Plasma lysosphingomyelin-509 – how to reach a prompt niemann-pick type c (NPC) diagnosis**
Sales F., Centro de Genética Médica Jacinto de Magalhães, Centro Hospitalar Universitário do Porto, Porto.

Speakers

Session I

The moving targets of expanded newborn screening for Inborn Errors of Metabolism

Rachel Carling
London, UK

Rachel graduated with a first class honours degree in Chemistry from Manchester University. She then gained a PhD in Analytical Chemistry before moving to Leeds and training as a Clinical Biochemist. She chose to specialise in metabolic biochemistry because of her interest in analytical techniques and obtainined FRCPath in 2007. Rachel is now a Consultant Clinical Scientist at Guys & St Thomas' Hospital where she is Director of South East Thames Regional Newborn Screening Laboratory, Scientific Head of Service, Clinical Lead for Biochemical Sciences and Scientific Director (GSTT site, Viapath).

Her main area of interest is inherited metabolic disease with a particular focus on the application of tandem mass spectrometry to the measurement of small molecules. Since 2012, Rachel has lead the national drive to improve harmonisation of expanded newborn screening results and in 2017 she was awarded the Chief Scientific Officer's Knowledge Transfer Partnership, and the opportunity to work with the UK's National Measurement System to implement innovative ideas to improve patient care. The aim of Rachel's project was the harmonisation of expanded newborn screening in the UK.

Rachel is committed to service improvement and has a keen interest in Continuous Quality Improvement (CQI) and A3 thinking. A3 thinking provides a structured and evidence based approach to problem solving and delivering change and is an invaluable tool to enable the NHS to improve patient pathways with minimal resources whilst providing development opportunities for staff. Rachel has recently implemented a programme of Analytical CQI at Viapath.

Alberto Burlina
Padova, IT

Dr Alberto Burlina is the Head of the Division of Inborn Errors of Metabolism, Department of Pediatrics, University Hospital of Padova, Padua, Italy. He gained his Medical Degree from the University of Padova, and subsequently recieved National Board Certification in Pediatrics. Dr Burlina then became a Clinical Research Fellow at the Department of Clinical Chemistry, Hospital for Sick Children, Toronto, Canada, before returning to Italy to work at the Metabolic Unit of the Department of Pediatrics, University of Padova. Dr Burlina has authored and coauthored over 100 research publications and book chapters. His research interests include clinical and biochemical characterisation of inborn errors of intermediary metabolism, metabolic diseases in adulthood, and clinical application of tandem mass spectrometry. Dr Burlina's major research contributions include identification of novel inborn errors of metabolism (ethylmalonic aciduria, hyperinsulinism hyperammoaemia syndrome), definition of the biochemical role of orotic acid and orotidine in ornithine transcarbamylase deficient patients, development a therapeutic approach using hepatocyte transplantation, and contributing to the study of neurotransmitter modifications in amino acid disorders. He is Director of the Norh East Italy Expanded Neonatal Screening Program for for inborn errors of metabolism including the pilot screening program for lysosomal disorders.

Ana Marcão
Porto, PT

Ana Marcão is a genetic specialist in the Portuguese neonatal screening laboratory, where she is enrolled in the metabolic screening through MS/MS. She obtained her first degree in Biochemistry (1994) and her PhD in Biomedical Sciences (2004) at the University of Porto (PT). She has always been interested in the genetic of rare diseases, and for ten years she was a team member of UniLipe from the Molecular and Cellular Institute (IBMC) of Porto, where she developed her scientific activity in Lysosomal Storage Disorders (LSD), namely in the genetic characterization of LSD patients and in the biochemical and functional characterization of mutated proteins.

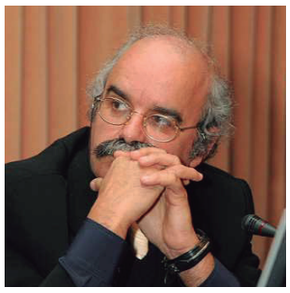
In 2004, she moved to the neonatal screening laboratory and integrated the team that was implementing metabolic expanded newborn screening in Portugal. While remaining part of this team, she was also actively involved in the implementation of Cystic Fibrosis screening in Portugal. Currently, she is starting a new project to establish Sickle Cell Disease screening. She is a founder member of the Portuguese Society for Metabolic Disorders (SPDM).

Session II

Politics and economics in the treatment of Inborn Errors of Metabolism

Nadim Habib
Lisboa, PT

Nadim Habib has a Master's degree in Economics by the London School of Economics and is currently a lecturer at the NOVA School of Business and Economics in Lisbon, teaching in the Master's and Executive Education programmes. Before becoming a scholar, he worked in banking, consulting and communications.
From 2008 to 2015, he was the CEO of the Executive Education programme at the NOVA School of Business and Economics and a member of the Board of the European Foundation for Management Development. His programme "From Creativity to Innovation" was voted the Best in The World for 2 consecutive years (2014 and 2015) by the CEMS Network, a Global Alliance of 27 Business Schools and 90 Corporations.
Nabim Habib has an important role as an international consultant for leading organizations, in the fields of strategy, innovation and creativity. He also receives frequent invitations to be a speaker in conferences and debates.



Carlos Fontes Ribeiro
Coimbra, PT

Carlos Alberto Fontes Ribeiro, MD, MSc, PhD, is Director of the Institute of Pharmacology and Experimental Therapeutics of the Faculty of Medicine, University of Coimbra, and is Full Professor of Pharmacology, Therapeutics and Exercise Prescription. He is specialist in Clinical Pharmacology and Coordinator of the Master Degree in Sports Medicine and co-coordinator of the Master Degree and PhD Course in Medicinal Chemistry, as well as Co-coordinator of the Coimbra Pharmacovigilance Unit. He is consultant for the area of Pharmacoeconomics and Health Technology Assessment (DATS and SIATS) of Infarmed. He has almost 300 full papers published, in national and international journals, and 38 chapters of books. He performed almost 600 lectures or conferences. He is member of 14 Scientific Societies.

Teresa Cardoso
Porto, PT

Specialist and Senior Consultant in Internal Medicine. Expert in evaluation, diagnosis, management and follow-up of adult patients with inborn errors of metabolism mainly lysossomal, mitochondrial and urea cycle disorders. Head of Internal Medicine A Unit in the Department of Medicine, and head of the adult team of the Metabolic Unit of University Hospital Center São João, Porto, Portuguese Reference Center for Inherited Metabolic Disorders (IMD). President of Portuguese Society of Metabolic Disorders (2018-2019). Member of the Board of Portuguese Internal Medicine Specialty College (2009-2015).Chair of the Stroke Group of Portuguese Society of Internal Medicine. (2006-2018). Competence in Management of Health Services by the Portuguese Medical Association. Member of Scientific Council of the Portuguese Internal Medicine Journal (2006-2015). Developing clinical research in internal medicine and IMD, has published extensively. Participation on International projects of prospective registry of patients with intoxication type metabolic diseases, MPSV and NPC and a multicentric project about characterize the effect of sphingomyelin accumulation on NKT cell development and activation. FCT and University of Porto approved projects in the field of IMD. National and multicentric projects in Lysosomal Storage diseases, pathogenic mechanisms, biochemical and immunologic characterization, Gaucher disease, Pompe disease, MPSI and next generation sequencing methods for the diagnosis of Lysosomal Diseases. Assistant of Medicine in Clinical Practice 6th year, at the Faculty of Medicine of Porto University.

Session III

Inborn Errors of Metabolism I: an update

Deborah Elstein
Jerusalem, IL

Dr. Deborah Elstein, PhD (Medicine) was Coordinator of Clinical Research at the Gaucher Clinic in Shaare Zedek Medical Center in Jerusalem, Israel under the directorship of Prof. Ari Zimran from 1993 to 2015.

She has authored more than 250 papers and book chapters with clinical observations and lab-bench studies, as well as having been involved in seminal clinical trials for new drugs for Gaucher disease including imiglucerase, miglustat, velaglucerase alfa, eliglustat, taliglucerase alfa, and a pilot study with ambroxol.

In addition to her involvement in Gaucher disease, she has an interest in Late-onset Tay-Sachs disease, and other Lysosomal Storage Disorders, especially Fabry disease where she was an Editor of the first textbook dedicated to this disorder. Since 2016 she serves as a part-time contractor for Shire's Global Medical Affairs team with a mandate for Gaucher disease.

Paul Gissen
London, UK

Professor Paul Gissen, MBChB, PhD

UCL Great Ormond Street Institute of Child Health and Great Ormond Street Hospital for Children NHS Foundation Trust, London, UK

Paul Gissen is the Head of the Genetics and Genomic Medicine academic programme at the UCL Great Ormond Street Institute of Child Health, London, UK, as well as Honorary Consultant in paediatric metabolic diseases at Great Ormond Street Hospital for Children NHS Foundation Trust.

Professor Gissen obtained his medical degree from the University of Glasgow, UK, in 1995, before completing his paediatrics training at Manchester, Sheffield and Birmingham Children's Hospitals (all within the UK); this included sub-specialty training in inherited metabolic disorders.

Professor Gissen completed his PhD at Birmingham University, where he investigated the genetics of rare paediatric liver disorders.

Professor Gissen's clinical interests lie with intracellular trafficking disorders such as arthrogryposis, renal dysfunction, cholestasis syndrome, Niemann-Pick disease type C (NPC) and NCL. His research achievements so far include the identification of more than 20 novel disease genes mutations which are responsible for inherited paediatric disorders. Professor Gissen's research group is also investigating the molecular and cellular basis of intracellular trafficking disorders, in addition to developing novel methods for diagnosis and treatment of inherited metabolic disorders. He is also an investigator on clinical trials of cerliponase alfa sponsored by BioMarin.

Stephanie Grünewald
London, UK

Dr Stephanie Grünewald PhD FRCPCH

Dr Stephanie Grünewald joined the Consultant team of Inherited Metabolic Diseases at Great Ormond Street Hospital (GOSH) in London / UK in 2004. She is also a Senior Lecturer at the Institute of Child Health.

After having completed her paediatric training in Düsseldorf / Germany, she commenced her sub-speciality training in Inborn Errors of Metabolism and trained in four leading European Metabolic Centres, including Düsseldorf, Nijmegen / The Netherlands, Leuven / Belgium and London. Whilst being on a postdoctoral and clinical fellow position at the University of Leuven, her main clinical and basic research interest was focused on the emerging field of congenital disorder of glycosylation (CDG), resulting in the discovery of several new disorders.

She was granted a Marie Curie Fellowship, completed her Habilitation and was elected as Privatdozent at the University of Essen / Germany. This was followed by a PhD on "Congenital Disorders of Glycosylation – Clinical and Molecular Studies" in 2006 at the University of Nijmegen. Prior to her appointment in GOSH, she worked as a Consultant in Neuropaediatrics with special interest in Metabolic Medicine at the University Children's Hospital in Essen/Germany.

In her current position, she combines clinical and academic work on a broad spectrum of IMD. Dr Grünewald is Chief and Principle Investigator of several international clinical trials/registries and is a member of various International disease specific networks and advisory boards.

Elsa Rodrigues
Lisboa, PT

Elsa Rodrigues is an Assistant Professor at Faculty of Pharmacy Universidade de Lisboa (iMed.ULisboa-FFUL). She holds a degree Biology and a PhD in Molecular Biology.

During her Doctoral studies at Maria Celeste Lechner's lab at the FFUL in collaboration with Patrick Maurel (Unité INSERM 128), she elucidated transcriptional mechanisms involved in gene regulation of liver-specific Cytochrome P450 genes. In the last 10 years, Elsa's main goal is to characterize the regulatory pathways involved in brain cholesterol homeostasis, and therefore to provide a basis for the development of therapeutic approaches for diseases that stretch from genetic disorders, such as Niemann Pick Type C, to neurodegenerative disorders such as Alzheimer's Disease.

Her focus has been on the potential beneficial modulation of cholesterol homeostasis through ectopic expression or pharmacological up-regulation/ activation of the neuronal specific cholesterol 24-hydroxylase encoded by the cytochrome P450 CYP46A1 gene.

Session IV

Metabolic pathways and subcellular organelles: new connections

Cláudia Pereira
Coimbra, PT

Cláudia Maria Fragão Pereira, Faculty of Medicine & Center for Neurosciences and Cell Biology, University of Coimbra, Portugal.

C Pereira received, in 2000, her PhD from the University of Coimbra where she is presently "Investigadora Auxiliar" at the Faculty of Medicine. She is also Principal Investigator of the research line "Endoplasmic reticulum (ER) stress response and RE-mitochondria axis" in the group "Cell Signaling and Metabolism in Disease" at the Center of Neurosciences and Cell Biology (CNC) from the same university.

Her laboratory has three major research goals: i) To elucidate how the disturbance of the Endoplasmic Reticulum (ER) stress response and of ER-mitochondria contacts can trigger neuronal dysfunction in Alzheimer's disease (AD); ii) To understand whether perturbations in mitochondria-associated ER membranes (MAM) are implicated in the impairment of cellular resilience in psychiatric disorders, namely Bipolar disorder (BD). Iii) to obtain experimental evidences supporting the therapeutic potential of compounds obtained from Portuguese natural resources.

To tackle these fundamental questions, her laboratory employs multidisciplinary approaches, which range from a combination of biochemical and cell biology methodologies to in vivo, in vitro and ex vivo models such as genetically-modified animal models, primary cultures of dissociated neurons, cell lines and patient-derived cellular models.

Cláudia Cavadas
Coimbra, PT

Cláudia Cavadas (CC) is PharmD, Master in Cell Biology, and PhD in Pharmacology, University of Coimbra. During her PhD, CC spent 3 years at the University of Lausanne and CHUV, Lausanne, Switzerland.

CC is Assistant professor, with tenure and habilitation, at the Faculty of Pharmacy of the University of Coimbra and Coordinates "Neuroendocrinology and Aging group" at CNC - Center for Neuroscience and Cell Biology.

CC was the principal investigator of 15 funded projects and is co-author of around 70 international papers. CC was the elected President of the Portuguese Society of Pharmacology and coordinator of the Science Communication Office at CNC. Since March 2019, Cláudia Cavadas is vice dean of the University of Coimbra.

Henrique Girão
Coimbra, PT

Henrique Girao (HG) is Investigator at the Faculty of Medicine of University of Coimbra (FMUC), where he is Deputy Director for Research and Development, Vice-chairperson of the Cardiovascular Council, Leader of the Group "Ubiquitin-dependent Proteolysis and Intercellular Communication" and Director of the Laboratory of Biostructural Imaging.

HG also coordinates the PhD programme in Health Sciences and the Master Course of Biomedical Research, and integrates the Board of Directors of the Inter-University Doctoral Programme in Ageing Chronic Diseases.

HG is specialized in cellular and molecular mechanisms involved in the regulation of protein degradation and intercellular communication, necessary for the maintenance of cell homeostasis.

In particular, HG has been interested in understanding how disturbance of proteolysis, namely non-canonical functions of ubiquitin in signalling lysosomal degradation, and intercellular communication, mediated by gap junctions and exosomes, contribute to cardiovascular disorders.

Session VII

Nutritional paradigms in Inborn Errors of Metabolism

Peter Clayton
London, UK

Peter Clayton qualified in medicine from King's College Cambridge and University College Hospital London. He undertook paediatric sub-speciality training at UCH, the Brompton, Guy's and Great Ormond Street Hospitals. His laboratory training in the Institute of Child Health led to a thesis on the measurement of bile acids in plasma in children by gas chromatography and gas chromatography – mass spectrometry.

He was appointed as a consultant in the Department of Metabolic Medicine at Great Ormond Street Hospital London in 1987. He was appointed Professor of Paediatric Metabolic Disease and Hepatology at the UCL Institute of Child Health in 1998.

His research interests include inborn errors of bile acid and sterol metabolism, inborn errors affecting neurotransmitter and vitamin B6 metabolism, disorders of manganese homeostasis, inborn errors of fatty acid oxidation, mitochondrial disorders and peroxisomal disorders. He has been awarded various prizes for research including best research presentation at SSIEM meetings, the Horst Bickel Prize and the Komrower lectureship.

He was Chairman of the Society for the Study of Inborn Errors of Metabolism from Sept 2010 until Sept 2016.

Anne Daly
Birmingham, UK

Anne Daly (BSc Hons, MMed Sci RD)

Joined the Birmingham Children's Hospital team in 1995, after gaining a foundation in many aspects of paediatric dietetics and a Master's degree an opportunity arose to specialise in paediatric dietetic metabolic disease. In 2013, she became a part-time PhD student at Birmingham University, the title of the thesis is: The Nutritional Profiling of Special Feeds for Inborn Errors of Protein Metabolism.

She has worked on many new formulae for inherited metabolic disorders, paediatric enteral feeding and nutritional support over the last 20 years.

She has an outstanding record of achievement evidenced by 56 publications, 82 abstracts and invitations to speak on work produced within Birmingham Children's Hospital, both within the UK, European and not European countries. She is a member of the working group for the BDA/University of Plymouth Masters course on IMD dietetics. Her motto to improve is to change, so to be perfect is to have changed often.

Maria João Pena
Porto, PT

Maria João Pena is graduated in Nutritional Sciences by the Faculty of Nutrition and Food Sciences of the University of Porto. Then, she got her Master's degree in Molecular Medicine and Oncology from the Faculty of Medicine of the same university.

Since December 2015, she is attending a PhD in Metabolism – Clinical and Experimental from the previous institution. Her main areas of work are clinical nutrition and research in health sciences. Currently, she is a PhD fellow.

Session VIII

Mitochondrial diseases: from clinics to basic research and back

Shamima Rahman
London, UK

Professor Shamima Rahman is Professor of Paediatric Metabolic Medicine at the UCL Great Ormond Street Institute of Child Health (ICH), and honorary consultant at Great Ormond Street Hospital for Children, London. She trained in Medicine at Oxford University, and in Paediatric Metabolic Medicine at Great Ormond Street Hospital. Professor Rahman established the Mitochondrial Research Group at ICH in 2000, with a particular focus on enhancing the outcomes for children affected by mitochondrial and other rare metabolic diseases by discovering mitochondrial disease genes, developing novel computational diagnostic strategies, and investigating therapeutic approaches where there are currently no disease-modifying treatments.

Professor Rahman is an Editor of the Journal of Inherited Metabolic Disease, a Senior Editor of the Annals of Human Genetics and Senior Adviser to the Society for the Study of Inborn Errors of Metabolism's Education and Training Advisory Committee. She sits on the Scientific Advisory Board of the French Muscular Dystrophy Association (AFM-Telethon), the Australian Mitochondrial Disease Foundation's Clinical and Scientific Review Panel, and the Medical Advisory Boards of the Lily Foundation and the Freya Foundation, and acts as a special adviser to the Human Fertilisation and Embryology Authority.

Manuela Grazina
Coimbra, PT

Manuela Grazina is a specialist in Biochemical and Human Genetics, particularly in Mitochondrial Biomedicine, Bigenomics and Theranostics, with special focus on mitochondrial disorders. She is a PhD in Biomedical Sciences (specialization in Biochemical Genetics) and an MSc in Cell Biology (specialization in Neurogenetics). She has a strong and solid professional experience for more than 20 years, as a university teacher, as a researcher, as Clinical Laboratory Geneticist and as a Science communicator.
Professional experience: - Researcher and group leader at the Center for Neurosciences and Cell Biology since 1992. - Founder and Director of the Laboratory of Mitochondrial Biomedicine and Theranostics since march 1995. - Assistant Professor (Senior Lecturer) at the Faculty of Medicine, University of Coimbra - FMUC) since 2006, teaching at the same faculty since 1997. - Member of the Pedagogical Council of the FMUC, elected on June 3, 2015; member of the Quality Council of the University of Coimbra, since July 1, 2016; member of the Coordinating Committee of the Integrated Masters in Medicine, in the Coordination of the component Pedagogical Quality, since the 2 of September of 2016; Director of the Office of Support to the Quality Management System of the FMUC, since July 2017.
She has coordinated 18 Advanced Courses and supervised 50 theses – 9 PhD (6 completed), 41 MSc (40 completed) – and has participation in 22 Research Projects (PI in 8). She is a member of 2 consortiums: "Coenzyme Q (10) deficiency study group" and "CEIBA.FP Consortium of the Ibero-American Network of Pharmacogenetics and Pharmacogenomics (RIBEF)". She has organized several scientific meetings, co-authoring 57 publications "examined by experts", 4 book chapters, and 106 abstracts published in scientific meetings (mostly indexed), as well as over 518 scientific communications in Congresses, 306 of which posters, 109 conferences per invitation and 103 oral communications. Additional she has performed more than 100 lectures in the scope of Science communication.
She has won several prizes, namely for best poster/oral communication, a Gold medal for Science (2013) and best teacher at the Faculty of Medicine (2014).

Mirian Janssen
Nijmegen, NL

Mirian Janssen Ph.D., is internist specialized in metabolic disease at the Radboud University Medical Center, department of internal medicine. She also works at the department of Pediatrics, taking care of the transition of the children into adulthood. She has been appointed as principle clinician for the care of adult metabolic patients. Research focus is natural history studies, outcome measures for patients with mitochondrial diseases and clinical trials.
3 related publications

Janssen MCH, Koene S, de Laat P, Hemelaar P, Pickkers PP, Spaans E, Beukema R, Beyrath J, Groothuis J, Verhaak C, Smeitink JAM. The KHENERGY study: safety and efficacy of KH176 in mitochondrial m.3243A>G spectrum disorders. Clin Pharm Ther 2019.
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Session X

Inborn errors of metabolism II: an update

Amaya Bélanger-Quintana
Madrid, ES

Dr. Amaya Bélanger-Quintana studied Medicine at the Universidad Autónoma de Madrid and did her Pediatric residency at the Hospital Ramón y Cajal de Madrid.
The Metabolic Unit of this hospital is of national reference, and she soon became interested in the field, working with them first as a Fellow in an investigation level and soon after as full-time Paediatrician. She is currently Head of the Metabolic Unit of this hospital, which includes both paediatricians and adult specialists.

She is interested in the expansion of knowledge on metabolic diseases both among paediatricians, other medical specialists, and the society in general, being one of the paediatric resident tutors, giving classes both in medical school and doctorate settings and participating with several foundations for the social advancement of rare diseases. Within the metabolic field she has worked mainly on aminoacid disorders, especially on PKU, developing her doctoral degree on this disease. She is currently a member of several national and international inborn errors of metabolism scientific advisory boards and has published extensively.

Manuel Schiff
Paris, FR

Dr Manuel Schiff is an Associate Professor of Pediatrics and Head of the Reference Centre for Inborn Errors of Metabolism at the Robert-Debré University Hospital in Paris, France.

After an undergraduate degree in Biochemistry and a residency in Paediatrics, he completed a PhD in mitochondrial biology, under the supervision of Dr Pierre Rustin at the University of Paris Descartes. He then was a post-doctoral fellow at Dr Jerry Vockley's laboratory at the University of Pittsburgh, USA.

His clinical research interests include mitochondrial energy metabolism, homocystinurias/ B12 and folate metabolism disorders for which he is a partner in the European collaborative network (EHOD). His basic research interest is mitochondrial energy metabolism with a focus on mitochondrial disorders. He has been appointed Honorary Secretary of the SSIEM in September 2016.

Session XI

Treating inborn errors of metabolism: future directions

Sérgio Sousa
Coimbra, PT

Sérgio B. Sousa, MD, PhD, is a medical geneticist at Hospital Pediátrico, Centro Hospitalar e Universitário de Coimbra, Portugal, with a special interest in intellectual disability syndromes, dysmorphology and genetic skeletal disorders.

Sérgio is the coordinator of the local skeletal dysplasias multidisciplinary team. This team has been reorganized and improved since 2015 and is integrated in the European Reference Network on Rare Bone Disorders ERN BOND. Sérgio trained in multiple centres across Europe, including the Centre de Référence des Maladies Osseuses Constitutionnelles, Hôpital Necker-Enfants Malades, Paris, and completed his PhD at the UCL Institute of Child Health, London, focused on identifying novel genes for rare unsolved syndromes.

Currently, Sérgio has also been involved in implementing a local multidisciplinary genomics interpretation team; is Board Member of the European Society of Human Genetics; and Assistant Professor at the University of Coimbra Medical School, strongly involved in training medical students, future medical geneticist and other professionals.

Paul Gissen
London, UK

Professor Paul Gissen, MBChB, PhD
UCL Great Ormond Street Institute of Child Health and Great Ormond Street Hospital for Children NHS Foundation Trust, London, UK

Paul Gissen is the Head of the Genetics and Genomic Medicine academic programme at the UCL Great Ormond Street Institute of Child Health, London, UK, as well as Honorary Consultant in paediatric metabolic diseases at Great Ormond Street Hospital for Children NHS Foundation Trust.

Professor Gissen obtained his medical degree from the University of Glasgow, UK, in 1995, before completing his paediatrics training at Manchester, Sheffield and Birmingham Children's Hospitals (all within the UK); this included sub-specialty training in inherited metabolic disorders.

Professor Gissen completed his PhD at Birmingham University, where he investigated the genetics of rare paediatric liver disorders.

Professor Gissen's clinical interests lie with intracellular trafficking disorders such as arthrogryposis, renal dysfunction, cholestasis syndrome, Niemann-Pick disease type C (NPC) and NCL. His research achievements so far include the identification of more than 20 novel disease genes mutations which are responsible for inherited paediatric disorders. Professor Gissen's research group is also investigating the molecular and cellular basis of intracellular trafficking disorders, in addition to developing novel methods for diagnosis and treatment of inherited metabolic disorders. He is also an investigator on clinical trials of cerliponase alfa sponsored by BioMarin.

Patrício Aguiar
Lisboa, PT

Patrício Aguiar graduated at Lisbon University Medical School in 2006 and completed his trainee in Internal Medicine, in 2017, at Centro Hospitalar Lisboa Norte (Lisbon, Portugal). He completed his PhD at Lisbon University Medical School, in 2018, in the field of inborn errors of metabolism (biomarkers of Anderson-Fabry disease) in partnership with the University College of London. He performs the evaluation and follow up of patients with inherited metabolic disorders, mainly lysosomal storage disorders. He is also member of the core team of one of the national reference center in inherited metabolic disorders (Centro Hospitalar Lisboa Norte), as well as member of the board of the rare diseases study group of the Portuguese Society of Internal Medicine
.
His main research areas are Lysosomal Storage Disorders and Autonomic Nervous System Diseases, with several ongoing research projects on Anderson-Fabry disease (AFD) biomarkers, autonomic manifestations of AFD, immunogenicity against recombinant proteins used for enzyme replacement therapy, factors affecting quality of life in patients with type 1 Gaucher disease and neuroimaging prodromic signs of Parkinsonism in Gaucher disease. In 2014, he was awarded the prize of the Federation for the Development of Internal Medicine in Europe for research in the field of rare disorders.

He is invited lecturer of Lisbon University Medical school and has published 22 articles in national and international peer-reviewed journals and presented more than 100 communications in national and international conferences and meetings.

SESSION I.

The moving targets of expanded newborn screening for Inborn Errors of Metabolism Lectures

CHAIRPERSONS

Helena Santos

MD, Unidade de Neurociências da Infância e Adolescência, Serviço de Pediatria CHVNG/E, Centro de Referência de Doenças Hereditárias do Metabolismo do CHS.João, Porto, Portugal

Laura Vilarinho

PhD, Unidade de Rastreio Neonatal, Metabolismo e Genética, Instituto Nacional de Saúde Dr. Ricardo Jorge, Porto, Portugal

The experience in the United Kingdom

Rachel Carling
Guys & St Thomas' Hospital
London, UK

The Moving targets of expended newborn screening for inborn errors of metabolism: The experience in the United Kingdom. Dr Rachel Carling, Viapath, Guys & St Thomas' NHSFT.

England screens for 6 disorders (PKU, MCADD, IVA, HCU, GA1, MSUD) by tandem mass spectrometry. The screening programme is tightly governed: all 13 laboratories adhere to national protocols with common cut-off values (COV) so it is important that inter-laboratory variation is minimal to ensure analytical reliability of results. However, the lack of traceable reference materials, predominant use of in-house reagents and limitations of the existing methodology make this challenging. Inter-laboratory variation at the 90th centile ranges from 17% for octanoylcarnitine to 50% for decanoylcarnitine. The situation is compounded by the use of 'calibration factors' in many laboratories, ranging from 0.74 to 1.64. There is no clear evidence base for these factors and they make it difficult to separate out true differences due to instrument and reagent variation, from gross error. For most analytes there is good discrimination between the COV and the affected population so whilst there is minimal risk of false negative results due to inaccuracy, this is not necessarily the case for false positive results.

We believe the key contributors to inter-laboratory variation are instrument set up and internal standard (IS). To investigate the latter, we compared the inter-laboratory variation of 4 laboratories using in-house IS mix (n=100,000) with that of the same laboratories using a common IS mix (n=100,000). Results indicated a common internal standard significantly reduced inter-laboratory variation for most analytes. For example, the CV at the 90th centile for isovalerylcarnitine common IS group was 8% vs 24% for the in-house group, likewise glutarylcarnitine at 6% vs 23%.

We also investigated instrument set up by preparing a pooled bloodspot sample and analysing it in triplicate on instruments from 5 different manufacturers, pre and post optimisation of the method. Extraction efficiency was investigated by replicate analysis of 3 control samples at n=7 laboratories Acetonitrile and methanolic mobile phases were compared, with and without modifiers. The method of sample introduction was also optimised. The RSD of each analyte was compared. Prior to optimisation of the method the RSD across instruments ranged from <10% to 46%, (16%, 24%, 11%, 12%, 46%, 25%, 4%, 30% for methionine, leucine, phenylalanine, tyrosine, isovalerylcarnitine, glutarylcarnitine, octanoylcarnitine and decanoylcarnitine respectively). Post optimisation the RSD across the 5 instruments was reduced to <10% for all 8 analytes.

Newborn Screening of Lysosomal Storage Disorders

Alberto Burlina
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Background: Lysosomal storage disorders (LSDs) are rare inborn errors of metabolism that comprise approximately 50 different inherited defects.The growing availability of treatment options for LSDs has stimulated consideration of newborn screening efforts to diagnose LSDs and allow for appropriate early treatment initiation that may prevent or delay irreversible impairment or disability. We present our experience from a regional pilot newborn screening program in the North East Italy for four LSDs, using a multiplexed tandem mass spectrometry assay system for Pompe, Fabry, Gaucher, and Mucopolysaccharidosis Type I (MPS I)diseases.

Methods: Enzyme activity levels of acid β-glucocerebrosidase (ABG; Gaucher), acid α-glucosidase (GAA; Pompe), acid α-galactosidase (GLA; Fabry), and acid α-L-iduronidase (IDUA; MPS I)on all dried blood spots (DBS) collected over a period of 15 months were determined by tandem mass spectrometry using the NeoLSD ® assay system (PerkinElmer).Enzymatic activity cutoff values were determined from 6000 anonymus newborn blood spots. In the screening study, samples were retested if the value was below the instrument cutoff and a second spot requested depending on risk level, with referral for confirmatory testing and follow-up where appropriate.

Results:, 41,534 newborns were screened for the four LSDs. We identified 39 patiients with initial positive screening test. 19 of those underwent to confirmatory testing. 9 were affected confirmed by mutation analysis by a LSD (2 Pompe disease, 2 Gaucher disease, 5 Fabry disease). The incidence for Pompe disease is 1/20767, Gaucher disease 1/20767, Fabry disease 1/8307- No MPS ! were detected.The total incidence for the 4 defects is of 1 in 5,192 births.

Conclusion: Our experiences suggests that the technology for simultaneously measuring multiple enzyme activities (NeoLSD assay) by MS/MS was successful to detect patients with LSD. We define cutoffs levels for our population and implemented the entire system from screening to confirmation, treatment and follow-up.

Keywords: Expanded Newborn screening; Lysosomal storage diseases; Dried blood spot; Fabry disease, Pompe disease, Gaucher disease, Mucopolysaccharidosis Type I disease

Expanded newborn screening in Portugal

Ana Marcão
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Porto, Portugal

The Portuguese programme for newborn screening (NBS) includes 26 diseases (Congenital Hypothyroidism, 24 metabolic disorders and Cystic Fibrosis), presenting an estimated overall incidence of 1: 1.100 affected newborns (NB). It was established in the late 70s, starting with phenylketonuria (PKU), and soon after, congenital hypothyroidism (CH) screening. It is performed over the whole country, with a single laboratory performing around 400 samples every workday, which represents near 100% coverage rate (86.180 NB screened in 2017). It is a non-mandatory program, working in an implied consent-basis, with permanent dissemination of information to the parents, thus allowing an informed consent.

Since 2004, the screening for inborn errors of metabolism (IEM) started to be done through tandem mass spectrometry (MS/MS) which allowed extension to 24 metabolic diseases. The global frequency of all IEM integrated into the programme is estimated to be 1: 2.253. As expected, an increase in the detection rate of IEM was observed after extended-NBS implementation. MCAD deficiency revealed to be the most frequent metabolic disorder screened by MS/MS in Portugal, with a frequency even higher than PKU (1: 7.499 and 1: 10.772, respectively). The detection of other diseases like carnitine uptake deficiency (CUD), very long chain acyl CoA dehydrogenase deficiency (VLCADD), carnitine palmitoyl translocase type I deficiency (CPTID) or carnitine palmitoyltranslocase type II deficiency (CPTIID), also started to be a reality. While for most of these diseases newborn screening revealed tremendously beneficial for newborns and families, in other cases like methylcrotonyl CoA carboxylase deficiency (MCCD) and methionineadenosyltransferase (MAT I/III) deficiency, the benefits are not equally evident and raise some questions about their inclusion in the panel of screened disorders, which since 2019 also includes Cystic Fibrosis.
Enlarging the number of screened diseases, some of them demanding urgent clinical intervention in the first days of life, allowed the increase in the number of NBS-detected cases, but also brought additional challenges. Some subjects like the collection time frame, the time that it takes to arrive into the laboratory and the laboratory turnaround time became critical, and required special attention. Additional issues like specificity and sensitivity have also been carefully assessed along these years, and measures as the recent implementation of additional second tier tests for IEM screening allowed an important improvement in NBS-performance. Quality management is equally important and efforts have been made for ISO 15189 accreditation, which was already achieved for CH screening. Always attentive to new scientific and medical advances and to international recommendations, the Portuguese programme always tries to keep as an updated and dynamic program.

SESSION II.

Politics and economics in the treatment of Inborn Errors of Metabolism Lectures

CHAIRPERSONS

José Manuel Silva

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António Freire Gonçalves

MD, PhD, President of the Portuguese Brain Council
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Economic perspective

Nadim Habib
NOVA Business School
Lisboa, PT

A comprehensive understanding of the ethics and economics involved in the access to safe and effective orphan drugs is essential, since concerns have been raised about their prices. Pricing and reimbursement of orphan drugs are issues of high priority for policy makers, legislators, health care professionals, industry leaders, academics and patients. Although orphan drug pricing follows the same economic logic as drug pricing in general, there are some caveats that demand an individual approach to their effectiveness, cost-effectiveness and economic viability studies. There is also a need for a transparent and evidence-based approach towards orphan drug pricing.

Despite the implementation in 2000 of a EU specific policy to encourage the development of orphan drugs, and the recent increase in drug approvals, marketed orphan drugs address only a fraction of the large number of rare diseases, that affect millions of patients worldwide, showing that the unmet needs of this population remain a challenge and the associated economic burden will probably increase in the future.

Regulatory perspective

Carlos Fontes Ribeiro
Institute of Pharmacology and Experimental Therapeutics,
Faculty of Medicine of the University of Coimbra
Coimbra, Portugal

Since the year 2000 drug reimbursement in Portugal is based on Evidence-Based Medicine, and there must be non-inferiority, therapeutic equivalence or superiority of a new drug regarding efficacy and safety over a comparator, which could be non-pharmacological therapies. In 2015, by the Decree-Law 97/2015, June 1, was created the SiNATS, which maintained and developed the rules of evaluation of drugs for exclusive hospital use and reimbursement.

The product must have market authorization (by national, mutual recognition, decentralized or centralized (currently the majority) procedure), after analysis of administrative documentation, including SPC and information leaflet, and pharmaceutical (quality of the drug), pharmacological-toxicological (preclinical studies) and clinical studies. Phases I and II are always mandatory and observational studies are rarely considered, although they are quite useful in orphan or ultra-orphan drugs. However, to have marketing authorization only means that there is a positive benefit/risk ratio, and the drug may be less effective or safe than others that already exist on the market. Under current legislation, the Portuguese State can not pay for a new drug that has a worse benefit/risk ratio than its comparator (in the same clinical indication). For the others, there must have an economic evaluation that justifies the cost of the drug. In other words, there is a first phase of obtaining marketing authorization and a second phase which is the evaluation of health technology to be paid by the national financing system. The pharmaco-therapeutic assessment of the drug is currently carried out taking into account the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system. Initially a PICO assessment (patient/intervention/comparator/outcome) is performed and then a more detailed drug-therapeutic evaluation of the drug is made, mainly considering the robust randomized and controlled clinical trials, with the lowest possible bias, and comparative systematized reviews, namely meta-analyzes. PICO analysis is decisive in relation to this assessment, since the patient population for which the drug is intended must be well defined and cannot be different from that of the comparator, the intervention should reflect clinical trials, the comparators should be the medications used in the clinical indication and outcomes or endpoints should be critical or important. After this economic evaluation is done (cost/effectiveness or cost utility), since almost always the new drug is more expensive than the comparators.

Clinical perspective

Teresa Cardoso
Internal Medicine, Centro Hospitalar e Universitário de S. João,
SPDM President, Porto, PT

Great progress has been made in recent years in Inherited Metabolic disorders that have passed from a limited group of intractable and often fatal diseases, predominantly pediatric, to a large group of diseases with increasing treatment solutions. They are often the cause of potentially treatable acute unbalance, with chronic evolution reaching even a large number of patients to adulthood.

Patients suffering from these rare conditions should be entitled to the same quality of treatment as other patients.

The number of therapies approved for Inherited Metabolic disorders for the past two decades has grown a lot. Incentives for the development of orphan medicinal products have been available in Europe since 1999.The designation of potential medicinal products as orphan medicinal products is a long and complex procedure.
The granting of a marketing authorization for an orphan medicinal products in Europe (cover ing only those therapeutic indications which fulfil the orphan drug criteria) does not mean that the medicinal product is available in all the countries of the European Union. The accessibility of a certain orphan medicinal product in a certain country depends on the strategy of the laboratory and the decision taken by national health authorities concerning reimbursement.
Despite joint efforts, the heterogeneous approaches among countries make patients access to orphan drugs more complex.

It is mandatory to highlight the importance of convergence of stakeholders in the orphan drug industry to discuss and interact with government, hospitals, clinicians, pharmaceuticals, biopharmaceuticals, non-profit organizations and orphan drug developers.
Increase the knowledge on Inherited Metabolic disorders, improve communication and cross-border collaboration between the various research centres, the institutions and the patients continues to be a priority.

SESSION III.

Inborn Errors of Metabolism I: an update
Lectures

CHAIRPERSONS

Sílvia Sequeira

MD – Pediatria, Centro de Referência de Doenças Hereditárias do Metabolismo, Hospital D. Estefânia, CHLC, Lisboa, Portugal

Isabel Rivera

PhD - Instituto de Investigação do Medicamento (iMed.ULisboa), Faculdade de Farmácia da Universidade de Lisboa, Lisboa, Portugal

Therapeutic goals in Gaucher Disease: the best definition of treatment response

Deborah Elstein
Gaucher Clinic in Shaare Zedek Medical Center
Jerusalem, Israel

Care of patients with Gaucher disease has improved in the past decade by virtue of safer disease-specific therapies, especially the less immunogenic VPRIV, that allows patients to aspire to near-normalization of the visceral parameters of their disease. Moreover, with the advent of newer modalities of treatment, there is hope of even more effective and convenient options in the near future. This is especially relevant because of the recently documented increased risk for Parkinson disease and some cancers in persons with Gaucher mutations. Monitoring patients, therefore is more critical than ever, and with the highly specific biomarker, lyso-Gb1, patients can to attain an early warning system of disease progression or improvement. The patient-centric approach is the most innovative paradigm for patient empowerment in all phases of care, and, with the use of the Gaucher-specific Patient Reported Outcome questionnaire, affords a dialogue that includes psychological, social, and economic concerns that may be integral to the patient's perspective of his/her disease burden.

Neuronal Ceroid Lipofuscinoses: assessment and treatment

Paul Gissen
UCL Great Ormond Street Institute of Child Health &
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London, UK

Neuronal Ceroid Lipofuscinosis (NCL) is a group of related neurodegenerative disorders characterised by progressive dementia, epilepsy, vision loss and loss of mobility. Mutations in at least 13 different genes cause different types of NCL. There is phenotypic variability in the NCL whereby patients with mutations in the same gene may present at different ages.

Mutations in the CLN2/TPP1 gene, encoding lysosomal serine peptidase (TPP1 enzyme) causes classical late infantile form of NCL (CLN2). The estimated incidence of CLN2 is ~0.5 per 100,000 live births. Patients may experience early language delay but >50% may appear developmentally normal until about 3 years of age when they start developing seizures and ataxia followed by language and motor loss, dementia and finally loss of vision and early death around the age of 10. Until recently the standard of care was purely supportive.

The effect of intraventricular (ICV) infusions of 300mg of recombinant human TPP1 (cerliponase alfa) was evaluated in a multicenter, open-label study in children with CLN2 disease who were between the ages of 3 and 16 years. Cerliponase alfa administered via ICV infusion every 14 days was well tolerated and no patients discontinued treatment due to AEs. The primary outcome was the time until a 2-point decline in the score on the motor and language domains of the CLN2 Clinical Rating Scale (ML score, which ranges from 0 to 6, with 0 representing no function and 3 representing normal function in each of the two domains), which was compared with the time until a 2-point decline in 42 historical controls.

There was greater than 13-fold reduction in risk of a 2-point loss in ML score which resulted in attenuation in the loss of motor and language function compared with natural history control patients after 96 weeks of treatment. There was also attenuation of cortical grey matter volume loss on MRI that is delayed in relation to the attenuation seen in clinical scores. Patients had fewer and less severe seizures reported over time.

Expanding treatment options for Methylmalonic aciduria

Stephanie Grünewald
Great Ormond Street Hospital (GOSH) & Institute of Child Health
London, UK

Isolated methylmalonic aciduria (MMA) is a devastating inborn error of metabolism most commonly caused by complete (mut0) or partial (mut-) deficiency of methylmalonyl-CoA mutase (MUT).

Mainstay of treatment is symptomatic and preventive: mainly based on a protein restricted diet, cofactor supplementation, aggressive treatment of metabolic decompensations and early monitoring and treatment of secondary events / complications.

Several factors have contributed to the extension of life expectancy of patients: earlier diagnosis (including Newborn Screening), better treatment (more aggressive correction of hyperammonaemia / (lactic) acidosis, tighter metabolic control (eg using gastrostomies) and use of haemofiltration in acute decompensations. Better understanding of the condition has led to earlier recognition of longterm complications (eg kidney failure, pancreatitis, optic atrophy, metabolic stroke, cardiac abnormalities).

Bringing individual cases of MMA together in registries and natural history studies confirms the broad spectrum of the disease.

However extension of life expectancy does not run in parallel to better life quality and the disease burden of MMA is substantial. Patient reported outcome studies (PROMS) are essential to capture the impact and bothersome of the different aspects of the disease.

Organ transplantation, as in (earlier) liver or combined liver/kidney or kidney only transplantation has been performed on several patients worldwide. It carries it's own risk though; however for those patients that have tolerated the procedure well enough, post transplantation a decrease in metabolic crisis and overall better well-being has been documented. Unfortunately not even combined transplantation normalises MMA levels completely.
Ongoing research on newer treatment of MMA is into gene induction, stop codon read through, cell therapy-hepatocyte transplantation / tissue engineered liver, lentiviral gene therapy and mRNA (codon-optimized mRNA encapsulated in biodegradable lipid nano particles) for transient protein expression.

There are still plenty of unmet needs in the management of MMA and decision around the individual patient will really need to meet the concept of personalised medicine to match the most appropriate treatment options with the individual MMA profile of any patient and – indeed - their families.

CYP46A1 as a new therapeutic target in Niemann-Pick type C disease (2018 SPDM research grant winner)

Elsa Rodrigues
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Dysfunctions in brain cholesterol homeostasis have been extensively related to brain disorders. The neuronal-specific CYP46A1 is responsible for the conversion of cholesterol into 24S-hydroxycholesterol, the major pathway for brain cholesterol elimination. Interestingly, increased expression of this hydroxylase improves cognition, while its reduction leads to a poor cognitive performance. Moreover, increasing amount of epidemiological, biochemical and molecular evidence suggests that CYP46A1 has a role in the pathogenesis or progression of neurodegenerative disorders, in which the up-regulation of this enzyme is clearly beneficial. We have identified that membrane cholesterol reduction by CYP46A1 is the necessary trigger to increased neuronal dendritic outgrowth and dendritic protrusion density, and to elicit in vitro and in vivo increase of synaptic proteins in crude synaptosomal fractions. Taking into account its role in cholesterol reduction and neuronal function, we hypothesized that CYP46A1 could be a potential therapeutic target in Niemann Pick Type C Disease (NPC). Human fibroblasts from NPC1 and NPC2 patients and stable NPC1-knockdown human neuroblastoma cells, were transduced with and an adenovirus encoding green fluorescent protein (GFP), or GFP and CYP46A1 and maintained for 96h. In NPC fibroblasts ectopic expression of CYP46A1 led to a reduction in cholesterol accumulation and sequestration in the late endosome/ lysosome compartment. Moreover, CYP46A1 expression partially restored the mRNA levels of cholesterol homeostasis related genes. In stable NPC1-knockdown SH-SY5Y cells, CYP46A1 ectopic expression, could also reduce cholesterol accumulation, and concomitantly rescue mitochondrial function and integrity, modulating mitochondria dynamics in favor of mitochondrial fusion. These data suggests that regulation of neuronal CYP46A1 might be a novel and promising strategy for NPC disease.

This work was supported by FEDER and national funds from Fundação para a Ciência e Tecnologia (FCT) (PTDC/MED-NEU/29455/2017, fellowships SFRH/BPD/95855/2013 (MJN) and SFRH/BPD/98023/2013 (ANC)), Bolsa de Investigação da Sociedade Portuguesa de Doenças Metabólicas (SPDM), and BrainVectis Technologies.

SESSION IV.

Metabolic pathways and subcellular organelles: new connections
Lectures

CHAIRPERSONS

Catarina Resende de Oliveira

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Isabel Santana

MD, PhD, Head of the Neurology Department, Centro Hospitalar e Universitário de Coimbra e Faculdade de Medicina da Universidade de Coimbra Coimbra, PT

Endoplasmic reticulum stress: new insights in Inborn Errors of Metabolism

Cláudia Pereira
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Impaired cellular response towards stress, mitochondrial dysfunction and Inflammation have been implicated in the pathophysiology of several human diseases, including metabolic disorders. Mitochondria-Associated Membranes (MAMs) are endoplasmic reticulum (ER)--mitochondria contacts crucial for mitochondrial metabolism as well as ER stress and inflammatory responses. These lipid raft-like domains allow physical and functional communication between ER and mitochondria, which is crucial for inter-organelle Ca2+ and lipids transmission controlling pro-survival/death pathways. Taking these evidences in mind, our research is aimed to address the role of ER stress in innate immunity and to investigate the role of MAMs on ER stress-induced sterile inflammation. Using a human monocytic cell line (THP-1 cells) treated with a classical ER stressor (tunicamycin), protein levels of markers of the ER stress-induced unfolded protein response (UPR) were measured. Concomitantly, activation of the NLRP3 inflammasome was investigated by analyzing its components and IL-1 secretion to support inflammation induction upon ER stress in innate immune cells. In tunicamycin-treated THP-1 monocytes, ER-mitochondria contacts were evaluated by determining the levels of ER-mitochondria tethering proteins and MAM's resident chaperones. Functional parameters were also investigated, namely mitochondrial ROS production and membrane potential, as well as mitochondrial dynamics and mitophagy. Finally, cell viability under stressful conditions was analyzed. Overall, results suggest the establishment of a deleterious axis consisting of ER stress- inflammasome activation in innate immune cells involving alterations of ER-mitochondria contacts.

This study provides a proof-of-concept for the "MAM hypothesis" for innate immunity deregulation in several diseases in which ER stress is implicated and can unveil novel targets for early monitoring and therapeutic intervention.

Hypothalamic dysfunction and neurodegeneration

Cláudia Cavadas
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Coimbra, PT

The hypothalamus has relevant physiological functions such as feeding, body temperature, stress response, sexual behavior and reproduction, and circadian rhythm and sleep The hypothalamic regulation of the overall homeostasis is achieved by connections between different hypothalamic nuclei and major metabolic organs. More recently, several studies suggest that hypothalamus is a key region for lifespan and aging.

Moreover, neurodegenerative and metabolic diseases have impact on several hypothalamic functions, such as circadian rhythm, stress response, and energy balance. In this conference, I will present and discuss the major physiological functions of the hypothalamus, highlighting its contribution for metabolic and neurodegenerative disorders.

Intercellular communication in Inborn Errors of Metabolism

Henrique Girão
Faculty of Medicine of University of Coimbra
Coimbra, PT

Protein homeostasis is the process by which an integrated network of biological processes that maintain a functional group of proteins in their native state and degrades damaged, misfolded or proteins that are no longer necessary, ensuring normal functioning of cells, tissues and organs.

Protein degradation, or proteolysis, relies on 2 different systems: i) the lysosomes, which are membrane-bound organelles with an acidic lumen containing proteolytic enzymes and ii) the proteasome, which constitutes a barrel-like structure, with a limited access of substrates to its catalytically active interior.

The Ubiquitin-Proteasome System (UPS) is the main cytosolic proteolytic system in eukaryotes, being implicated in a wide variety of cell functions with relevance to health and disease. In general, degradation of a protein mediated by the UPS consists in two successive steps. The first step involves the covalent attachment of a polyubiquitin chain to the target protein, in a process generally called ubiquitination, while in the second step the ubiquitin-tagged protein is recognized and degraded in the proteasome complex, with the prior release of ubiquitin, that is subsequently used in new cycles of protein ubiquitination. Conjugation of ubiquitin to a substrate is an highly regulated and orchestrated three step cascade of enzymatic reactions catalysed by an ubiquitin activating enzyme (E1), ubiquitin conjugating enzyme (E2) and ubiquitin ligase (E3), sometimes acting as a ubiquitin chain elongation factor.

It has been widely shown that different types of polyubiquitin chains are associated with diverse biological functions, including the regulation of DNA repair, endocytosis, autophagy, protein activity and proteasomal degradation. Importantly, the role of ubiquitin in such processes has not only to do with the targeting proteins for degradation but also with the modulation of protein activity. Although ubiquitin-dependent degradation was initially described as a signal for the proteasome, more recent studies have ascribed a role to protein ubiquitination in targeting lysosomal degradation. Disturbance of proteostasis has been associated with various biological processes including ageing, cancer, neurodegenerative diseases and metabolic disorders. Indeed, mounting evidence suggest that an impairment in the mechanisms of protein quality control, including autophagy, accounts for the progress of metabolic diseases, namely lysosomal storage disorders.

SESSION VII.

Nutritional paradigms in Inborn Errors of Metabolism Lectures

CHAIRPERSONS

Ana Faria

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Júlio César Rocha

PhD, Nutritionist, Instituto Jacinto Magalhães, Centro Hospitalar do Porto, Porto, Portugal

Micronutrients: speculations in Inborn Errors of Metabolism

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

Many essential enzyme reactions in living organisms use trace element co-factors and/or vitamin-derived co-factors because they are chemically reactive. Humans have to maintain the right concentrations of co-factors in cellular organelles to allow catalysis of necessary reactions but avoid unwanted reactions. Failure of the homeostatic mechanisms can lead to levels of a trace element that cause pathology because they are too high or too low. We also manipulate the availability of micronutrients to pathogens in our fight against infection. Finally, the interchange of micronutrients allows the human host to affect the gut flora (microbiome) and vice versa.

If we take manganese homeostasis as an example, it is clear that inborn errors affecting different transporters can have different but sometimes overlapping effects. Uptake into cells is impaired in SLC39A8 deficiency and this leads to low blood levels and cellular deficiency manifested by impairment of glycosylation and mitochondrial function. Failure of export from the liver into the bile (SLC30A10 deficiency) can lead to cirrhosis and polycythaemia, failure of liver uptake (SLC39A14) or biliary excretion (SLC30A10 deficiency) leads to hypermanganesaemia and increased Mn levels in the basal ganglia producing parkinsonism/dystonia with a characteristic hyperintensity on MRI imaging. Mutations in the transporter that pumps iron and manganese out of the phagosome (NRAMP1) leads to susceptibility to mycobacterial infection. Mutations affecting the lysosomal Mn transporter, ATP13A2, can cause Kufor Rakeb syndrome and hereditary spastic paraplegia 78. ATP13A1 transports Mn from the cytosol to the lumen of the endoplasmic reticulum and defective function in model systems leads to low Mn levels in the ER lumen with impaired function of Mn-dependent enzymes and enhanced function of cytosolic Mn enzymes. Clinically, mutations have been found in children with intellectual disability, attention deficit hyperactivity disorder, recurrent chest infections and dysmorphic features.

Inborn errors of pyridoxal phosphate (PLP) homeostasis commonly present with anticonvulsant-resistant epilepsy, typically in the first weeks of life but sometimes even in adult life. Diagnosis of ALDH7A1 deficiency, PNPO deficiency and PLPBP (PROSC deficiency) will be discussed. Traditionally, we have regarded B vitamins as non-toxic. However, treating patients with disorders of PLP homeostasis with high doses of pyridoxine can lead to neuropathy and the use of high doses of PLP has been associated with cirrhosis and hepatocellular carcinoma. The concept of unwanted reactions of PLP (a form of "aldehyde stress") will be discussed. The gut flora contribute to our supply of vitamin B6. Manipulation of the diet/gut flora in C .elegans can profoundly affect the metabolism of the host. It is thought that variants in enzymes contributing to PLP homeostasis may have an effect on resistance to malaria.

Nutritional Intervention after hepatic transplant in Inborn Errors of Protein Metabolism

Anne Daly
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Many inborn errors of metabolism are life threatening, lethal conditions, which can lead to death or severe morbidity. A successful liver transplantation may offer a complete cure of the disorder preventing further neurological damage and frequent hospitalization for metabolic decompensation. Liver transplantation swaps one set of problems for another; balancing the risks of a complex surgical procedure and life long immunosuppression with acute and chronic brain injury.

We reviewed nutritional status, growth and survival post liver transplantation in 31 children with an IEM from one centre over 22 years.

Overall survival was 71%. Categorising survival according to disorder: 100% survival was reported in GSD1b (n=7) and later onset UCD (UCDL) (n=6). Survival was lower in UCD diagnosed at birth (UCDn) 86% (n=6), with the poorest outcome in PA, 25% (n=3) and no survival in MMA (n=2) and MSUD (n=1). Median age at transplant was 3.1 years (1.8-5.1years), and median post transplant follow up was 3.5 years (0.4- 19 years). Pre transplant all PA, GSD and UCDn children were nasogastric tube dependent. Post transplant 100% PA, 43% GSD 1b and 30% UCDn continued to need nasogastric tube feeding support.

Weight and height z scores measured pre- transplant, 12 months and current show in all groups PA, GSD 1b, UCDn and UCDL weight z scores fell over time, while height z scores failed to improve significantly. Caregivers identified several feeding issues post transplant including retching, gagging, poor swallow. Tantrums, food refusal and a slow transition onto oral intake were commonly reported particularly in GSD1b and UCDn groups. In the GSD group mouth ulceration was a common problem preventing transition to oral feeding.

Common complications post transplant were rejection, two children needed re- transplantation and one of these needed a third transplant. One child with PA needed renal dialysis post transplant and one child developed insulin dependent diabetes.

Liver transplantation has removed the immediate risk of serious neurological damage. It fails to bring about an immediate change in feeding behaviour; psychological food associations need to be further studied in both children and caregivers. A return to a 'normal' diet is not instantaneous and requires skilled nutritional support for both the child and caregivers.

The effect of the nitrogen source on metabolism in Phenylketonuria (2018 SPDM/Orphan Europe research grant winner)

Maria João Pena
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Synthetic protein derived from L-amino acids (AAs) are the cornerstone for treating patients with Phenylketonuria (PKU). Glycomacropeptide (GMP), an intact protein very low in phenylalanine (Phe) in its native form, has been modified and adapted for PKU due to its potential to provide an alternative protein source through supplementation with rate-limiting amino acids (GMP-AAs), although it still has residual Phe in its formulation. The aim of this study was to systematically evaluate published intervention studies on the use of GMP-AAs in PKU by considering its impact on blood Phe control (primary aim) and changes in tyrosine control, nutritional biomarkers, and patient acceptability or palatability (secondary aims). Four electronic databases were searched for articles published from 2007 to June 2018. Of the 274 studies identified, 8 were eligible for inclusion. Risk of bias for randomised clinical trials was assessed using the Cochrane Collaboration Risk of Bias and for observational studies, Risk of Bias in Non-randomised Studies - of Interventions (ROBINS-I) tool was applied. For quality appraisal of the body of evidence, Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system was carried out. A meta-analysis was performed in two studies with sufficient methodological similarity which showed no differences between GMP-AAs and AAs for any of the interventions analysed. The results of this study flag important aspects, mainly the shortage and nature of studies for GMP-AAs interventions. All of the included studies were short-term with small sample sizes. There is a need for better-designed studies to provide the best evidence-based recommendations.

SESSION VIII.

Mitochondrial diseases: from clinics to basic research and back
Lectures

CHAIRPERSONS

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Sandra Jacinto

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The challenges in the clinical evaluation of mitochondrial diseases

Shamima Rahman
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London, UK

Primary mitochondrial diseases have been defined as disorders caused by mutations that lead primarily or secondarily to oxidative phosphorylation dysfunction or other disturbances of mitochondrial structure and function including perturbed mitochondrial ultrastructure, aberrant synthesis of cofactors and vitamins, or other impaired metabolic processes within the mitochondrion.[1] These disorders are characterized by enormous clinical, biochemical and genetic heterogeneity, leading to considerable diagnostic challenges. The human phenotype ontology[2] has enabled homogenization of clinical phenotypic terms and led to the evolution of the discipline of phenomics, which can be defined as the systematic study of all measurable physical and biochemical characteristics of an organism on a genome-wide scale.[3,4] In this lecture I will discuss recent advances in the utility of phenomics in the diagnosis of primary mitochondrial diseases, using the Leigh Map as an example.[5]

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Current role of functional mitochondrial study in the genomic era

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AIM: Ascertaining the prospect of results from genetic investigation of the patients affected with mitochondrial cytopathies, particularly optic atrophy/LHON in our Laboratory in the last 24 years and illustrating both the genetic heterogeneity of the pathology and the use of the functional genomic studies as a mandatory tool for illuminating pathogenicity underlying genetic alterations.

BACKGROUND: The diagnosis of oxidative phosphorylation (OXPHOS) diseases is complex given the heterogeneity in clinical presentation and involvement of two genomes. Tissue specificity is a critical issue. Optic atrophies, particularly LHON, have been extensively studied and most cases remain without a clear genetic cause identified1,2. Furthermore, there is a scientific gap in LHON, considering that pathogenesis remains poorly understood and there are issues remaining unsolved, namely the incomplete "penetrance", sex bias, specificity of affected tissue/ cells (RGCs), persisting the key question: what are the real genetic causes?

METHOD AND MATERIALS: Biochemical evaluation of OXPHOS complexes' activities was accomplished by double wavelength spectrophotometry. Genetic screening of both genomes is currently performed by NGS techniques followed by extensive bioinformatics analysis. In order to understand the functional impact of the genetic alterations, biochemical and functional studies are performed, such as Seahorse Bioscience analysis to evaluate metabolic changes; luminescence for determining ATP levels; electron microscopy to verify the mitochondrial morphology; fluorimetry to assess mitochondrial membrane potential and ROS content; western blotting analysis for protein semi-quantitative expression analysis; real time PCR for quantifying RNA transcripts.

RESULTS: During 1995-2017, more than 16,000 samples of cases suspected of OXPHOS disease entered our Laboratory. From the 169 patients assigned with optic atrophy, mostly suspected of LHON as first diagnostic hypothesis, 1 patient with DOA has the mutation c.635_636delAA (p.Lys212Argfs – OPA1) and 13 (8%) had mtDNA mutations identified: m.11778G>A in MTND4 – 8 patients from 4 families; m.14484T>C in MTND6 – 3 patients from 1 family; m.3460G>A in MTND1 – 2 unrelated patients. Also, three cases had atypical results: 1 with novel mtDNA mutation; 1 with classic mtDNA mutation m.14484T>C plus nDNA mutations (both heterozygous); 1 LHON-plus case with classic mtDNA mutation m.11778G>A + novel nDNA mutations (confirmed compound heterozygosity). The development of NGS approaches allow the identification of a growing number of genetic alterations, but a new challenge arises. Additionally, a few examples will be presented to illustrate the gathering of data for demonstrating the functional impairments underlying the energy failure related to novel genetic alterations.

CONCLUSIONS: The genetic information underlying the disease is essential for genetic counseling, but the recent technological advances bring also additional difficulties in validating the novel mutations identified in patients. The most recent developments and guidelines include functional studies, in which biochemical genetics approaches play a key role for clarifying pathogenicity. In our team, efforts are being made to accomplish these outlines. Furthermore, in face of the results, it is worth to hypothesize that LHON may be not a single disease, but instead a "spectrum" of optic neuropathies.

What is new in the treatment of mitochondrial disorders?

Mirian Janssen
Radboud University Medical Center
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Mitochondrial diseases are progressive debilitating multi-system disorders with limited therapeutic options. Despite major advances in our understanding of the pathophysiology of mitochondrial diseases, clinical management of these conditions remains largely supportive. The use of supplemental ***vitamins*** and ***cofactors*** is largely unproven and their use is therefore controversial in patients with mitochondrial diseases.

A new wave of experimental drugs aims to change that by reversing the debilitating fatigue, muscle weakness, neurological problems, and myriad other health issues that have come to define daily life for this desperate patient population. Although trial design is improving, there is a critical need to develop new biomarkers and outcome measures of mitochondrial disease. Also knowledge of the natural disease course is important.

Approved treatment for mitochondrial disease is limited to Idebenone for Leber Hereditary Optic Neuropathy (LHON). However, unmet medical need remains in patients with mitochondrial disease for additional therapies that delay disease progression or strengthen the benefit of other treatments.

An update on currently running clinical trials in mitochondrial disease will be presented, the results of the KHENERGY study in more detail.

SESSION X.

Inborn Errors of Metabolism II: an update
Lectures

CHAIRPERSONS

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SPDM and SSIEM Council Member

Anabela Bandeira

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Urea Cycle Disorders: what is old, what is new, what can we change?

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Urea cycle disorders seem to be a well known pathology in which there are little innovations over time. However, hyperammoniemia is still diagnosed or treated late in many cases, with severe neurological consequences for the patient. Recent guidelines and treatment protocols have been published that will be discussed in this presentation. New therapeutic options or indications of known products will be reviewed. Also, controversial topics will be presented in order to give a complete overview of up to date knowledge in this topic.

Riboflavin-Responsive Disorders

Manuel Schiff
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Riboflavin (7,8-dimethyl-10-ribityl-isoalloxazine, vitamin B2) is a water soluble vitamin which is the precursor of the active coenzymes flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD), important cofactors for more than 80 enzymes (called flavoproteins) involved in carbohydrate, amino acid and lipid metabolism, most of them located in the mitochondrion and acting as mitochondrial oxidoreductases.

More importantly, FAD is the essential cofactor for the 2 electron transporters: Electron Transfer Flavoprotein (ETF) and Electron Tranfer Flavoprotein Ubiquinone Oxidoreductase (ETF-QO). FAD is also the essential cofactor for 11 ETF dependent dehydrogenases involved in 5 different categories of metabolic pathways. In terms of biochemistry, inborn errors of riboflavin metabolism or ETF/ETF-QO deficiencies have in common a multiple acyl-CoA dehydrogenase deficiency (MADD) profile on the acylcarnitine profile. Of note, this MADD profile is not always present in inborn errors of riboflavin metabolism and when present may be incomplete.

In clinical practice, riboflavin-responsive disorders, defined as diseases for which the clinical course is improved by pharmacological doses of riboflavin, are probably overlooked. They encompass inborn errors of riboflavin metabolism: disorders of intestinal riboflavin transporters (previously called Brown Vialetto-Van Laere [BVVL] or Fazio Londe [FL] syndromes) and disorders of intracellular riboflavin metabolism including FAD synthase and mitochondrial FAD transporter deficiencies. As a whole, defects of riboflavin metabolism present with a wide spectrum of clinical severity from early onset severe mitochondrial disease-like neurodegenerative disorder to late onset exercise intolerance. Even in the setting of a severe neuromotor presentation, riboflavin supplementation may be life saving leading to a dramatic improvement of the clinical condition especially in BVVL/FL syndromes.

Besides inborn errors of riboflavin metabolism, late onset ETF-QO deficient patients presenting with exercise intolerance were shown to exhibit substantial clinical improvement upon riboflavin supplementation. Similarly, a significant number of acyl-CoA dehydrogenase 9 (ACAD9, a mitochondrial respiratory chain Complex I assembly factor) defective patients were recently reported to exhibit clinical improvement upon riboflavin therapy.

SESSION XI.

Treating Inborn Errors of Metabolism: future directions
Lectures

CHAIRPERSONS

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Isabel Tavares de Almeida

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The development of new enzyme replacement therapies: the example of Hypophosphatasia

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Hypophosphatasia (HPP) is a rare metabolic disorder caused by loss-of-function mutations in the ALPL gene that encodes the mineralization-associated enzyme, tissue-nonspecific alkaline phosphatase (TNSALP). The clinical presentation is a continuum ranging from a prenatal lethal form with limited skeletal mineralization to a mild form with late adult onset presenting with nonspecific manifestations. Symptoms include fractures, bone deformities, skeletal pain, and extra-skeletal manifestations such as premature deciduous tooth loss, tissue calcification, and respiratory and neurological complications. Severe forms are very rare and recessively inherited, whereas moderate forms are more frequently observed and can either be recessively or dominantly inherited. The diagnosis can be challenging and is based on clinical and radiological findings, a constantly low alkaline phosphatase (AP) activity in serum and APLP genetic testing. A clear but imperfect genotype-phenotype correlation has been observed, suggesting that other genetic or environmental factors modulate the phenotype.

Management of HPP require a multidisciplinary encompassing nutritional support, adjustment of calcium and phosphate intake, monitoring of vitamin D levels, careful and personalized physical therapy, and regular dental monitoring and care. Bisphosphonates treatment in HPP should be avoided. Recently and following comprehensive preclinical studies and clinical trials, an enzyme replacement therapy employing bone-targeted recombinant human TNSALP, asfotase alfa (AA), was approved in patients with pediatric-onset HPP to treat the bone manifestations of the disease. This new therapy has been shown to be safe and transformative in several cases, leading to dramatic reversal and improvement of skeletal defects and improving survival in severely affected infants. Effects on other manifestations are not uniform. The impact in overall quality of life in children and adults with high-disease burden HPP seems significant. On the other hand, currently, no data have been reported on AA treatment of individuals with less symptomatic HPP and in whom numerous questions need to be addressed. Other therapies under investigation, such as gene therapy, will also be discussed.

Lenti-D Autologous Hematopoietic Stem Cell Gene Therapy for the Treatment of Cerebral Adrenoleukodystrophy.

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X-linked adrenoleukodystrophy (ALD) is a severe progressive metabolic disease affecting children and adults. It is caused by mutations in ABCD1 leading to impaired expression of the peroxisomal half-transporter ALD protein (ALDP) needed to transport very-long chain fatty acids (VLCFA) into the peroxisome for degradation. Toxic levels of VLCFAs can be detected in adrenal and nervous system. The estimated incidence of ALD is ~1 in 17,000. 35-40% of boys with ALD will develop cerebral ALD (CALD). Early manifestations of CALD include deterioration in school performance and symptoms of ADHD. As the disease progresses patients develop severe neurological impairments and major functional disabilities including cortical blindness, total loss of communication, feeding and mobility.

The only effective therapy for CALD is haematopoietic stem cell transplantation (allo-HSCT), which is associated with life-threatening complications, particularly when cells from a donor who is not a matched sibling are used. These include >10% treatment-related mortality, ~5% graft failure, 10-40% acute grade II-IV graft-versus-host-disease (GVHD), 20% chronic GVHD.

Starbeam (ALD-102): global, multi-center study of Lenti-D HSCT gene therapy recruited patients were aged ≤17 years, with evidence of active CALD with early disease (Loes score 0.5-9.0; NFS ≤1), and no matched sibling donor.

Of the 17 patients who completed 24 months of follow-up, 15 (88%) remain alive and free of major functional disabilities, as of the data cut-off date.

No graft failure, GVHD, and no evidence of insertional oncogenesis were reported as of the data cut-off date. The safety profile of Lenti-D is generally consistent with myeloablative conditioning. Lenti-D gene therapy helps stabilize neurologic disease progression, and may offer an alternative to allo-HSCT in patients with early cerebral disease, particularly for patients with no matched sibling donors.

Oral treatment for Fabry Disease: the evolution in chaperone therapies

Patrício Aguiar
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As a multisystem condition, a comprehensive therapy for Fabry disease (FD) is warranted, not only including disease specific treatment, but also conventional medical treatment for complications and adjunctive therapies. Until recently the former was not available and its management mainly consisted of other treatment strategies. However, in 2001 a disease specific enzyme-replacement treatment (ERT) was approved as the gold standard in the treatment of FD and, more recently, in 2017, European regulatory authorities approved the pharmacological chaperone migalastat for treatment of FD patients with amenable mutations. New treatment strategies are currently under development in clinical trials, namely substrate reduction therapy (lucerastat) and modified forms of plant derived ERT (pegunigalsidase-α).

Migalastat is a pharmacological chaperone, which binds to the active site of α-galactosidase A and stabilizes certain mutant enzymes (amenable mutations), thus facilitating proper trafficking to lysosomes, where dissociation of migalastat allows α-galactosidase A to catabolize accumulated substrates. This treatment is an orally administered small-molecule, with apparently higher volume of distribution than ERT and does not present the burden of immunogenicity associated with ERT.

The pharmacologic chaperone migalastat has been studied in two phase III clinical trials, one in naive patients (comparison with placebo) and another in patients previously treated with ERT (comparison between switch patients and the ones maintained in ERT). In the placebo-controlled trial, after 6 months of migalastat, in the subgroup of patients with suitable mutations there was a significantly greater reduction in the mean number of Gb3 inclusion per kidney interstitial capillary than was in placebo group; moreover, there was a significant decrease in left ventricle mass index in patients treated with migalastat for up to 24 months, with a trend toward a larger reduction in patients with LV hypertrophy at baseline. In the switch trial, measured and estimated GFR remained essentially stable for up to 24 months of treatment and the patients switched from ERT to migalastat presented a significant decrease in LV mass index, whereas in patients remaining on ERT there was a smaller, non-significant decrease. In the same trial the percentage of patients who experienced renal, cardiac or cerebrovascular events during the 18-month treatment period was non--significantly different between switch and ERT groups.

Concluding, although long term follow-up studies and real-world data are warranted, migalastat seems a promising oral alternative to ERT in patients with amenable mutations, under close follow-up of treatment response.

Selected Oral Free Communications

Session V - March 14th

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Patrícia Janeiro

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OC - 01

TRANSCRIPTOMICS PROFILING OF NIEMANN-PICK TYPE C PATIENTS – ACTIVATION OF THE UNFOLD PROTEIN RESPONSE IN A SPECIFIC CASE

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Text body: Background: Niemann-Pick type C (NP-C) is a neurodegenerative Lysosomal Storage Disease (LSD) with a heterogeneous clinical presentation secondary to abnormal intracellular accumulation of cholesterol. We have studied a patient with clinical diagnosis of NP-C but presenting inconclusive results regarding biomarkers testing and molecular analysis. To better characterize this patient, we have performed NGS-based technologies (targeted DNA sequencing and single cell-RNA sequencing). Methods: For the molecular diagnosis we used a NGS gene panel followed by the analysis of cDNA (in the patient and both parents). Latter, we have used massively parallel single cell RNA-seq (MARS-Seq) to address gene profiling changes and better characterize the pathomechanisms related to specific disease-causing mutations in this patient as well as in two NPC patients. The most prominent hits from this transcriptomics analysis were validated by qRT-PCR. Results and Discussion: Using our targeted NGS panel we identified two novel mutations in NPC1 gene (p.V505G; p.V562V). Next, through cDNA analysis of one of the patient parents we were able to understand the impact of the V562V silent mutation located in the middle of the exon 11. This mutation leads to exon 11 skipping giving origin to an out-of-frame transcript and eliciting the nonsense-mediated decay pathway. This mechanism contributed to the almost absence of the mutant transcript in the patient. Thus, we were not able to easily detect it in the sequencing electropherogram of the patient which turned the molecular diagnosis more challenging. By its turns, apparently the presence of the other mutation (the missense V505G) impairs the proper NPC protein folding leading to its ER retention. In fact, the MARS-Seq analysis of this patient showed that a number of genes were upregulated and a significant number of the highly enriched genes are related to the unfold protein response (UPR) and ER stress, when compared with the controls, which deserves further studies. ER stress is a hallmark of many neurodegenerative diseases, including LSD but our preliminary results suggest that the activation of the UPR is variable among NPC patients. Several factors may contribute to this, which could explain the heterogeneous presentation of this pathology. Acknowledgments: This work is supported by NORTE-46-2015-03 "DESVENDAR-DEScobrir VENcer as Doenças rARas" and RISE program.

OC - 02

GLUTARIC ACIDURIA TYPE I – FUNCTIONAL AND STRUCTURAL CHARACTERIZATION OF TWO GLUTARYL-COA DEHYDROGENASE DISEASE-ASSOCIATED VARIANTS

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Text body: Glutaric Aciduria Type I (GA-I), is an autosomal recessive neurometabolic disease caused by mutations in the GCDH gene that encodes for Glutaryl-CoA Dehydrogenase, a flavoprotein involved in the metabolism of tryptophan, lysine and hydroxylysine [1]. GA-1 is clinically characterized by encephalopathic crisis resulting in striatal injury and severe movement disorder. Over 200 disease mutations have been reported, and in some cases, it has been shown that missense mutations result in protein loss of function due to structural and/or functional impairment. Even though the number of reported cases increased in recent years, a clear correlation between genotype and phenotype has been difficult to establish. Aiming to clarify the molecular mechanism behind GA-1 we undertook a detailed molecular study on two GCDH disease-associated variants, GCDH-p.Arg227Pro and GCDH-p.Val400-Met. Patients harbouring these two variants in heterozygosity exhibit increased residual enzymatic activity in relation to homozygous patients, suggesting a complementation effect between the two variants [2, 3]. Combining biophysical, biochemical and structural methods we showed that although the variants retain the overall protein structure, they have compromised enzymatic activity. Our results suggest that GCDH-p.Arg227Pro has impair function due to deficient substrate binding, and GCDH-p.Val400Met lower activity is probably due to weaker interaction with its partner, the electron transfer flavoprotein (ETF). Moreover, GCDH--p.Val400Met variant has lower stability, and impair cofactor binding. The data gather illustrates how point mutation can impair protein function via different pathways and underpins the necessity to carefully evaluate protein structure, conformation, and enzymatic activity to better predict the functional outcome of gene mutations. References: 1. Hedlund, G.L., N. Longo, and M. Pasquali, Glutaric acidemia type 1. Am J Med Genet C Semin Med Genet, 2006. 142C(2): p. 86-94. 2. Pineda, M., et al., Glutaric aciduria type I with high residual glutaryl-CoA dehydrogenase activity. Dev Med Child Neurol, 1998. 40(12): p. 840-2. 3. Busquets, C., et al., Glutaryl-CoA dehydrogenase deficiency in Spain: evidence of two groups of patients, genetically, and biochemically distinct. Pediatr Res, 2000. 48(3): p. 315-22.

OC - 03

DESIGN OF SMALL MOLECULES THAT INCREASE HUMAN PHENYLALANINE HYDROXYLASE THERMOSATBILITY

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Text body: Protein misfolding is the general molecular mechanism of a high number of Inherited Metabolic Disorders. In the cell misfolded proteins are recognized and targeted for degradation lowering their intracellular levels thus exerting a pathogenic effect. For these disorders novel therapeutic approaches have been investigated aiming to induce misfolded variant proteins to adopt native-like conformations by the use of pharmacological chaperones (PCs). Phenylketonuria (PKU) is presently included in this group of diseases thus being amenable to be rescued by PCs. PKU is caused by a deficient activity of human phenylalanine hydroxylase (hPAH) a non-heme iron homotetrameric enzyme that hydroxylates L-Phe into L-Tyr in the presence of O2 and tetrahydrobiopterin (BH4). In this work, small molecules (12) were designed based on the properties and structural characteristics of the catalytic hPAH ligands (L-Phe, BH4 and Fe) aiming its use as PCs. The effect on the activity and thermostability of the recombinant hPAH was used as a first approach to select the most promising molecules which were further tested by: (i) electron paramagnetic resonance (EPR), to confirm Fe interaction; (ii) limited proteolysis, to identify the mechanism of action and; (iii) cytotoxicity to confirm the molecules biocompatibility. Four molecules were considered the most promising candidates. They presented a slight inhibitory effect (17 to 40% enzyme activity decrease) but allowed further activation by L-Phe (1.3 to 1.7-fold). Two of the selected molecules stabilized the hPAH regulatory domain (ΔTm1: +8.3 and +4.0 ºC). An interaction with the catalytic iron was suggested by the observed changes in the EPR spectra and the molecular docking studies, which also indicated that the poses adopted by the quinoline ring and the side chain of the molecules significantly overlapped the position of BH4 and the substrate analog, respectively. At 100 µM the selected compounds did not present any toxic effect either on cell viability (62 ± 4% to 101 ± 5%) and membrane integrity (propidium iodide intake ≈1). From our series of molecules compounds 4 and 12, although being classified as enzyme inhibitors, could be regarded as promising hit molecules for development of a new class of PCs of hPAH. Our data also provided proof-of-concept for the utilized strategy of compound design targeting the hPAH catalytic center. Work funded by FCT: project PTDC/MED-QUI/29712/2017 and grant UID/DTP/04138/2013 (iMed.ULIsboa).

OC - 04

THE CONSTRAINTS OF THE TREATMENT IN A PEDIATRIC POPULATION: A PARENTAL SURVEY

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Text body: Background: The treatment of some metabolic diseaeses implies chronic dietary and pharmacologic interventions. Besides the attempts to minimize the embarrassments intrinsic to these therapeutics, the patients and their families still experience many constraints in daily life. Objectives: Knowledge of the limitations and concerns related to diet and medicines. Methods: An anonymous questionnaire was sent by e-mail to 34 parents of children and adolescent with PKU, MSUD, UCD, homocystinuria, glutaric aciduria 1, 3HMG-CoA lyase deficiency and methylmalonic aciduria type cblC. Families without e-mail contact were excluded. Results: Received 25 questionnaires, with age distribution: 12y-15,6%.44% perform treatment with diet and medication, while the remainder only need dietary intervention. In the first group, according to caregivers, medicines cause more constraints to children (75%) and themselves (58,3%) than the diet. The meddling of medication in the quality of life of the children seem to be very important in 27,2% and moderate in 36,3%, with the most significant complaints being the flavour and the schedule of intakes. For parents, the medicines cause very important (36,3%), moderate (27,4%) and slight (36,3%) interference in regular life, with the main problems being related to need of multiples administrations, refusal by the children and concern with collateral effects. Regarding diet (both groups), according to parents, the limitations seem to be very important in 12,5% of children, moderate in 41,7% and slight in 33,3%, and they are related to the restriction of common foods and difference from the pairs. The constraints of the diet are very important for 32% of caregivers and moderate for 24%, and result mostly of the need of cooking different meals (although 48% changed family meals after diagnosis) and adaptation of diet at restaurants, parties and holidays. Most of parents (58.3%) always weight foods. All believe the treatment is essential and 81,1% say that is always accomplished, with the remainder assuring fulfilment most part of time. All are aware of the cost of the treatment and 87,5% referred that could not afford it if it was ceased to be reimbursed. Conclusions: Treatment remains an important obstacle in daily life, for children and caregivers. Should be kept a continuous search by families, healthcare professionals and pharmaceutical industry of better strategies to minimize these chronic constraints.

OC - 05

PEDIATRIC LIVER TRANSPLANTATION IN PORTUGUESE WILSON´S DISEASE PATIENTS

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Text body: Background: Wilson's disease (WD) is a rare autosomal recessive inborn error of copper metabolism due to mutations of the ATP7B gene, resulting in copper deposition in liver and extra-hepatic tissues. Symptomatic patients are treated with chelating agents. Liver transplantation (LT) is an option for those with acute liver failure (ALF) and with decompensated liver disease unresponsive to medical therapy. LT for neurological WD is controversial. Aim: Report the experience of pediatric LT in Portuguese WD patients and in their outcomes. Methods: Retrospective study of WD patients submitted to liver transplant under the age of 18, since 1994. Revision of patients' medical records to determine: WD presentation and symptoms, indication for LT, therapeutics before transplant, transplant details, histology of explanted liver, immediate and long-term complications and follow-up. Results: From the 221 patients submitted to LT under the age of 18, five (11%) were WD patients, 4 of them female, with a median age at diagnosis of 12 years (10-14 years). Three patients presented as ALF (two with encephalopathy); one with neurological symptoms in addition to liver disease; one with neurological symptoms. All were unsuccessfully treated with chelating agents prior to LT. Neurological symptoms in the two affected patients got worse after chelating therapy, which was the reason for LT. LT, performed with cadaveric donors in all cases, was done within a month after WD diagnosis in the 3 patients presenting ALF and one year after in the patients with neurological symptoms. Neurological manifestations markedly improved (median follow-up of 31 months), namely with recovering the step walk in one affected patient. Median PICU stay was 7 days. All had transitory immediate post-operative complications, like non WD transplanted patients. Three patients developed acute cellular rejection in the first month after LT, but all responded to immunosuppression intensification. Three had biliary complications. During follow-up (1-19 years) graft and host survival was 100%. Conclusion: Short and long-term survival in LT WD patients was excellent. LT might be an option in neurological WD, even in patients with minimal liver disease. Neurological manifestations improved shortly after LT. Chelating therapy must be carefully implemented and monitored by an interdisciplinary team, due to the risk of neurological symptoms get worse.

OC - 06

OVERVIEW OF GLYCINE ENCEPHALOPATHY IN A METABOLIC REFERENCE CENTER

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Text body: Introduction: Nonketotic hyperglycinemia (NKH) is a rare metabolic disorder caused by a defect in the glycine cleavage enzyme system resulting in high glycine levels in the brain. No effective treatment is known. Clinical outcome is usually devastating. Patients surviving the neonatal (NN) period typically develop severe intellectual disability, seizures, axial hypotonia and peripheral spasticity. Currently, prognosis can be accessed using clinical, biochemical and genetic results of each patient. Objectives: Characterization of the patients with NKH observed at a Metabolic Reference Center, analyzing the clinical presentation, EEG, neuroimaging, biochemical and genetic findings and neurologic outcome. Material and Methods: Retrospective analysis of the patient clinical files between 2004 and 2019. Results: The authors present five cases of NKH (3 boys). The clinical presentation was in the NN period except in one (1-75 days; median: 2 days). The most common clinical findings during NN period were seizures, hypotonia, feeding difficulties, hiccups, apnea, lethargy and coma. The child with 75 days of age at presentation had multifocal seizures that evolved to epileptic encephalopathy. The CSF to plasma glycine ratio ranged from 0,07 to 0,24 (median: 0,19). Seizures were predominantly epileptic spasms or tonic seizures and EEG revealed a burst-suppression pattern. Three patients performed brain-MRI that showed increased T2-signal intensity in the posterior limbs of the internal capsules and corpus callosum hypoplasia. Two patients, who had MR-spectroscopy, presented an elevated glycine peak on. Molecular genetic diagnosis revealed homozygous mutations in ATM gene in three children and in GLDC gene in one. One child died with 30 months. Present ages of the surviving children vary from 2 months to 11 years old. All progressed to severe neurodevelopment delay with partially controlled seizures. Conclusion: Most of our patients had the classic NN presentation, as expected. The child with a later onset is an example of the heterogeneous phenotype of the disease. The CSF to plasma glycine ratio should be investigated in all suspected cases and diagnosis confirmation done by mutation analysis. Contrary to literature reports, ATM gene was the most frequently affected in our cohort. Although it may not significantly change the disease course, early diagnosis is important to define prognosis, for family counseling and to prevent unnecessary investigations.

Selected Oral Free Communications

Session VI - March 15th

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OC - 07

EFFECT OF ARGININE AND THIAMINE ON PYRUVATE DEHYDROGENASE COMPLEX DEFICIENT PATIENT-DERIVED CELL LINES

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Text body: Oxidative decarboxylation of pyruvate into acetyl-CoA is fundamental in aerobic energy metabolism, being catalyzed by the Pyruvate Dehydrogenase Complex (PDC), located in the mitochondrial matrix. Genetic deficiency of this enzymatic complex (PDCD) is defined by reduced PDC activity in patients' cells, leading to lactic acidemia and neurological abnormalities. PDCD belongs to the field of nuclear-encoded mitochondrial diseases. Most PDCD cases are caused by missense mutations in the PDHA1 gene, encoding the α-subunit of the heterotetrameric PDC-E1 enzyme (αα'ββ'). Thus, PDCD can be considered a conformational disorder with a potential to be corrected by chaperone-based therapy. Encouraged by a case of a PDCD male patient with mild neurological involvement, carrying the p.R253G mutation in PDHA1 gene and positively responding to arginine aspartate intake, and by the fact that thiamine supplementation is often used as a therapeutic approach in PDCD, we undertook a study of the ability of arginine and thiamine in restoring PDC function in patient-derived cell lines bearing the p.R88C, p.R253G, p.R263G and p.R378C mutations in the PDHA1 gene. Skin biopsies were used to prepare primary fibroblast cultures and routinely cultivated to obtain an adequate amount of material for analysis. After 48h preincubation in modified DMEM with concentrations of arginine and thiamine adjusted to plasmatic levels, cells were cultured for 12/24h with the respective compounds at physiological vs. therapeutic levels. PDC activity was assayed by a standard method of [1-14C]-pyruvate decarboxylation with addition of cofactors. Protein levels were evaluated by Western blot analysis of cell lysates and by immunofluorescence microscopy using anti-PDC-E1α and E1β and a set of other appropriate monoclonal antibodies. To determine the effect of the compounds on the cellular metabolism, relevant metabolites were analyzed by standard methodologies. All studied cell lines exhibited different levels of PDC-E1α expression and different rates of PDC activity. None of them responded positively to treatment with thiamine alone, but, in several of them, the rescuing role of arginine was confirmed. Interestingly, a synergistic effect of arginine and thiamine was observed in some of the cell lines, thus opening new prospects for exploring this therapeutic approach. SFRH/BD/91729/2012; PEst-OE/SAU/UI4013/2011; SPDM (educational grant)

OC - 08

SCARB2 MUTATIONS AS MODIFIERS IN GAUCHER DISEASE: THE WRONG ENZYME AT THE WRONG PLACE?

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Text body: Unlike most lysosomal proteins, β-glucocerebrosidase (GCase), the hydrolase defective in Gaucher disease (GD), is delivered to lysosomes through its interaction with the transmembrane protein LIMP2. A few years ago, mutations in its coding gene, SCARB2, were reported to modify the severity of GD phenotype. The existence of a great variety of GD phenotypes is well-known, with numerous patients who carry identical genotypes presenting remarkable phenotypic variability. Over the years, that variability has been attributed to other genetic, epigenetic and/or environmental factors. Still, there is still much to learn on this subject. Recently, an association between Parkinson's disease (PD) and the presence of mutations in the GBA gene has been demonstrated. Moreover, there are also studies suggesting that genetic variants in the SCARB2 gene may also be risk factors for PD. We analysed the SCARB2 gene in the Portuguese cohort of 91 GD patients, having identified 3 different SCARB2 coding variants. Of those, 2 were known polymorphisms with high prevalence in the normal population (p.M159V and p.V396I) and the third was a novel coding variant, p.T398M, present in heterozigousity in a single patient. Our study demonstrated that, at least for the Portuguese population, genetic variability at SCARB2 does not account much to the GD phenotypic spectrum. Nevertheless, in vitro analyses of the novel p.T398M are envisaged, in order to further characterize the effect of this variant on the levels and sub-cellular location of GCase. The clinical presentation of the patient harbouring this coding variant will also be discussed.

OC - 09

NEURONAL CEROID-LIPOFUSCINOSES: FROM CLINICAL TO MOLECULAR BASES

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Text body: Neuronal ceroid-lipofuscinoses (NCL) are the most common neurodegenerative disorders in childhood. Clinical symptoms include mental regression, blindness, epilepsy, motor impairment and premature death. Traditionally NCL were classified according to the age at onset as infantile (INCL), late-infantile (LINCL), juvenile (JNCL) and adult (ANCL), and until recently characterization of the autofluorescent storage material by electron microscopy (EM) of tissue biopsies offered the only diagnostic confirmation. Today at least 14 affected genes are identified, CLN1 to CLN14, allowing the definitive diagnosis of these diseases.
Retrospective study of patients followed at our Reference Centre for Metabolic Diseases with diagnosis of NCL from 1980 to the present date.
Thirteen children (including 2 family cases) were diagnosed with NCL: 8 males, 1 of African origin, 3 had consanguineous parents. Clinical manifestations included decreased visual acuity, psychomotor regression, mental retardation and epilepsy (mainly myoclonic type); all children presented a progressive course with variable progression of the symptoms. According to the clinical picture, 8 children were classified as LINCL, and 5 as JNCL. EEG was obtained in 12 patients showing overall lentification in all. Brain imaging was performed in 12 children and revealed brain atrophy or periventricular white matter hyperintensities in 8 of them. Electroretinogram was conducted in 7 patients, revealing absent response in 5. The oldest patients (N=10) were diagnosed through clinical disease characterization which was confirmed by the typical findings of "fingerprints" on EM. Instead, molecular tests were crucial for diagnosis confirmation on the 3 youngest children (1 single gene test and 2 panels of genes) identifying mutations at CLN5 (R112P, D279N), CLN6 (p.Ala22Ser, p.Ile154del) and CLN7 genes.
NCL should be considered in the investigation of psychomotor regression, especially if associated with visual impairment or epilepsy. Nowadays, genetic diagnosis is becoming a non-invasive, accessible and specific method available for all types of NCL, which increases understanding of the condition, influence treatment options and allow genetic counselling in affected families. In recent years new treatments are under development and can be able to change the prognosis of theses diseases, so it is imperative to diagnose affected patients as soon as possible.

OC - 10

THE DIAGNOSTIC PARADIGM SHIFT: MITOCHONDRIA ARE INNOCENT UNTILL PROVEN GUILTY

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Text body: Introduction: Diagnosis of a mitochondrial disorder is particularly challenging with variable clinical presentations and laboratory findings. Since no single score system is satisfactorily accurate, it is currently accepted that a definite diagnosis is only provided by genetic studies. Methods and results: Within patients followed in the last 20 years in our tertiary center with a suspected mitochondrial disorder, we have been establishing some different definite diagnosis. Here we present the most striking examples: P1. 14-year old female with muscular weakness, whose father had progressive hypotonia with proximal tetraparesis, and combined complex deficiency. Both have Emery-Dreifuss muscular dystrophy (LMNA). P2. 20-year-old female with early-onset epilepsy, ataxia, myopathy, tubulopathy, elevated CK, hyperlactacidemia and complex II deficiency. She has megaconial muscular dystrophy (CHKB). P3. 20-year-old male, that had regression after acute gastroenteristis at 13 months. At the age of 5 he had limb girdle myopathy and ophtalmoparesis; at 17 developed epilepsy and MRI showed diffuse atrophy. Histological studies were unspecific; respiratory chain studies showed complex I deficiency. His final diagnosis is DPAGT1-CDG. P4. 10-year old male with refractory epilepsy, severe global delay, hyperlactacidemia and basal ganglia, central tegmental tract and midbrain hyperintensities. His diagnosis is epileptic encephalopathy associated with STXBP1 gene. P5. 6-year-old male with development delay, failure to thrive and metabolic acidosis with high lactate and recurrent urinary organic acids with Krebs metabolites and methylmalonic, glutaric and dicarboxylic aciduria. The 11p15.5 hypomethylation analysis confirmed Russell-Silver syndrome. P6. 15-year-old female with growth impairment, development delay, epilepsy, progressive muscular hypotonia and partial complex I deficiency. Subtelomeric region analysis revealed a 4p microdeletion. Discussion: Any patient with a diagnosis of probable mitochondrial disorder not genetically proven by a wide NGS approach, despite the functional respiratory chain deficiency or MRI findings, must be further studied. Evaluation should include a multidisciplinary approach with metabolic, neurologist and geneticist specialists. With this diagnostic paradigm shift, a significant number of patients can now be diagnosed with other diseases allowing adequate genetic counseling and follow-up.

Selected Oral Free Communications

Session IX - March 15th

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OC - 11

NUTRITIONAL MANAGEMENT OF MATERNAL PKU IN CHUP (NMMPKU): RETROSPECTIVE STUDY AND OFFSPRING OUTCOME

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Text body: Background: Optimal nutritional management during pregnancy is essential to prevent maternal phenylketonuria (MPKU) syndrome. We retrospectively studied the nutritional management practices compared with infant outcome in a series of MPKU case reports followed at our centre. Methods: Data on metabolic control, nutritional intake, anthropometry and biochemical markers of 5 pregnancies, 4 single and 1 multiple, from 2007 to 2017 was collected. A total of 4 early diagnosed PKU women, 1 was pregnant twice, had an age range at conception of 25-31 y. Data was collected before (BP), during (DP) and post pregnancy (PP). Body composition BP and PP was interpreted. Intrauterine development and neonatal anthropometry was recorded for the 6 offspring (2 females and 4 males). Results: BP median blood [Phe] was 2.6-11.4 mg/dL (20-95% of the values within target range). Two pregnancies were planned. DP median blood [Phe] range reduced into 2.5-5.5, 1.2-3.7 and 1.0-4.0 mg/dL by the end of trimester 1, 2 and 3, respectively. PP median blood [Phe] range increased to 6.7--20.2 mg/dL. All women were treated with a Phe-restricted diet. In 4 cases Phe-free L-amino acids mixtures (AAM) (28-84 g/d) and in 1 pregnancy a combination of GMP and AAM were used. Phe intake BP was between 414-1415 mg/d and, by the end of trimester 1, 2 and 3, was 460-1018, 469-1259 and 1336-1520 mg/d, respectively. Protein equivalent intake DP was 0.9-1.3 g/kg/d. Maternal weight gain was 13.5-21 Kg. Body fat % increased from 25.8-32.7% (BP) to 30.9-37.7% (PP). No significant biochemical deficiencies were found. Four were eutocic births with one elective caesarean. Infants born at 36-39 w, with 2420-3410 g (weight), 45-49 cm (length) and 31.5-34 cm (head circumference) and were breastfed until 1-7 months. Only one woman stopped diet PP. Conclusion: Although sub-optimal metabolic control BP, excellent blood Phe control was achieved throughout all pregnancies, allowing normal neonatal outcomes in all 6 children.

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BIOPSYCHOSOCIAL PROFILE OF PKU PATIENTS THROUGHOUT LIFE: CHALLENGES IN PSYCHOLOGICAL SUPPORT

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Text body: Introduction: Phenylketonuria (PKU, OMIM 261600), is an autosomal recessive disorder caused by pathogenic variants on the enzyme phenylalanine hydroxylase (PAH) gene. It results in a decreased conversion of Phenylalanine (Phe) into tyrosine with neurotoxic plasma Phe levels. Studies on patients who started diet after newborn screening showed that the level of global intellectual development seems to be preserved if a correct dietary control in childhood was achieved. However, specific neurocognitive deficits observed in this group suggest a degree of neurobiological impairment that must be investigated taking into account the knowledge about the effects of high blood Phe levels in the structural integrity of specific brain regions and on neurotransmission throughout life. Methods: We studied 139 PKU aged 2 to 37 years based on the following inclusion criteria: early diagnosed at the neonatal screening, without additional disorders. We studied 4 groups of age: patients aged 1 to 6 years, patients aged 7 to 12 years, patients aged 13 to 17 and, group 4 – patients aged ≥ 18 years. The neonatal screening blood Phe concentrations, used to classify the disease severity, was considered as independent variable. Patient's outcome was evaluated according to the global quotient development (QD)/ intelligence quotient (IQ) value on the Griffiths Mental Development Scales, Wechsler Intelligence Scale for Children (WISC-III) and Wechsler Adult Intelligence Scale (WAIS-III) at different group of ages, the quality of dietetic control (QDC), as well as educational level, school curriculum, and comorbidities. Differences between groups were analysed. Results: We observed significant differences between the PKU groups according PKU classification on DQ/IQ global values and QDC after the age of 6, with classical PKU patients having the lower mean DQ/IQ global values, the worse dietary compliance, the bigger percentage of individuals with adapted curriculum or special education and more severe comorbidities. Patients with hyperphenylalaninemia were the only ones showing a good QDC in all groups of age, with annual medians of Phe < 6 mg/dL. Conclusion: These results point to the need for a regular psychological follow-up and neurocognitive evaluations in the mild and classical forms of the disease with an intervention in different contexts in order to help and motivate the PKU patients to maintain a good metabolic control throughout life.

OC - 13

PYRUVATE DEHYDROGENASE DEFICIENCY – REVIEW OF 6 CLINICAL CASES

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Text body: Introduction: Pyruvate dehydrogenase (PDH) deficiency is one of the inborn errors of mitochondrial energy metabolism. Clinical features are heterogeneous ranging from fatal lactic acidosis on newborn period to chronic neurodegenerative abnormalities. Material and methods: Authors reviewed the clinical charts from 6 patients with genetically confirmed PDH deficiency (PDHA1, n=3; PDHX, n=2; DLD, n=1). Clinical manifestations, outcome, laboratory evaluation and treatment were evaluated. Results: Parental consanguinity was reported in only one patient although two of them, that have the same mutation, share the same residence place. The six subjects aged between 1-35 years. Age of onset varied from neonatal period (n= 3) to infancy or childhood (n=3). Clinical manifestations can be divided in four different phenotypes: congenital lactic acidosis (n=3); recurrent ataxia (n=1); Leigh syndrome (n=1) and delayed neurodevelopment with mild hyperlactacidemia (n=1). Interestingly two nonrelated patients with the same PDHX mutation had visual impairment. The main neuroimagiologic findings were absence or thinning of corpus calosum (n=2), cortical atrophy predominantly affecting white matter (n=2), periventricular cysts (n=1) and necrotic lesions of basal ganglia (n=1). Blood and cerebrospinal fluid lactate and pyruvate measurements were important findings for the recognition of PDH deficiency, specially when lactate was increased and lactate/pyruvate ratio was below 10. Almost all patients with the neonatal form developed lactic acidosis with blood lactate in the range 8-17 mmol/L (RV: 0,5-2mmol/L), whereas patients presenting in infancy usually had blood lactate concentrations in the range 3-5 mmol/L. The residual PDH complex activity measured in linfocytes varied from 5,3% to 30% of mean normal activity. One patient had a normal enzymatic study, although a pathogenic homozygous mutation was identified by a panel for nuclear genes regarding mitochondrial cytopathies. All patients started cetogenic diet and thiamine at diagnosis, 3 patients also received arginine aspartate and 2 lipoic acid. Lactic acidosis resolved upon specific treatment.. Neurodevelopmental improvement was noted in all patients although still have cognitive impairment. Conclusion: Genotype/phenotype correlation is hampered by clinical diversity of PDH deficient cases. Large genetic panels are becoming an utmost important tool for achieving diagnosis when the clinical picture is atypic.

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CONGENITAL DISORDERS OF GLYCOSILATION – RETROSPECTIVE ANALYSIS OF A COHORT WITH N-GLYCOSILATION DEFECTS

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Text body: Background: Congenital disorders of glycosylation (CDG) are a rapidly expanding group of rare genetic defects in glycan synthesis, processing or transport. Glycosylation involves many different genes, encoding proteins in the cytosol, endoplasmic reticulum or Golgi compartment. Most are due to defects on the N-linked glycosylation pathway. CDG are associated to broad multisystemic manifestations varying from mild to severe, disabling or life-threatening. For many types of CDG, the phenotype spectrum is not completely known due to the reduced number of reported patients, and, occasionally, data from transferrin glycosylation studies is not informative. Objectives: Clinical, biochemical and molecular characterization of all cases with CDG observed at Centro Hospitalar e Universitário de Coimbra. Material and methods: Retrospective analysis of patient medical records from January of 2001 to January 2019. Results: From the last 18 years, since the first confirmed biochemical CDG diagnosis, we achieve a cohort of 12 patients: PMM2-CDG (5/12), ALG1-CDG, SLC35A2--CDG, COG1-CDG, CCDC115-CDG, ATP6AP2-CDG, DPAGT1-CDG and MAN1B1-CDG (one each). The earliest clinical manifestation in 50% (6/12) of our cohort was development delay, with the remaining patients presenting a variability of signs and symptoms such as myopathy, hypotonia, seizures, jaundice, peritonitis and prenatal biventricular hypertrophy. In 67% (8/12) of the patients in this cohort the diagnostic algorithm was initiated by %CDT and transferrin IEF analysis enzymatic assays and glycan structure analysis whenever necessary, followed by genetic confirmation, and 33% (4/12) were diagnosed directly by molecular genetic testing, including one case with normal transferrin analysis. Conclusion: PMM2-CDG is the most common diagnosis within our CDG patients' cohort, as reported in literature. CDG was a rather challenging diagnosis in most of our cases since more than half did not present the typical phenotype, including one patient with normal transferrin analysis. Clinical exome/WES/WGS may be considered as a diagnostic tool if the phenotype is insufficient to support gene-targeted testing or, if a CDG specific panel fails to confirm diagnosis in the presence of abnormal transferrin and suggestive clinical features. Furthermore, glycan analysis can be helpful in giving some clues about the defective step in the pathway or to complement information in patients with atypical biochemical and/or genetic results.

OC - 15

FISH ODOR SYNDROME GENETIC INVESTIGATION: HOW FAR CAN WE GO?

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Text body: Introduction: Fish odor syndrome is a metabolic disorder usually caused by a deficiency in flavin-containing monooxygenase 3 (FMO3) enzyme. A much rarer disease, deficiency in dimethylglycine dehydrogenase (DMGDH) has been reported in one case. The first increases levels of trimethylamine (TMA) in body fluids and the second blocks choline catabolism, both leading to an unpleasant fish odor with serious social consequences. Material and methods: Genomic DNA characterization of 30 pediatric patients presenting with fish odor syndrome. Results: Thirty patients were included, 15 male and the median of age was 1.2 years (minimum 0.1; maximum 13.5). All 30 individuals had unpleasant fish odor and were screened for mutations of the FMO3 gene coding region. Twenty seven individuals had mutations at this gene and 18 different variants were identified, some of which had not been previously documented (p.G148R, H149Y, p.E208K, p.T307P, p.S310L and p.E461K). Twenty three individuals presented the common variant p.E158K (c.472G>A) until now recognized as a polymorphism. The 3 individuals without FMO3 mutations were screened for DMGDH mutations. 8 variants were found on DMGDH coding region. All presented with the same mutation p.G124G in heterozygoty. Two of these individuals also presented heterozygoty for the polymorphism p.G489G and for the pathogenic p.S646P mutation. No muscular symptoms such as fatigue were noted in the studied patients or abnormal levels of the muscle form of creatine kinase in serum. Conclusion: This study states for the inclusion of DMGDH study as a differential diagnosis of Fish odor syndrome when FMO3 genetic study is unrevealing. The presence of the same DMGDH polymorphisms in the symptomatic patients may reveal a pathogenic correlation. Further studies, such as enzymatic, are necessary to clarify this hypothesis as well as the pathogenicity of the 6 novel variants identified. Key words: Dimethylglycine dehydrogenase deficiency; DMGDH; Fish odor syndrome; FMO3; Trimethylaminuria

Selected Poster Communications

Session XII - March 15th

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PC - 01

CTNS MOLECULAR GENETICS PROFILE IN A PORTUGUESE CYSTINOSIS POPULATION

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Text body: Background: Cystinosis is a multisystemic autosomal recessive deficiency of the lysosomal membrane transporter protein (cystinosin) caused by mutations in CTNS gene. Objective: This study summarizes the Portuguese experience in the diagnosis and management of patients with this rare disease over the past few years and reports recurrent mutations in the CTNS gene. Methods: Unrelated patients from different pediatric and adult hospitals all over Portugal with non-nephrotic proteinuria, hypercalciuria, hypokalemia impaired proximal reabsorption of amino acids, glycosuria and hypophosphatemia, suggestive of a Fanconi syndrome and ocular problems, were studied. Intraleukocyte cystine levels were determined and molecular analysis performed, to determine the presence or absence of the 57-kb deletion in CTNS, followed by direct sequencing of the coding exons of CTNS. Results: From 1998 to 2017, twenty-one cystinotic patients were biochemically diagnosed. From the remaining seventeen (four deceased), eleven were studied for CTNS gene. Five out of eleven patients were homozygous for the 57-kb deletion (10/22; 45.5%), and other five were compound heterozygous for this variant (15/22; 68.2%). The other mutations found were p.Q128X (c.721 C>T; 2/22), p.S139F (c.755 C>T; 4/22) and c.18-21delGACT (p.T7FfsX7; 1/22). All of these seventeen cystinotic patients are in treatment. Approximately 84% are adults, 16% are young children, and 54,5% are kidney transplant recipient. Conclusions: The authors would like to emphasize the importance of first screening for the 57-kb deletion since it is very common in our population. This genetic study is the first in our country and it could be the basis for future genetic counseling in Portuguese population.

PC - 02

TRANSITION FROM PAEDIATRIC TO ADULT CARE IN PHENYLKETONURIA (TRANS-PAC-PKU): THE 2 YEAR'S IMPACT ON METABOLIC CONTROL AND ADHERENCE

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Text body: Background: In PKU, transition to adult care (TAC) is challenging and information on adults follow-up is limited. We aimed to see how TAC affects metabolic control and adherence. Methods: 55 PKU patients (55% females; 5 HPA, 26 mild PKU and 24 classical PKU) in whom TAC occurred between 2011 and 2015, were analysed in two different study periods: 2 y pre and post-TAC (SP1 and SP2, respectively). Mean age at TAC was 23.3 ± 4.3 y. None of the patients received sapropterin, but there was one pregnancy in SP2. Retrospective data on metabolic control (median blood [Phe], number of blood spots and % of blood [Phe] < 8 mg/dl) and number of clinic visits was collected for SP1 and SP2. Natural protein (NP, g/kg), protein equivalent (PE, g/kg), total protein (TP, g/kg) and Phe (mg/day) intakes closest to TAC were compared with those recorded on the first appointment after SP2. Results: In SP2, 3 patients (2 females) were lost in follow-up (6%) resulting in a final sample of 52 patients. Median number of analysed blood spots significantly increased in SP2: 22 [13-30] vs. 29 [15-41]; p=0.002. Mean (SD) of the median blood [Phe] remained stable from SP1 to SP2 (8.7 ± 4.1 vs. 9.1 ± 3.7; p=0.100) while the median % of blood [Phe] < 8 mg/dl significantly decreased in SP2 (51.5 [3.7-95.7] vs. 36.5 [4.6-84.6]; p=0.041). Median number of total clinic visits significantly increased in SP2 (5 [4-6] vs. 11 [8-13]; p

PC - 03

MOLECULAR DIAGNOSIS OF MITOCHONDRIAL DISEASE WITH TARGETED NEXT GENERATION SEQUENCING: A COHORT OF 250 PATIENTS

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Text body: Background: Mitochondrial diseases are a group of rare inherited disorders characterized by extreme phenotypic heterogeneity that can be transmitted by any mode of inheritance, with hitherto no effective therapy options. It is estimated that 1:5,000 individuals will develop a mitochondrial disease. The molecular diagnosis in mitochondrial disorders is a great challenge and compared with traditional diagnostic testing approaches, the recent evaluations of Next Generation Sequencing (NGS) for mitochondrial disorders have shown that this methodology is more likely to provide a diagnosis, being quicker and cheaper. Many of the newly nuclear gene loci linked to mitochondrial disease genes have been discovered with NGS methods as well as novel phenotypes associated to genes previously linked to mitochondrial disease.

Objectives: The purpose of our project* was to develop a NGS strategy to identify the genetic defects in 250 patients suspicious of mitochondrial disorders, to confirm the clinical and biochemical diagnosis of the disease.

Methods: NGS was performed in a MiSeq Illumina instrument using a custom gene panel with 209 nuclear genes involved in mitochondria metabolism, and the entire human mitochondrial genome, applying SureSelect QXT target enrichment and Nextera XT, respectively.

Results: A molecular diagnosis was attained in 62/250 (25%) of the studied patients that harbored 21 pathogenic variants, previously reported in the literature, 11 novel variants probably pathogenic and 54 novel variants of unknown significance. These mutations were confirmed by Sanger sequencing in the index cases and in their relatives.

Discussion and Conclusion: Our NGS approach revealed to be an useful strategy to provide a molecular diagnosis in a substantial fraction of patients with mitochondrial diseases of unclear etiology, expanding the mutational spectrum of these disorders. Undiagnosed patients will be selected for Exome Sequencing.

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PC - 04

PROLIDASE DEFICIENCY: REPORT OF THREE PATIENTS

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Text body: Introduction Prolidase deficiency (#170100) is a rare autosomal recessive metabolic disorder characterized by facial dysmorphisms, hepatomegaly and splenomegaly, variable intellectual disability, skin lesions, skin and respiratory recurrent infections. Anemia, thrombocytopenia, hypergammaglobulinemia and hypocomplementemia are also common features. This diagnosis is established when biallelic PEPD pathogenic variants are found or when reduced prolidase enzyme activity is detected in a proband who has characteristic clinical findings and iminodipeptiduria. The prevalence of prolidase deficiency is unknown. Approximately 100 affected individuals have been reported in the literature; however, prolidase deficiency likely remains underdiagnosed as a result of under-recognition by physicians. We present the three patients diagnosed in our Reference Center, two children and one adult with molecular and enzymatic diagnosis respectively. Patients and Methods The first two patients are siblings, a female and a male, 7 and 4 years-old respectively, that presented with facial dysmorphisms, pectus excavatum, generalized hyperlaxity, mild hepatomegaly and splenomegaly, xerotic skin with mild lesions and nasal voice. Both had recurrent respiratory infections and speech delay. The female had mild intellectual disability, a small interventricular communication and gastric reflux. In both, imidodipeptiduria was found and the diagnosis of prolidase deficiency was made after detection of c.692_694delACT (p.Y231del) variant in homozygosity in PEPD gene. Parental study confirmed the carrier status and a recurrence risk of 25% was given. The third patient is a 25 years-old female observed at our center since early infancy. She has mild intellectual disability and learning difficulties, mild depression, skin with eczema and chronic ulcers (on proline based ointment), splenomegaly and episodic vomits. The diagnosis was made based on clinical manifestations and iminodipeptiduria levels. Genetic confirmation is ongoing. Conclusion With this work, the authors wish to emphasize the importance of a detailed physical examination, complementary to the anamnesis to consider this diagnostic hypothesis, as well as the importance of genetic confirmation of the biochemical results. Only with an adequate diagnostic workflow and multidisciplinary approach becomes possible to reach a diagnosis and offer accurate follow-up and genetic counselling.

PC - 05

MITOCHONDRIAL PROTEIN IMPORT GENES INVOLVEMENT IN LEBER'S HEREDITARY OPTIC NEUROPATHY (LHON)

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Text body: : INTRODUCTION: LHON is a rare maternally inherited disorder, characterized by the loss of retinal ganglion cells that leads to optic nerve degeneration, causing a sudden and painless loss of central/total vision. The main confirmed genetic mutations are m.3460G>A (MT-ND1), m.11778G>A (MT-ND4) and m.14484T>C (MT-ND6). They are located in mitochondrial DNA (mtDNA) genes, encoding subunits of NADH-ubiquinone oxidoreductase (complex I) of the mitochondrial respiratory chain. The high number of mutation carriers without disease manifestation suggests other genetic influencers for the phenotype disclosure. The presence of nuclear gene variants in proteins involved in the mitochondrial protein import (MPI) and processing have been implicated in various mitochondrial disorders and may contribute as genetic modifiers in LHON. METHODS & SUBJECTS: A search for MPI genes variants was performed in whole-exome sequencing data of 29 subjects: 6 LHON patients with mtDNA pathogenic mutations; 2 non-carrier and 13 carrier family members from two LHON patients; and 8 unrelated LHON-suspected patients. The prediction of functional impact of the relevant variants was evaluated using bioinformatics' tools. RESULTS: Seven variants with high probability of being pathogenic were found. An additional frequency filtering was performed, which resulted in the identification of the promising missense c.280-C>T (rs147048880) and frameshift c.170delA/c.172_176delGGCAC (rs752079244/rs760772539) variants from MIPEP and TOMM20L gene, respectively, in a LHON individual with the m.14484T>C mutation. These variants were confirmed using two additional methods: Sanger sequencing and PCR-RFLP. CONCLUSION: The results suggest that protein import to mitochondria may contribute to LHON phenotype, but further functional studies are required for the evaluation of implications at the protein level and validation of the pathogenicity. SUPPORT: financing by Feder funds through the Operational Competitiveness Program – COMPETE2020 (Strategic project POCI-01-0145-FEDER-007440; HealthyAging2020 CENTRO-01-0145-FEDER-000012-N2323 and Portugal CENTRO-07-ST24-FEDER-002002/6/) and National Funds by FCT–Portuguese Science and Technology Foundation through the strategic plan UID/NEU/04539/2013; project Pest-C/SAU/LA0001/2013--2014; PTDC/DTP-EPI/0929/2012 (FCT grant); SPDM prize 2014; PhD grant FCTSFRH/BD/86622/2012; Portugal. Santhera Pharmaceuticals (Switzerland) provided a grant for LHON genetic investigation.

PC - 06

GENETIC STUDIES – A USEFULL TOOL FOR DIAGNOSIS OF HETEROGENEOUS MITOCHONDRIAL DISORDERS

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Text body: Background: Mitochondrial disorders include a wide range of oxidative phosphorylation defects, leading to a decrease in cellular energy production. Clinical and genetic variability is huge, especially in childhood, bringing difficulties for diagnosis, but genetic tests play a fundamental role for definitive diagnosis. Material and methods: We present a study of 20 patients followed at a metabolic diseases Centre with confirmed genetic diagnostic of mitochondrial disorder. Results: Our clinical setting presented an equal gender distribution with a median age at the diagnosis of 36 months (7 months – 276 months). Fifty percent had family history suggestive of mitochondrial disorder, with 3 pairs of siblings. Most frequent symptoms included hypotonia (70%), abnormal psychomotor development (50%) and failure to thrive (45%). Muscle biopsy was performed in 14 patients (70%), from which 3 presented "ragged-red-fibers". Regarding molecular studies, thirteen patients had nuclear DNA mutations (65%) and seven had mitochondrial DNA mutations (35%). Nine patients (45%) deceased (younger with 2 months, older with 12 years). Conclusion: Clinical diagnosis of mitochondrial disorders is complex, presenting high variability between relatives or between patients with the same clinical syndrome. Laboratorial evaluation of respiratory chain enzymes activity and anatomopathology of the muscle requires invasive methods and are often ineffective for achieve diagnostic confirmation, especially in childhood. Genetic studies have emerged has the most accurate noninvasive method for confirming clinical heterogeneous diseases such as mitochondrial disorders.

PC - 07

ASSEMBLY OF OXPHOS SYSTEM IN PATIENTS WITH RESPIRATORY CHAIN DISEASE

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Text body: Defects in oxidative phosphorylation (OXPHOS) induce varied clinical phenotypes. Functioning of OXPHOS system requires proper assembly of the ~80 proteins in five complexes, by diverse assembly factors. Pathogenic mutations affecting mtDNA-encoding subunits, assembly factors and post-transcriptional regulatory proteins of mitochondrial gene expression have been identified in disease. The implicated derived effects in OXPHOS assembly are roughly clear. We present a study aiming to elucidate the effects in OXPHOS system assembly, comprising three patients: P1) LHON-plus - m.11778G>A, MT-ND4; P2) Leigh syndrome - novel homozygous deletion (c.-11_13del, SURF1); P3) Epileptic encephalopathy - novel homozygous variation (FASTKD2). Mitochondrial enriched fractions from patients-derived fibroblasts were obtained and native OXPHOS complexes were separated by Blue Native Electrophoresis (BN-PAGE). Combination with western blotting using antibodies against the OXPHOS complexes (CI-CV), allowed observation of several defects, compared to controls. Complexes assembly was impaired in all patients' fibroblasts. Analysis of native blots complexes bands intensities of the patients against controls showed that assembled CI was significantly reduced in P1; P2' sample demonstrated absence of assembled CIV; and CI assembly was also significantly altered in P3. The observed assembly defects were concordant with OXPHOS activity. The OXPHOS-assembly profiles provided further information about consequences of identified disease-causing mutations and/or phenotype, either validating recognized assembly factor function (SURF1 – P2) or adding insight in the role of specific proteins concerning the biogenesis of the OXPHOS system (FASTKD2 – P3). The results suggest that OXPHOS assembly investigation should be considered in diagnosis of disease, reinforced by the correlation with OXPHOS activities. SUPPORT: Feder: COMPETE2020 (POCI-01-0145-FEDER-007440; HealthyAging2020 CENTRO-01-0145-FEDER-000012-N2323; Portugal CENTRO-07-ST24-FEDER-002002/6/8); FCT: UID/NEU/04539/2013; Pest C/SAU/LA0001/2013--2014; PTDC/DTP-EPI/0929/2012 (FCT grant); SPDMprize2014; PhD grant FCTSFRH/BD/86622/2012.

PC - 08

BRAIN MAGNETIC RESONANCE IMAGING FINDINGS IN CHRONIC PROGRESSIVE EXTERNAL OPHTHALMOPLEGIA

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Text body: Background: Chronic Progressive External Ophthalmoplegia (CPEO) is one of the most frequent phenotype of Mitochondrial Disease (MD) in adults. Despite being classically considered a predominantly muscular disorder, there is growing evidence of significant extramuscular involvement in CPEO. Brain magnetic resonance imaging (MRI) abnormalities are common in patients with MD and some patterns are suggestive of different phenotypes. However, neuroimaging findings in CPEO have rarely been described. Objectives: To characterize brain MRI findings in patients with CPEO. Methods: We selected patients with a diagnosis of MD, supported by histopathological and/or genetic study, with CPEO phenotype, who performed brain MRI. We retrospectively collected clinical (sex, age of onset, age at MRI, extramuscular involvement, cardiovascular risk factors), imaging (brain MRI), histopathological (muscle biopsy), biochemical (mitochondrial respiratory chain function) and genetic (mtDNA) variables. Results: We included 20 patients (60% female) with mean age 48.1±14.1 years and mean age of onset 30.5±11.7 years. Extramuscular involvement was present in 30%. Muscle biopsy was suggestive of MD in 80%. Biochemical study (n=15) supported the diagnosis in 67% and genetic study (n=13) in 77%. Abnormalities in brain MRI were reported in 10 patients (50%), namely multiple small subcortical white matter T2 hyperintensities in 5 patients (25%), brain atrophy in 3 patients (15%) and 1 patient (5%) had a single cerebellar T2 hyperintense lesion. Discussion: Brain MRI abnormalities were present in half of the patients with CPEO. Those changes were non-specific and less significant than in other forms of MD with predominantly muscular involvement. Despite these findings, the potential involvement of the central nervous system in CPEO must be further characterized and brain imaging should be considered in the follow-up of this group of patients.

PC - 09

ARNT2 MUTATIONS: EXPANDING THE SPECTRUM OF MITOCHONDRIAL DISORDERS

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Text body: Introduction Severe multisystem disorders are the hallmark of mitochondrial disorders. They should always be considered a diagnostic hypothesis, especially when mitochondrial DNA (mtDNA) depletion is associated. However, mitochondrial depletion can be a secondary phenomenon, and the differentiation is crucial to achieve a correct diagnosis. Clinical report: We present the case of two siblings, with young, healthy, non-consanguineous parents, and one normal sibling. The first sibling was a male, born in breech presentation, with normal birth anthropometry. He showed neonatal hypoglycemia, feeding difficulties and marked hypotonia, retrognatism, and reduced hip abduction. He developed severe developmental delay, amblyopia with horizontal nistagmus, hypernatremia, diabetes insipidus, pielic ectasy, tracheomalacia, and progressive emaciation. Etiologic investigations - cerebral MRI, auditory potentials, karyotype, metabolic evaluation (aminoacids, lactate, pyruvate, organic acids, acilcarnitines, sterols), muscle biopsy with respiratory chain evaluation and fibroblast beta-oxidation studies - were inconclusive. He died at 4 years of age. The second sibling was a female, , admitted in neonatology in D1 for feeding difficulties. She developed the same clinical manifestations as his late brother, plus epilepsy and recurrent urinary tract infection associated to neurogenic bladder and vesicoureteral reflux. All etiologic studies were repeated with no further clarification, and mtDNA quantification in muscle biopsy showed depletion of 80% in both siblings. Mitochondrial 209 genes panel was normal. She died at 10 years old. Whole Exome Sequencing was performed and a compound heterozygous was identified, including a novel frameshift variant and a novel nonsense variant in ARNT2 in both siblings, responsible for Webb-Dattani syndrome (OMIM #615926). Discussion Webb-Dattani syndrome is an autosomal recessive disorder previously described in an highly consanguineous Saudi Arabian family, and is characterized by frontotemporal hypoplasia, global developmental delay, pituitary and hypothalamic insufficiency with multiple endocrine anomalies, seizures, post-retinal blindness, genitourinary disease, hip dislocation, amongst others. MtDNA depletion was not previously described in patients with ARNT2 mutations and could be explained by a failure of normal response to hypoxia dependent of ARNT2 encoded transcription factor, expanding the spectrum of Mitochondrial Disorders.

PC - 10

PLASMA LYSOSPHINGOMYELIN-509 – HOW TO REACH A PROMPT NIEMANN-PICK TYPE C (NPC) DIAGNOSIS

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Text body: Introduction: Niemann-Pick type C (NPC) disease (OMIM#257220; OMIM#607625) is an autosomal recessive neurodegenerative disease caused by mutations in NPC1 or NPC2 gene. Pathogenic variants in these genes cause an abnormal endosomal-lysosomal traffic leading to lipids accumulation in the acidic compartment of lysosomes/ late endosomes. Heterogeneous clinical phenotype and a wide range of nonspecific symptoms, are reasons for a delayed diagnosis. Until now cultured skin fibroblasts, filipin staining has been considered the biochemical gold standard diagnostic method.
Among sphingolipids accumulated in NPC patients plasma there is a slight increase of lysosphingomyelin (LysoSM) and a higher increase of its carboxylated analogue, lysosphingomyelin-509 (LysoSM-509). Furthermore, both compounds are also increased in acid sphingomielinase deficiency affected patients (ASMD- former Niemann-Pick type A/B).
Objective: The aim of this work was to illustrate how LysoSM-509 quantification in plasma can be a straight forward method to diagnose NPC suspected patients, and correlate it with filipin staining and genotype.
Methods: Using an in-house LC-MS/MS developed method to quantify NP disease biomarkers, we tested, as a proof of concept, plasma samples from 18 NPC (10 infantile and 8 adult) and 11 ASMD diagnosed patients, as well as 7 NPC obligate carriers, along with a control population. Filipin staining of cultured skin fibroblasts was performed as classically described and pathogenic variants were identified in NPC1 and NPC2 genes using Sanger sequencing.
Results: NPC patients revealed a LysoSM-509 and LysoSM concentration range of 293-9223 and 13.3-32.6 µmol/L, respectively. ASMD presented a LysoSM-509 and LysoSM concentration range of 2984-17082 and 258-527 µmol/L, respectively. These results allow discrimination between NPC, ASMD and controls. LysoSM-509 concentration in this cohort had a direct correlation with the qualitative result of the filipin staining and with pathogenic variants associated with infantile and adult clinical phenotype.
Conclusions: LysoSM and LysoSM-509 quantification in plasma is an innovative screening method that uses an accessible biological sample, reduces diagnostic delay for NPC suspected patients, and has a good correlation with filipin staining test and to patient's genotype. Moreover, as these compounds are not prone to oxidation, this method allows retrospective diagnostic of NPC and ASMD diagnosis in a single run.

Selected Posters

PO - 01

CLINICAL FOLLOW-UP OF PEDIATRIC PATIENTS WITH OSTEOGENESIS IMPERFECTA TREATED WITH BISPHOSPHONATES

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Text body: Background: Osteogenesis imperfecta (OI) is a group of genetic disorders of bone metabolism resulting in lower bone density and increased risk of fractures. Treatment with bisphosphonates, such as pamidronate, increases bone density in these patients, but the role of bisphosphonates on the natural history of OI is still being understood. Here, we aim to contribute to the ongoing effort to understand the utility of the treatment of bisphosphonates in OI. Methods: Twenty-one patients treated with pamidronate were included in this study. A descriptive analysis of the patients was computed. Multiple variables were compared before and two years after treatment with pamidronate in these patients using the Wilcoxon matched-pairs signed--rank test. To understand whether any pre-treatment factor predicted the patients who would have no fractures after treatment, the Mann–Whitney U test or Fisher exact were performed. Results: Nine female and 12 male patients followed up on a Pediatric Metabolic Diseases' Unit were included in this study, 12 with type I, four with type III and four with type IV OI. The median age of the first treatment with pamidronate was five years old. The median number of fractures before treatment was two, varying between none and 22. In the two years after treatment, 10 patients had no fractures while nine patients had between one and eight fractures. The total number of fractures was significantly lower after treatment (median before = 2, after = 0, p= 0.0014) as was the number of fractures/year (median before = 0.5, after = 0, p=0.0226). The bone density and z-score, evaluated by bone densitometry, were significantly higher after treatment (median before = 0.370, after = 0.562, p= 0.0022; median before = -2.8, after = -0.85, p= 0.0144). No differences were found on the bone markers of remodeling before and after treatment. No pre-treatment variants were different between patients who had or had no fractures after treatment, but a trend for patients with the highest number of fractures before treatment to have fractures after treatment was noted. Conclusion: The treatment of OI pediatric patient with bisphosphonates was effective on the reduction of the number of fractures and improving bone density and z-scores. No pre-treatment factor predicted which patients would have fractures in the two year after treatment, so all patients with OI need a close follow-up after treatment with bisphosphonates.

PO - 02

CLINICAL DESCRIPTION OF AN OSTEOGENESIS IMPERFECTA COHORT ON A TERTIARY CARE UNIT.

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Text body: Background: Osteogenesis imperfecta (OI) is a group of genetic disorders of bone metabolism caused by an imbalance between bone formation and destruction resulting in lower bone density and increased risk of fractures. Other features are blue sclera, dentinogenesis imperfecta, hearing loss, joint hypermobility, short stature, and progressive skeletal deformity. Patients and methods: The clinical features of 43 OI patients followed up on the clinical genetics and/or metabolic diseases pediatric unit were reviewed. For categorical variants, their frequency was calculated and for continuous variants, their mean value and P25--P75 were determined. Results: Our cohort is composed of 20 females and 23 males, with a median age of 18 years (13.5 to 32.25). Of these, 5 patients had a prenatal diagnosis of OI, while 38 had a postnatal diagnosis at the median age of 36 months (12, 120) with the oldest being diagnosed at the age of 33. The median age of the first fracture was 24 months (12, 72). A known or suspected autosomal dominant inheritance was described in 26 patients, while for the rest the inheritance remained elusive. Most patients (32) presented "mild" OI according to the classification proposed by van Dijk et al. in 2014, while 6 patients presented a "moderate" phenotype and 5 a "severe" phenotype. None of our patients had been diagnosed with an "extremely severe" phenotype or perinatal lethal form. Of the clinical features of OI, 26 patients presented blue/grey sclera, 10 hearing loss, 16 dentinogenesis imperfecta, and 22 some form of skeletal deformity. Vitamin D was prescribed to 27 patients. In addition, 27 patients were medicated with bisphosphonates, 13 of which at pediatric age. Conclusions: Our tertiary hospital follows a large cohort of patients with OI with a broad spectrum of clinical presentations with pediatric and adult patients. These results urge the integration of OI patients on a multidisciplinary team that follows them from the prenatal period throughout life.

PO - 03

MILKY BLOOD IN AN INFANT - A MANIFESTATION OF LIPOPROTEIN LIPASE DEFICIENCY

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Text body: Introduction: Severe monogenic hypertriglyceridaemia has been associated with mutations in several genes including the Lipoprotein Lipase (LPL) gene. LPL is the primary enzyme responsible for the hydrolysis of triacylglycerol-rich lipoproteins into free fatty acids and monoglycerides. LPL deficiency is an extremely rare (1:106) autosomal recessive disorder characterized by severe type 1 hypertriglyceridemia, recurrent acute pancreatitis, cutaneous xanthomata, hepatosplenomegaly and lipemia retinalis. Related complications are pancreatic abscess and necrosis and eventually death. Several treatment options have been tried. Case Report: A 36-day-old baby was admitted with a 4-day diarrhea history and respiratory distress over the previous 30 minutes. Clinical examination showed signs of a sepsis-like disorder and hepatosplenomegaly. During sampling, his blood was found to be milky. Laboratory investigations showed 2.26X1012/L red blood cells(RBC), hematocrit 19.1%, leukocytosis and neutrophilia, metabolic acidosis, hypognatremia and severe hypertriglyceridemia (24,129mg/dl). Blood cultures reveled Citrobacter braaki. Other investigations such as hemoglobin, C-reactive protein, lipase and amylase levels were initially difficult to analyze because of lipemic samples. Abdominal ultrassongraphy confirmed hepatomegaly with hepatic and pancreatic steatosis and ophthalmologic examination showed lipemia retinalis. Molecular studies revealed a homozygous c.644G>A, p.(Gly215Glu) mutation in exon 5 in LPL gene and parents were carriers for the same mutation. The initial management included fasting, fluid therapy, antibiotics, RBC transfusion and partial exchange transfusion with clinical and laboratory improvement. Five days later on, day feeding was restarted with a nutritionally complete, low fat formula with sustained improvement. He maintains a low fat diet with normal growth and development. Comments: While high levels of triglycerides disorder are usually secondary to several different causes, milky blood, a manifestation of chylomicronaemia/severe hypertriglyceridemia, is related to a primary monogenic disorder. We report a case of LPL deficiency an extremely rare disorder of lipid metabolism. Despite the several therapeutic approaches, dietary fat restriction seems to be essential and effective as in our case. We also emphasize the importance of a quick diagnose and proper management to improve morbidity and mortality.

PO - 04

ELEVATED URINARY EXCRETION OF 3 - METHYLGLUTACONIC ACID IN ORGANIC ACID PROFILES

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Text body: Increased urinary excretion of 3-methylglutaconic acid (3-MGA) is a relatively common finding in patients with metabolic disordes in general but is emerging as an important biomarker for mitochondrial dysfunction. Consistently and significantly elevated urinary excretion of 3-MGA is the hallmark of a growing group of inborn errors of metabolism that present 3-methylglutaconic aciduria (3-MGA-uria) as discriminating feature. While primary 3-MGA-uria is due to 3-methylglutaconyl-CoA hydratase deficiency (leucine catabolism pathway), secondary 3-MGA-urias have at least two different pathomechanisms: a) defective phospholipid remodelling (Barth syndrome and MEGDEL syndrome) and b) defective mitocondrial membrane associated proteins (Costeff syndrome, DCMA syndrome, TMEM70 defect). There are other 3-MGA-urias with "not otherwise specified" pathomechanisms. In this work, we reviewed urinary organic acid profiles of patients diagnosed in our Unit that consistently presented 3-MGA-uria.

PO - 05

LEIGH SYNDROME – ONE DISORDER, MULTIPLE MONOGENIC CAUSES

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Text body: Mitochondrial disorder of energy generation is the most frequent group of inborn errors of metabolism due to an impairment in the oxidative phosphorylation process (OXPHOS). It rises from distinct types of transmission (X-linked, autosomal, mitochondrial/maternal) due to nuclear, mitochondrial genome or in the interplay between two genomes resulting in great heterogeneity and wide range of presentation, from prenatal to adulthood. In childhood the most common presentation is Leigh syndrome or subacute necrotizing encephalopathy: a severe, heterogeneous mitochondrial disease that causes mostly neurologic symptoms and ophtalmological abnormalities (developmental delay and regression, hypotonia, dystonia, ataxia, progressive respiratory failure, optic atrophy and nystagmus), usually starts before 2 years of age and leads to early death. Unfortunately diagnosing these patients is still challenging despite initial biochemical approach (lactate and pyruvate serum measurements, aminoacid and organic acids profile, blood gas profile). This struggle was mitigated as the molecular biology came in to identify the specific variant despite biochemical profile results. As biochemical evaluation is not always possible, positive or safe, the next generation sequencing (NGS) advance is a real breakthrough achieved so far, preventing from invasive procedures in these patients and providing a great cost-effective choice to diagnosis. In the "NGS Era", over 75 genes, nuclear and mitochondrial, are associated with Leigh syndrome already and more than one third of them characterized in the last decade. New variants of unkown significance (VUS) are identified, requiring more studies to elucidate disease-related variants, resulting in one of the main challenges in human molecular genetics: their interpretation. Despite in silico predictors are available they may be inconclusive. It has stimulated new advances in molecular biology and set the pathway towards a more accurate demonstration of protein impact, culminated on functional studies to observe their dynamic bioprocess: the functional studies. These studies are key to prove the impact on protein function. The ultimate techniques applied to that, CRISPR-cas9 and iPSC, provide an alteration to the wild-type gene DNA and access the repercussion in related protein: a chance to establish new understanding of the genetic causes of this disease.

PO - 06

FROM FIBROBLAST TO CARDIOMYCOCYTES IN LYSOSOMAL STORAGE DISORDERS

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Text body: Lysosomal storage disorders (LSDs) are a group of approximately 70 LSDs, with a combined birth frequency of about 1:5000 live births, characterized by the accumulation of specific molecules in organelles of the endosomal-autophagic-lysosomal system, mainly due to defective lysosomal proteins. In this work we model, into induced pluripotent stem cells (iPSCs) and cardiomyocytes, two of the commonest LSDs: Fabry disease (FD) and Gaucher disease (GD). Fabry disease is X-linked and results from mutations on GLA gene which cause deficient activity of the lysosomal hydrolase alpha-galactosidase A (α-GAL A) leading to multisystemic accumulation of globotriaosylceramide (Gb3) and related lyso-sphingolipids. Gaucher disease is usually caused by mutations in the GBA gene resulting in deficient activity of the lysosomal enzyme glucocerebrosidase, leading to accumulation of glucocerebroside and related lyso-sphingolipids. Our aim is to study FD since this is a disease with cardiac involvement. In this work, GD fibroblasts and a normal control fibroblast line (human dermal fibroblasts – HDFa) were used, respectively as LSDs control and normal control. All cell lines were reprogramed from fibroblast to iPSCs using Sendai Virus or Episomal vectors to deliver the pluripotency factors. Cardiomyocytes were generated by using the addition of specific factors to the iPSCs. To determine the quality of our iPSCs we performed checkpoints regarding pluripotency factors integration, karyotype, and capacity to differentiate into the three germ layers. Cardiomyocytes were also characterised with specific markers. The results obtained are presented. In the future, the resulting iPSC-derived cardiomyocytes will be analysed against the initial fibroblast to see if the disease features are replicable in the new cell lines. The ultimate objective is to produce a disease-specific cellular model to use in future studies for gene editing or therapy testing.

PO - 07

FIRST STEPS TO GENERATE A NEW TAY SACHS DISEASE VARIANT B1 CELLULAR MODEL

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Text body: In the Portuguese population, lysosomal storage diseases (LSDs) have a prevalence of 1/5000 live births. Tay Sachs disease (TSD) variant B1 is a neurodegenerative lysosomal storage disease (LSD) which, although rare, is the most frequent form of TSD in Northwestern Iberia. The TSD variant B1, with mutation p.R178H (c.533G>A), is frequent in specific population groups of Iberian heritage. Since TSD variant B1 is very specific of these groups, investigation of TSD variant B1 may have a relevant impact in variant B1 patients of the Ibero-American community. This p.R178H mutation leads to a mutant HEXA protein with altered kinetics and reduced residual activity, and results in a specific neurodegenerative phenotype. The p.R178H HEXA mutation has a carrier frequency of 1:340 in the Portuguese population and 1:119 in the North of Portugal, in agreement with previous studies. The ability to reprogram somatic cells back to a pluripotent state has created new opportunities for generating models of disease-relevant cells by inducing patient cells into pluripotent stem cells (hiPSCs). LSD patient-specific hiPSCs have the advantage of having the patient's genetic background, and upon differentiation into disease-relevant cells, they also display morphologic, biochemical, and/or functional hallmarks of the disease. Availability of disease-relevant cell types derived from LSD patient hiPSCs will provide an ideal model for studying the pathogenic mechanisms and testing therapeutic agents. The CRISPR- associated protein nuclease (CRISPR/Cas) gene editing technology can be used to create genetic knockouts for molecular studies, to correct a mutation or to introduce patient mutations for disease modelling. LSD patient-specific hiPSCs, together with CRISPR/Cas gene editing tools, enable unprecedented capacity for disease modelling, correction and therapy. In this first year of this PhD project we will generate hiPSCs from TSD variant B1 patient skin fibroblasts and we will attempt to start the study the effect of CRISPR/Cas gene editing technology in these TSD variant B1 patient-specific hiPSCs.

PO - 08

IMPAIRMENT OF PYRUVATE DEHYDROGENASE CONPLEX ACTUVUTY MAY POTENTIATE A DECREASED FATTY ACID OXIDATION IN AN ANIMAL MODEL OF LIVER-INDUCED MITOCHONDRIAL DYSFUNCTION

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Text body: Acetyl-coenzyme A (acetyl-CoA) is a critical signaling metabolite that regulates key processes from mitochondrial energy metabolism to protein acetylation. Previous work from our group has revealed that the mechanisms underlying valproate (VPA)-associated hepatic steatosis and liver toxicity involve: (i) inhibition on dihydrolipoamide dehydrogenase activity1,2, the E3 subunit of pyruvate dehydrogenase complex (PDC) (ii) altered fatty acid oxidation (FAO) and CPT 1a-mediated regulation3; (iii) inhibition of lysine deacetylases KDACi, with important changes at the epigenetic level. To better understand the implications of acetyl-CoA in the regulation of hepatic functions we aimed to study overall PDC activity, major source of acetyl-CoA essential to the TCA cycle. A radiochemical method was used based on the conversion rate of [14C]-pyruvate to 14CO2 in rat liver homogenate. Using GC-MS, different intermediate metabolic products of acetyl-CoA generating pathways, including branched-chain and free fatty acids are studied in vivo, through the analysis of urine samples of controls and VPA-treated Wistar rats. The pattern of acetylated proteins isolated of rat liver homogenates was analyzed by Western-blot. Results show that PDC activity was clearly diminished in liver tissues from rats exposed to VPA. Drug-associated differences on the profiles of acetylated proteins were also observed. To conclude, the VPA-mediated mitochondrial dysfunction may involve the modulation of enzymatic activity, as observed through inhibition of PDC activity. The decrease on acetyl-CoA availability in matrix may impair acetyl-CoA-dependent metabolic processes contributing to mitochondrial energy dysfunction. References: [1] Luis PBM et al, , Biochim Biophys Acta 1767,1126-33,2007; [2] Kudin AP et al, Int. J. Mol. Sci. 18,1912, 2017; [3] Aires CP et al, Biochem Pharmacol 79, 792–9, 2010;

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STEROID SULFATASE DEFICIENCY AND CONTIGUOUS GENE SYNDROME

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Text body: Steroid sulfatase deficiency, also named recessive X-linked ichthyosis (XLI, OMIM 308100) is an inborn error of metabolism caused by a deficiency of steroid sulfatase enzyme that causes an accumulation of cholesterol sulfate in the epidermis leading to an abnormal desquamation and hyperkeratosis in the skin. XLI has a genetic heterogeneity that ranges from a point variant in the STS gene to a large deletion on Xp22.3 involving several genes, resulting in a more complex phenotype associated with intellectual disability, autism spectrum disorder or Kallmann syndrome. Due to location of the STS within a small region of the X chromosome that escape inactivation, recessive XLI affects almost exclusively males. We report a male Portuguese patient with 15 years with a syndromic form of XLI.The patient is the third child of nonconsanguineousparents, with birth weight 2.700 kg (P3-10), length 49 cm (P25-50), head circumference 35.4 cm (P25-50). He has a family history of scaly skin affecting three maternal uncles and no relatives with cognitive impairment.Skin disease appeared in early infancy with dry skin and mild, diffuse scaling that developed gradually over time to dark brown scales involving predominantly the neck, trunk and extensor surfaces of the extremities. He also presented protruding ears corrected by otoplasty, brachydactyly, syndactyly of second and third toes bilaterally and flat feet.Developmental assessment showed a moderate global psychomotor delay (IQ 48). Magnetic resonance imaging was normal. Ophthalmologic evaluation detected myopia. During childhood growth the height followed between the P25-50 and weight above the P90 (BMI > P97%). He had nutritional evaluation due to overweight, elevated liver transaminase levels and moderate steatosis. The patient was investigated by chromosomal microarray that showed a 1642kb deletion in Xp22.31, involving STS, VCX, VCX3A, HDHD1, PNPLA4 and MIR651 genes, inherited from his asymptomatic mother. The complete deletion of the STS gene confirmed the diagnosis of XLI. However, the deletion of the contiguous genes, namely VCX and VCX3A, might contribute for a more complex phenotype including the intellectual disability, observed in this patient. Thus, in patients with XLI, genetic analysis is important to identify the underling molecular alteration, since those with contiguous gene syndromes require a multidisciplinary approach that is critical for management, prognosis and genetic counseling.

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A CASE REPORT OF GM1 GANGLIOSIDOSIS DETECTED BY FIND PROJECT

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Text body: Background: GM1 gangliosidosis (GM1) and mucopolysaccharidosis type IVB (MPS IVB) are caused by beta-galactosidase deficiency due to GLB1 mutations. GM1 is a neurodegenerative disorder characterized by the accumulation of GM1 ganglioside that can present with hepatosplenomegaly, cardiomyopathy, facial dysmorphism, and minor skeletal dysplasia. In contrast, patients with MPS IVB retain neurological functions, but develop evident generalized skeletal dysplasia, keratan sulfaturia and corneal clouding. Case report: A 9-year-old girl was referred to our genetic clinic for developmental regression suggested by speech and gait disturbances. At our observation, she had slightly coarse face, short neck with low posterior hairline, hyperlordosis, short trunk, genu valgum and no hepatosplenomegaly. She had signs of moderated platyspondyly and epiphyseal dysplasia, normal cardiac and ophthalmologic examination, and normal cerebral MRI. A hypothesis of lysossomal storage disorder was presumed and collection of dried blood spots for FIND PROJECT were made. Enzymatic studies revealed a beta-galactosidase deficiency, compatible with both MPS IVB or GM1. Sanger sequencing of GLB1 gene revealed compound heterozygosity for two mutations: c.602G A and c.1572_1577insG, previously reported in patients with both GM1 and MPS IVB. Further investigation showed normal urinary glycosaminoglycans and slight excretion of urinary gangliosides, concluding for GM1 diagnosis. Conclusion: FIND PROJECT is a simple and useful tool available to the physicians to diagnose symptomatic MPS patients at pediatric age. The approach to differentiate beta-galactosidase deficiency from GM1 or MPS IVB must take into account genetic analysis, urinary glycosaminoglycans and oligossacharydes as well as a close discussion with clinical physicians.

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HHH SYNDROME – A CHILDHOOD PRESENTATION

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Text body: Background: Hyperornithinemia-hyperammonemia-homocitrillinuria (HHH) syndrome, is a rare urea cycle disorder that can manifest from birth to adulthood. In addition to symptoms secondary to intermittent hyperammonemia, patients may present with chronic neurocognitive deficits or liver dysfunction. Case report: We present a 12-year-old boy, son of consanguineous Chinese parents. Parents reported a development delay since the first year of life, but due to moving to China, there was no follow-up in a Paediatric consultation. At the age of nine, he was referred by the family physician for the first time to a Paediatric consultation and was diagnosed with intellectual development disorder, language disorder and attention-deficit/hyperactivity disorder. One year later, he was admitted to the emergency department due to vomiting, transient incoherent speech and ataxia, with no other neurologic signs. His blood tests (ammonia not tested) and brain CT scan were normal, and he was discharged. There were no other episodes suggestive of acute encephalopathy. At this point he was referred to Neuropeadiatrics consultation and subsequently to the Neurodevelopment Unit. His neurologic exam and etiologic study (brain MRI and CGH array) were normal. He was later referred to Gastroenterology consultation due to isolated mild hypertransaminasemia (3 times normal). In his dietary history he had an aversion for protein rich foods. During the course of the investigation, increased serum ornithine and urinary excretion of homocitrulline were detected, associated with postprandial hyperammonaemia (322 µmol/L), suggestive of HHH syndrome. He started a low-protein diet and arginine supplementation with good metabolic control. As he became older, he began to present lower limb spasticity and motor incoordination. Conclusion: In HHH syndrome, symptoms are variable and data on long-term prognosis is limited. Patients are usually treated with a low-protein diet and citrulline or arginine supplementation with good biochemistry response. Prevention and rapid control of hyperammonemic episodes are crucial, but despite metabolic control, neurologic findings may still worse over time with progressive pyramidal signs and cognitive deterioration. Patients must have neurocognitive and school performance monitoring and these may be the clues that point out to the diagnosis. In cases with a later presentation, intellectual disability and gait abnormalities/spasticity are the predominant findings

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EXOME SEQUENCING AS A DIAGNOSTIC TOOL IN A CASE OF UNDIAGNOSED MAN1B1-CDG

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Text body: Unexplained developmental delay or intellectual disability is one of the most common reasons for referral to genetic counseling. Yet, in over 50% of the cases routine examination does not reveal the clinical entity. A systematic clinical approach can help to identify a genetic cause. Clinical exome sequencing has enabled a rapid progress in this field, reducing the mean cost per diagnosis and the diagnostic odyssey. A 2-year-old boy was referred to our genetic clinics for global development delay and autism spectrum disorder with aggressive behavior and stereotypies. At observation, it was noted mild facial dysmorphisms. Initial studies, including extensive metabolic investigation and brain MRI were not able to identify an etiology. Further cardiac evaluation revealed aortic dilation. Microarray analysis showed a 13 Kbp 5p15.33 deletion evolving CCDC127 and SDHA genes that did not correlate with the phenotype. Exome sequencing identified two compound heterozygous variants in MAN1B1 gene: c.1731C G (p.Tys577*) and c.1976T G (p.Phe659Cys), and an hemizygous variant in ZNF674 gene was detected: c.1512del (p.Ala505Profs*32). The first and third variants have not been reported before; they introduce premature stop codons leading to truncated proteins, being classified as likely pathogenic. The second variant has been reported in a patient with intellectual disability and in silico analysis supports its pathogenicity. Subsequent serum transferrin IEF showed a type 2 pattern, allowing to confirm a MAN1B1 defective congenital disorder of glycosylation (MAN1B1-CDG). Congenital disorders of glycosylation (CDG) comprise a group of inborn errors of metabolism, caused by deficient protein and/or lipid glycosylation. MAN1B1 gene variants have been associated with non-syndromic autosomal recessive intellectual disability and CDG. Recent publications, have reported patients with a common MAN1B1 phenotype, comprising mild intellectual disability, truncal obesity and facial dysmorphisms. Our patient did not present with obesity, and he is the first presenting aortic dilatation. ZNF674 gene variants have been associated with X-linked intellectual disability. Here, exome sequencing led to the discovery of MAN1B1 as the culprit gene in an unsolved case of global development delay and thereby, retrospectively, diagnosed CDG. In unexplained intellectual disability, serum transferrin should be included in the first-line screening.

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GALACTOKINASE DEFICIENCY: A CASE REPORT

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Text body: Background Cataracts are an early finding in galactose metabolism defects. Galactokinase deficiency (GALKD, OMIM 230200) is an autosomal recessive disorder associated to mutations in the GALK1 gene, located at the 17q25.1. It has been considered extremely rare in general, but frequent in Balkan countries. Neonatal screening in Germany found a prevalence comparable to classic galactosemia (1/40,000). Unlike classical galactosemia, the predominant feature of GALKD is bilateral cataracts, without liver or kidney damage. Due to GALKD patients lack the ability to phosphorylate galactose and accumulate galactose and galactitol. Objective To present a patient with GALKD and highlight the relevance of early diagnosis for treatment and genetic counselling. Case report A 1-year-old girl diagnosed with bilateral nuclear cataracts at 2-month and submitted to surgery in both eyes at 11-months, was referred for investigation. Her growth and psychomotor development were normal. Her healthy, nonconsanguineous parents are Moldavan immigrants and family history is negative. A systemic evaluation including determination of galactosemia was performed. The laboratory results showed high galactose (45.2 mg/dl, for a reference range A (p.A167D), a predictably pathogenic missense mutation, not previously described. Parent's molecular studies are being performed. At 17-months, adherence to the diet was good, as well as ophthalmologic evolution. Galactose blood levels was 4mg/dl. Discussion GALKD is a rare, although important, cause of congenital or infantile cataracts. The rarity and absence of systemic involvement, at least at an early phase, makes diagnosis highly improbable and a high index of suspicion is needed. The bilaterality of the cataracts and its nuclear characteristic might help to evoke that diagnosis. Upon suspicion, it is easily confirmed by galactose, galactose-1-P and galactitol levels determination. Galactitol accumulation, not investigated in our patient, is the direct cause of the cataracts in GALKD. Since normalization of blood galactose under diet was rapidly achieved, we believe that so has galactitol levels and that recurrence of the cataracts can be avoided by continuing the galactose restricted diet.

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THE USE OF A MODIFIED U1 snRNA AS A THERAPEUTIC STRATEGY TO CORRECT A 5' SPLICE-SITE MUTATION IN MUCOPOLYSACCHARIDOSIS IIIC: IN VITRO STEPS TOWARDS AN IN VIVO APPROACH

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Text body: Genetic therapy directed toward the correction of RNA missplicing is being investigated not only at basic research level but even in late-stage clinical trials. Many mutations that change the normal splicing pattern and lead to aberrant mRNA production have been identified in Lysosomal Storage Disorders (LSDs). The Mucopolysaccharidosis IIIC (MPS IIIC) is a LSD caused by mutations in the HGSNAT gene, encoding an enzyme involved in heparan sulphate degradation. Splicing mutations represent one of the most frequent (~20%) genetic defects in MPS IIIC. Approximately 55% corresponds to 5' splice-site mutations which thus constitute a good target for mutation specific therapeutic approaches. Recently, we demonstrated in fibroblast cells that a modified U1snRNA vector designed to improve the definition of exon 2 5'ss of the HGSNAT can restore splicing impaired by the mutation c.234+1G>A.(Matos et al., 2014). Presently our goal is to evaluate in vivo the therapeutic potential of the modified U1snRNA by testing it in mice expressing the human splicing defect. For this, in a first step we tried to generate full-length splicing competent constructs of wild--type (wt) and c.234+1G>A HGSNAT by cloning the wt or the mutated HGSNAT splicing-competent cassettes into the pcDNA 3.1 backbone. According to the protocol reported by other researchers (Pinotti et al., 2009), plasmid vectors will be used to promote transient expression of the human HGSNAT wt or mutant alleles in mice. Here, we describe the cloning process followed to obtain the aforementioned splicing constructs. During the cloning steps different difficulties were found as, for example, in fragments amplification, ligation, and obtainment of bacterial transformants. Even so, positive bacterial colonies were obtained, selected, and amplified by colony PCR. However, DNA sequencing data showed the presence of different nucleotide point alterations in the obtained clones, invalidating its use for further steps. Therefore, plasmid constructs were ordered commercially. Now we are performing its transfection in Hep3B/COS-7 cells to confirm that they recapitulate the splicing process observed in wt and patient cDNA being thus ready to be expressed in mice to test the therapeutic effect of the modified U1snRNA. This work shows the different steps and difficulties of the cloning process to obtain HGSNAT expression constructs towards testing of an in vivo U1snRNA therapeutic approach.

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CONGENITAL ADRENAL HYPERPLASIA- NEED TO RE-EVALUATE ITS INCLUSION IN PORTUGUESE NEWBORN SCREENING PANEL

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Text body: Introduction: Congenital adrenal hyperplasia (CAH) is a hereditary, autosomal recessive disease caused by the deficiency of different enzymes involved in cortisol's synthesis. The most common deficiency is 21-hydroxylase, which leads to accumulation of 17-hydroxyprogesterone (17-HOP). Cases: We describe three term male newborns, whose pregnancies were monitored and without intercurrences. Family histories were irrelevant. Case 1 was admitted at 23 days due to difficult feeding and failure to thrive (weight loss 7,7%), mild dehydration signs and discretely hyperpigmented scrotum. Analytically he presented hyponatremia, hyperkalaemia and hypochloremia, without metabolic acidosis and hypoglycaemia. Case 2 presented at 27 days with difficult feeding and failure to thrive (weight loss 12,2%), grunting, hypotonia, poor peripheral perfusion and signs of moderate dehydration. Slightly hyperpigmented scrotum was noted and analyses revealed hypoglycaemia, hyponatraemia, hyperkalaemia, hypochloremia, metabolic acidosis and acute pre-renal injury. Case 3 was admitted at 9 days presenting failure to thrive (weight loss 12%), hyponatremia, hyperkalaemia, hypochloremia and compensated metabolic acidosis, without hypoglycaemia. Clinically had good vitality and tone, slight scrotal hyperpigmentation, without signs of dehydration. Electrolytic and metabolic imbalances were corrected with intravenous fluids. Case 2 needed a saline bolus, sodium bicarbonate, calcium gluconate, salbutamol and antibiotics (because of septic appearance). 17-HOP on Guthrie card was elevated in all of them. They started hydrocortisone and fludrocortisone, with good response. Conclusion: Salt-wasting crisis, the most common presentation of CAH in newborn, leads to dehydration, hypovolemia, shock and death. It may be confused with other common diagnosis, delaying its recognition and treatment. All newborn screening programs should incorporate screening for CAH due to 21-hydroxylase deficiency. First-tier screens should use 17-HOP assays and a second-tier screen by liquid chromatography tandem mass spectrometry analysis of steroids is recommended to improve the positive predictive value of CAH screening. The authors alert to the importance of re-evaluating the possibility to introduce the CAH screening in the Portuguese Newborn Screening panel, in order to anticipate the onset of salt wasting crisis and associated morbimortality.

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DIAGNOSIS AND MANAGEMENT OF MUSCULOSKELETAL PROBLEMS IN A CHILD WITH C6ST-1 ENZYME

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Text body: CHST3-related skeletal dysplasia results from mutations in CHST3 gene, which provides information for the production of enzyme C6ST-1, essential for normal development of cartilage. Mutations in CHST3 gene reduce or eliminate the activity of C6ST-1, thus disrupting normal development of cartilage and bone.. CHST3-related skeletal dysplasia, also known as recessive Larsen syndrome, is characterised by hyperlaxity, facial dysmorphisms and bone and joint abnormalities that worsen over time. Joint dislocations, most often affecting the knees, hips, and elbows, are present at birth. Minor heart defects have been reported in a few patients. Early diagnosis is important, so that the patient can benefit from a multidisciplinary adequate management, in order to prevent morbidities and improve quality-of-life. The authors present a case of a child with CHST3 mutation and a right hip dislocation. In the first month of life conservative treatment with casts and gentle manipulation was tried for knee reduction. After 5 casts a 90º of knee flexion was obtained and orthesis applied with bad compliance. At 10 months x-ray revealed a persistent right hip and knee dislocation and the patient was proposed for surgical treatment. Patient suffered several respiratory infections, and was operated at 23 months. In the same surgical session, we performed: an open hip reduction, 2.5cm shortening of right femur, V-Y lengthening of quadriceps tendon, knee reduction and extra-articular ligamentoplasty of anterior and posterior cruciate ligaments using ispsilateral autologous graft of fascia lata and iliotibial band. We also performed a right Dega acetabuloplasty and patient was immobilized with unilateral spica cast after surgery. After 4 weeks, a mold was made to fit an articulated knee brace. Four weeks later the spica cast was removed. After 3 years, the girl has a subtle limping gait, 130º left knee flexion and 90º right knee flexion, no hip or knee instability. X-rays show reduction of both joints. On cervical spine, an odontoid hypoplasia is apparent and patient is now appointed for C1-C2 spinal fusion, in order to prevent neurological impairments. Family has been counseled to protect the child from any activities or events that could increase the risk of a spine trauma. Knowing the natural history of this disease, allowed us to monitor the child while s growing up and early detect cervical spine instability that was asymptomatic but could have tragic consequences.

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IMPROVEMENTS IN ARGINASE 1 DEFICIENCY-RELATED DISEASE MANIFESTATIONS FOLLOWING PLASMA ARGININE REDUCTION WITH PEGZILARGINASE: EARLY PHASE 2 RESULTS

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Text body: Background: Arginase 1 Deficiency (ARG1-D) is a rare, progressive, autosomal recessive disease characterized by hyperargininemia that causes spasticity, impaired mobility, and developmental delay, typically presenting in early childhood. Current methods to reduce plasma arginine are inadequate and problematic. Pegzilarginase is a pegylated, cobalt-substituted human arginase 1 that has been shown to lower plasma arginine in patients with ARG1-D. Methods: Data are from an ongoing Phase 1/2 clinical trial and Phase 2 Open Label Extension study of intravenously (IV) administered pegzilarginase in patients with ARG1-D. In addition to evaluations of safety, pharmacokinetics and effects on plasma arginine and related guanidino compounds (GCs), clinical outcomes assessments were incorporated at baseline and follow-up, including 6-minute walk test (6MWT), Berg Balance Scale (BBS), and Gross Motor Function Measure (GMFM--66). Safety assessments include physical examinations, laboratory tests, anti-drug antibody (ADA) evaluations and ECGs. Results: All enrolled patients had disease manifestations including hyperargininemia, neuromotor, and neurocognitive deficits. IV pegzilarginase, added to standard disease management, rapidly lowered plasma arginine into the normal range in all patients and was well tolerated except for a single infusion associated reaction in one patient. This infusion reaction was managed with dose interruption, medication, and a slower infusion rate without further adverse events. Sustained reductions in arginine, GCs, and improvements in several clinical tests of neuromotor function were observed in the first two patients during repeat dose treatment. Dietary protein intake also increased in these two patients. Discussion: These data from the Phase 1/2 clinical trial and Phase 2 Open Label Extension study demonstrated the first evidence of clinically relevant treatment effects in neuromotor function with pegzilarginase beyond what can be achieved with standard disease management. Pegzilarginase produced marked and sustained reduction of plasma arginine and GCs in patients with ARG1-D. Additional insights are expected from recently enrolled adult and pediatric patients, as well as from longer term dosing in previously enrolled patients.

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CLASSIC GALACTOSEMIA: TWO NOVEL GALT MUTATIONS IDENTIFIED IN BRAZILIEN PATIENTS

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Text body: Background: Classic galactosemia (MIM #606999) is an autosomal recessive disorder caused by deficient activity of galactose-1-phosphate uridylyltransferase (GALT). Patients usually develop symptoms in the neonatal period, the most dangerous being liver failure which can be successfully treated by dietary galactose restriction. Nevertheless, many patients develop long-term complications, mostly neurologic, whose pathophysiology is still poorly understood. This disorder is characterized by high allelic heterogeneity of the GALT gene, which is thought to play a determinant role in biochemical and clinical phenotypes. Objective: molecular characterization of a galactosemic population originating from Hospital de Clínicas de Porto Alegre, Brazil. Patients and Methods: A cohort of 6 patients, including a pair of siblings and corresponding to 10 independent mutant alleles, was studied. Four patients are Native Americans and the other two have African origins. After PCR amplification of individual exons and related intronic boundaries, GALT gene (GenBank accession NG_009029.1) was scanned for mutations by direct sequence analysis. Bioinformatic programs were used to evaluate mutations' pathogenicity (Polyphen2 and Human Splicing Finder). Results: Four different mutations were identified in this group of patients, being two already described in databases: c.512T>C (p.F171S) always identified in African-descent populations, and c.563A>G (p.Q188R) the prevalent in European-descent populations. The two novel variants are: c.90_91insG (p.H31Afs*9) and c.529A>G (p.M177V). Concerning these novel mutations, the insertion introduces a frameshift and most probably no protein will be synthesized, thus being considered pathogenic, whereas the nucleotide substitution is predicted to be a benign missense variant, though it might also affect the splicing process. Interestingly, patients' genotypes reflect their ethnic origins, since all the Native American patients carry the two novel mutations in homozygosity, whereas one African-descent patient is homozygous for the p.F171S mutation and the other is a compound heterozygote for the p.F171S and the p.Q188R mutations. Discussion and Future Perspectives: The present work unveils the mutational spectrum of classic galactosemia in South Brazil and future studies should include patients' study at transcriptional level in order to elucidate the molecular mechanism underlying the novel mutations.

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A DYSMORPHIC PATIENT WITH DEVELOPMENTAL DELAY: IS IT A RARE COBALAMIN DISORDER?

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Text body: Background: Patients with intellectual disability associated with nonspecific dysmorphic signs are a diagnostic challenge, needing a multidisciplinary approach to reach an etiology. Metabolic diseases, namely form intermediary metabolism are not the main suspected causes. Cobalamin disorders could have this presentation, and some rarer forms may not have the usual biomarkers. Clinical Report: We present a 12 month old male, with developmental delay, gross phenotype and recurrent otitis. Prenatal history was remarkable for increased nuchal translucency in 1st trimester, and possible exposure to Zika virus in Brazil. He was son of young, healthy and non-consanguineous parents. He developed microcephaly, moderate developmental delay, and a storage disorder phenotype, with soft blond hair, small gross hands and feet, increased intermammillary space, prominent abdomen. Initial investigations (blood count, basic biochemistry, abdominal ultrasound, karyotype, aCHG, CDT, GAGs, oligosaccharides and MPS enzymes were unremarkable. Cerebral MRI showed slight but generalized reduction in volume of white matter and short cerebellar vermis. He was evaluated in neurogenetics outpatient clinics, and clinical exome showed a hemizygous variant in HCFC1 gene, not previously described but probably pathogenic, that was associated with ¬X-linked mental retardation-3 (Methylmalonic acidemia and homocysteinemia, cblX type) - OMIM#309541. He is now 33 months old, walking without support since 30 months, saying only 3-4 words and showing a markedly hyperkinetic behaviour. He never had seizures. The plasmatic aminoacids, homocysteine, vitamin B12, acylcarnitines in dried blood spot and urinary organic acids were normal. Conclusion: CblX is a newly identified transcripitional regulation disorder, very different of previously known intracellular cobalamin metabolism disorders. Fewer of 20 cases have been described. Patients may show IUGR, congenital brain and other malformations, developmental delay, seizures, microcephaly, and dysmorphic features. Some expected metabolites are difficult to detect or not present at all. Our case seems to have a milder phenotype, and no cobalamin metabolism biomarker has been found yet. HCFC1 is known to interact with diverse proteins to regulate a variety of processes, and pathogenic variants of this gene have also been reported as being responsible for non-specific X-linked mental retardation without interference with cobalamin metabolism.

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CARNITINE PALMITOYLTRANSFERASE II DEFICIENCY: THE MYOPATHIC FORM

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Text body: Introduction Carnitine palmitoytransferase II (CPTII) deficiency is a recessively inherited metabolic disorder of lipid metabolism. The CPTII is located at the inner side of the inner mitochondrial membrane and catalyses the last step of the carnitine system. This step involves reconverting the acylcarnitine esters to their respective acyl-CoAs, which are then primed substrates for the β-oxidation process. There are three main types of CPTII deficiency classified on basis of tissue-specific symptomatology and age of onset: mild to severe adult myopatic form, severe infantile multisystemic form and lethal neonatal form. The myophatic form is characterized by episodes of rhabdomyolysis, usually triggered by extensive exercise, cold, fever or prolonged fasting. The authors will present biochemical and molecular findings of eight patients with CPTII deficiencies, myopatic form. Material and methods Genomic DNA was extracted from blood of eight patients with clinical symptoms by standard methods. Direct sequencing of PCR products was performed on an automatic sequencer (ABI Prism 3130XL). For this purpose the coding region of the CPTII gene was amplified. Sequences were compared with the genomic structure of the CPTII gene. Results Six different mutations were observed in the eight cases; four of these were never reported. The prevalent p.S113L mutation was found in seven of these cases. The patients with myophatic form may present mild alterations or completely normal profiles at neonatal screening time. Discussion The myopathic form, may only be detected with biochemical abnormalities during acute episodes. In these cases, accurate clinical characterization alongside with molecular analysis is the key for diagnosis.

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3- METHYLCROTONYL COA CARBOXYLASE DEFICIENCY: A HETEROZYGOUS MOTHER PRESENTING AN ABNORMAL BIOCHEMICAL PROFILE

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Text body: Introduction: 3-methylcrotonyl-CoA carboxylase deficiency (MCCD) was considered extremely rare before newborn screening being undertaken by tandem mass spectrometry (MS/MS) but is now found in numerous asymptomatic babies or sometimes their mothers. This disorder of leucine metabolism is the commonest organic aciduria found by screening, with a incidence of about 1:46494 in our country. The clinical phenotype has been shown to vary considerably, ranging from entirely asymptomatic to death in infancy. A recent review indicates that only 27% developed normally and stayed completely asymptomatic. Approximately 30% were reported to suffer from muscular hypotonia and psychomotor retardation, respectively, and almost 50% suffer from various other neurological symptoms. Even a lethality of 11% was observed. The metabolic phenotype characterizing MCCD is the elevated excretion in organic acids profile of the diagnostic compounds 3-methylcrotonylglycine and 3-hydroxyisovaleric acid, and the presence of abnormally elevated blood levels of 3-hydroxyisovalerylcarnitine (C5OH), in acylcarnitines profile, as determined by MS/MS. Patient and methods: The authors present a newborn screening case with an increase of C5OH in the newborn and his mother. Blood spot samples from newborns are collected between day 3 and 6 in Watman 903 filter paper. Acylcarnitines are analysed by MS/MS. Molecular characterization of genes MCCC1 and MCCC2, that encodes the enzyme 3-MCC, were studied by reported methods. Results: The molecular study has allowed the identification in MCCC1 gene of the splicing mutation c.640-2A>G and the missense mutation p.A291V in the newborn and of the splicing mutation c.640-2A>G, in heterozygosity, in the mother. Both mutations are described in the literature. Discussion: The identification of MCC deficiency in adults is already described in several articles, most patients are clinically asymptomatic and were identified by the detection of an increased C5OH acylcarnitine level identified through their infant's newborn screening. In the mother's case, there is recent evidence to suggest that the presence of a single heterozygous deleterious mutation in either MCCC1 or MCCC2 can lead to elevations of the metabolites characteristic of 3-MCC deficiency. The 3-MCC deficiency is a pathology not completely understood and its clinical phenotype is very heterogeneous, most patients showing different mutations making the phenotype-genotype correlation difficult.

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A QUICK SCREENING TOOL TO ASSESS MPSS AND OTHER DISORDERS

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Text body: Background Lysosomal Storage Diseases (LSDs) are a class of rare inherited metabolic diseases caused by mutations in proteins critical for lysosomal function which trigger lysosome enlargement and cell death. Patients with LSDs present a debilitating, multisystemic phenotype often associated with early-onset neurodegeneration. Unfortunately, the diagnosis is difficult due to considerable clinical overlap and clinical variability and patients may be undiagnosed for decades. PROJECT FIND was started by "Hereditary Metabolic Disorders Section of the Pediatric Portuguese Society" (HMDS-SPP) and "Human Genetics Department, National Institute of Health Dr. Ricardo Jorge" (DGH-INSA). One of its major aims is to improve the clinical awareness to the red flags for a specific group of LSDS, the Mucopolysaccharidoses (MPSs) and at the same time to provide an useful and practical tool to diagnose MPSs but potentially other related disorders. Some of the main features of MPSs are facial dismorphism, hepatosplenomegaly, skeletal dysplasia and progressive neurologic impairment, which could also be also present in other LSDs such as GM1 Gangliosidosis that's belongs to another sub-group of LSDs, the sphingolipidosis. Actually, GM1 gangliosidosis is due to mutations in the lysosomal acid -galactosidase gene, GLB1, the same gene that is mutated in Mucopolysaccharidosis IVB. Patients and Methods The diagnostic was done by performing enzymatic assays in dried blood spots (of symptomatic patients, at pediatric age) with identification of the deficient enzyme, responsible for the pathology. In positive cases it was performed the molecular study and when possible the quantification/identification of the metabolites stored, the glycosaminoglycans. Results The patients enrolled in the Project FIND were from all over the country (140 in total). Five LSDs patients were identified: 2 cases of GM1 gangliosidosis and 3 cases of MPSs. Conclusions The Project FIND allows the identification and the characterization, not only of MPSs patients but also of patients with GM1 gangliosidosis and potentially of other LSDs. In addition, due to the small amount of sample required and to the inexpensive and easy way to collect it makes available to the physicians a good way to identify and early characterize these patients.

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GTPBP3 MUTATION – A RARE MITOCHONDRIAL DISEASE

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Text body: Background: Mutations in GTPBP3 gene are associated with a severe mitochondrial translation defect resulting defective mitochondrial energy production. These mutations are responsible for hypertrophic cardiomyopathy with lactic acidosis, neurological symptoms including hypotonia and feeding difficulties in early childhood. CASE REPORT: We report two sisters, from a consanguineous healthy couple, with medium-chain acyl-CoA dehydrogenase deficiency detected in Newborn Metabolic Screening with a severe multiorgan involvement suggesting also a mitochondrial disease. Both sisters were born from a full term, uneventful pregnancy with normal birth weight. Generalized hypotonia, difficulty in suction were noted since birth and they rapidly developed failure to thrive associated with psychomotor development delay. They also had dysplasia of the hip, one with foot abnormalities and the other with subluxation of the knees. They had several hospital admissions due to metabolic decompensation during infectious episodes. The progression of their muscular disorder as well as hyperlactacidemia was noted, so a simultaneous neuromuscular disease was suspected. There was no cardiac involvement. Their muscle biopsy showed a significant decrease in the activities of respiratory chain complexes II, IV and V. Mitochondrial exome analysis allowed the identification of a homozygous pathogenic variant in the GTPBP3 gene, c.1103G>A p.R368H, consistent with a combined oxidative phosphorylation deficiency 23. Both parents were confirmed to be heterozygous carriers. DISCUSSION: These two cases illustrate unusual presentation of a rare mitochondrial disease caused by mutations in mt-tRNA genes, which emphasizes the importance of post-transcriptional modification of mitochondrial tRNAs for proper mitochondrial function. Further studies of these pathways, such as analysis of tissue--specific regulation of mt-RNA-modifying enzymes, might help to explain the clinical heterogeneity observed for mitochondrial diseases.

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MAPLE SYRUP URINE DISEASE (MSUD) NUTRITION MANAGEMENT: ASSESSMENT OF NUTRITIONAL STATUS

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Text body: Introduction: MSUD treatment consists in a dietary restriction of branched chain amino acids (BCAAs) and protein, closer monitored to maintain plasma BCCAs concentration within targeted values, thus reducing decompensations and achieving an adequate nutritional status to promote a normal growth. Objectives: To evaluate nutritional status during implementation of the recently published guidelines recommendations in the outcome of MSUD patients followed in our Paediatric Units. Methods: A cohort of 11 classical MSUD patients with a median age of 4.1 years (range 2 months – 14 years) were enrolled in this study from March 2017 to October 2017. Anthropometric (weight, height, body mass index, upper arm circumference, triceps skinfold, upper arm muscle area, body composition (fat and fat free masses) and nutritional intake data were collected at baseline (T0), 3 months (T1) and 6 months (T2). Statistical analysis was performed by SPSS® 24 version. Results: The patients were eutrophic and a significant improve in height according to z-score (T0=-2.56 and T2=-1.97, p=0.03) was observed. Body composition was assessed in 5 patients and the mean fat mass was 5.4 Kg at T0 and 6.4 Kg at T2. Concerning fat free mass, at T0 the mean was 29.7 Kg and at T2 was 31.3 Kg. The natural protein intake (g/day) increased significantly (T0=14.8g and T2=16.1g, p= 0.02). During the study the amount of synthetic BBCA-free protein (g/day) decreased from 27.0g (T0) to 24.0g (T2). Regarding micronutrient intake, more than 60% of the patients had an intake higher than the DRI for Ca, P, Fe, folic acid, Vitamins A, B6, B12, D and E, and also for Se and Zn. It was observed that only two patients reached the DRI for fiber, one reached the DRI for essential fatty acids (EFA) n6 and none reached the DRI for EFA n3. Conclusion: Overall, the patients were mostly eutrophic. Regarding dietary intake, all patients complied with the recommendations for energy and macronutrients (carbohydrates and lipids), reaching the recommended values for gender and age. By giving higher natural protein while reducing aminoacid mixture intake, we noted that body composition and stature improved. Nevertheless, it is evident that the intake of fibre and EFA remains highly deficient. These results underscore the importance of a systematic and detailed evaluation of the dietary intake in each individual patient, particularly emphasizing the need for supplementation in EFA since the required protein restrictio

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OTC DEFICIENCY IDENTIFIED BY ARRAYCGH FOR PSYCHOMOTOR DEVELOPMENT DELAY – CASE REPORT

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Text body: Background: ArrayCGH (Array Comparative Genomic Hybridization) enables high resolution genome-wide detection of copy number variations. It is a first line test for intellectual disability. Ornithine transcarbamylase (OTC) deficiency is the most common urea cycle disorder. Clinical presentation in females is highly variable due to X-linked inheritance. Diagnosis is based on clinical and laboratory findings, including genetic confirmation. OTC deletion is identified in up to 10%. Objectives: To present a case of OTC deficiency diagnosed by arrayCGH for psychomotor development delay. Case Report: This 6-year-old girl is the first child of healthy non-consanguineous parents with irrelevant family history. Expressive language delay and stereotypies were noticed at 2 years of age. Impulsive and aggressive behaviour prompted a diagnosis of attention deficit and hyperactive disorder and methylphenidate prescription at 5 years of age. It was discontinued because it caused her "apathy". ArrayCGH investigation disclosed a de novo contiguous gene deletion encompassing OTC, RPGR and TSPAN7. She presents normal somatic growth and visual impairment due to myopia and astigmatism. OTC deficiency was confirmed by biochemical findings: ammonia 127µmol/L (r.v.18-72), glutamine 883µmol/L (243-822), arginine 42µmol/L (20-140) and orotic acid 3,4µmol/mmol.creat. (0,1-1,9). Retrospectively, her diet was found to be moderately protein restricted (~1,2 g/kg/day), with sporadic vomiting when a larger amount of food was ingested. There were no episodes of coma or protracted vomits, even during banal childhood infections. Biochemical parameters normalized on sodium phenylbutyrate and arginine. Conclusion: While being the most frequent urea cycle disorder, OTC deficiency is not identified in newborn screening. A fifth of heterozygous females have symptoms. In this girl, diagnosis was reached through arrayCGH for a moderate psychomotor development delay. Retrospectively, an OTC deficiency phenotype could be recognized: she additionally presented a spontaneously restricted protein diet, vomiting related to food ingestion and behaviour abnormalities. The exact contribution of the deletion of RPGR and TSPAN7 genes to the patient's phenotype is not known. However, under specific treatment, which was readily started and can be lifesaving, improvements in behaviour and intellectual performance are expected. Finally, reaching an accurate diagnosis is of utmost importance for family counselling

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SLC35A2- CDG PRESENTING WITH SEVERE EARLY-ONSET SEIZURES

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Text body: Background Congenital disorders of glycosylation (CDG) are a heterogeneous group of diseases that result from disruption of the normal N-glycosylation pathway. SLC35A2 gene, on the X chromosome, codes for the only known transporter of UDP-galactose to the Golgi apparatus. The phenotype associated to variants of SLC35A2 includes developmental delay, early epileptic encephalopathy with hypsarrhythmia, hypotonia, dysmorphic features, skeletal abnormalities and cortical visual impairment. Case Report A 2 months-old girl, second child of non-consanguineous parents, born at term after an eventless pregnancy, was admitted with irritability and clusters of flexor spasms, mainly during the sleep-wake transition. On physical examination she had slight dysmorphic features, did not fixed or follow, and had axial hypotonia combined with limb hypertonia. Electroencephalogram showed hypsarrhythmia. Brain CT and MRI were normal. Ophthalmologic evaluation revealed ocular fundus with multiple yellowish white points deposits, and zones of hyperpigmentation on the periphery. Extensive metabolic investigation detected a type 2 pattern isoelectric focusing of transferrin. Next Generation Sequencing (NGS) panel for neurometabolic diseases identified a c.745del mutation at exon 5 in the SLC35A2 gene in heterozygosity (X-linked). Epilepsy was difficult to control with multiple trials of medication including ACTH, topiramate, vigabatrin and levetiracetam. The association of ketogenic diet was useful and partial control of seizures was achieved. Discussion Severe early-onset epilepsy is an unusual presentation of CDGs in general and seems to be unique in SLC35A2- related CDGs. Seizure control is difficult but can be achieved, at least partially, with anti-epileptic drugs combined with ketogenic diet.

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DIETETIC MANAGEMENT OF CITRIN DEFICIENCY – CASE REPORT

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Text body: Backgroud Citrin deficiency (CD) is a rare, autosomal recessive disease that results from mutations in the SLC25A13 gene, encoding the mitochondrial aspartate / glutamate transporter. This deficit interferes with important metabolic functions such as glycolysis, gluconeogenesis, the urea cycle and galactose metabolism. CD has a newly recognized extended phenotype: in newborns or infants can manifest as neonatal intrahepatic cholestasis (NICCD), in older children as failure to thrive and dyslipidemia (FTTDCD) and in adults as recurrent hyperammonemia with neuropsychiatric symptoms (CTLN2). Severity varies enormously, from spontaneous resolution in NICCD to liver failure in CTLN2. Recently, it has been reported that lactose-(-galactose) restricted diet, supplemented with medium chain triglyceride (MCT) is effective for NICCD babies and also in the prevention and treatment of hyperammonemic encephalopathy in CTLN2 patients. Case Report A 2 months female infant, chinese descendent, was admitted for jaundice and acholic stools. She had poor weight gain, axial hypotonia, large anterior fontanel with no dysmorphia or hepatosplenomegaly. Laboratory findings showed cholestasis, mildly elevated liver transaminases, hypoalbuminemia, prolonged prothrombin time, anemia and galactosuria. Plasma amino acids chromatography showed elevation of citrulline, tyrosine, methionine and threonine, raising a strong suspicion of CD. Genetic analysis confirmed compound heterozigozity in SLC25A13 gene. She was treated with lactose-free formula supplemented with MCT with a protein:fat:carbohydrate ratio of 9,8:50,5:40,3. Rapid clinical and laboratory improvement was observed. Complementary feeding started at 5 months of age, with carbohydrate restriction, lactose exclusion and MCT supplementation, established according to the nutritional requirements for the child's age and nutritional status. At 9 months follow-up, the child has regained weight, has normal psychomotor development and normal liver function. Comments: We emphasize the importance of nutricional intervention in the treatment of NICCD and probably in the prevention of hyperammonemic encephalopathy in adulthood.

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DIVERSITY ON BIOCHEMISTRY: METABOLIC DISEASE PRESENTING AS AN AUTO-INFLAMMATORY SYNDROME

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Text body: Background Mevalonic aciduria (MA) is the most severe form of mevalonate kinase deficiency (MKD) and characteristically presents in the first few months of life with recurrent attacks of fever, hepatosplenomegaly, lymphadenopathy, arthralgia, and skin rash. The prognosis is poor, as the central nervous system involvement is progressive and independent of inflammatory control. Case Report Newborn male, first child of non-consanguineous parents, born at 29 weeks by cesarian section for preclampsia, requiring advanced reanimation procedures and invasive ventilation. Pre-natal echography at 28 weeks showed fetal hydrops and indirect findings of anaemia needing intrauterine transfusion. The mother had a previous miscarriage at 21 weeks with fetal hydrops and dysmorphic features. At initial observation the baby had hepatosplenomegaly, ascites, hypoplasia of abdominal rectus, cholestatic liver disease, anemia and thrombocytopenia. Extensive investigation of non-immune hydrops foetalis at this time excluded mucopolysaccharidoses, oligosaccharidoses, sphingolipidoses and Niemann Pick type C. Criteria for hemophagocitic lymphohistiocytosis (HLH) were met with bicytopenia, splenomegaly, hypertriglyceridemia, hyperferritinemia and elevation of CD25. Primary HLH was excluded (normal degranulation, normal cytotoxicity) and secondary HLH was admitted in the context of an autoinflammatory disease, as the clinical condition evolved to recurring bouts of fever, urticariform rash, arthritis and enthesitis of the small joints. A therapeutic trial with interleukin--1 receptor antagonist (anakinra) lead to normalization of inflammatory parameters and disappearance of rash and arthritis. Genetic study found two compound heterozygous variants in the MVK gene (p.L297I and p.A214K), not reported in literature but probably pathogenic. Marked elevation of mevalonic acid in urine confirmed the diagnosis of MKD. The baby was discharged after 6 months, with controlled outbreaks under canakinumab, but with signs of neurological impairment like hypotonia and oculomotor apraxia. He is currently waiting hematopoietic stem cell transplantation Comments: The initial constellation of symptoms directed the investigation to lysosomal storage diseases, but further evolution revealed the full clinical picture allowing the diagnosis of MA and prompt treatment. Heterogeneous presentations stress the importance of multidisciplinary approach.

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HEMOPHAGOCYTIC SYNDROME REVEALING GAUCHER TYPE 2 DISEASE

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Text body: Background: Hemophagocytic lymphohistiocytosis (HLH) is a rapidly progressive, life-threatening syndrome of excessive immune activation, characterized by fever, hepatosplenomegaly, and cytopenia. HLH may have genetic origin (familial or primary HLH) or be secondary to infectious, rheumatic, malignant or metabolic conditions. Case report: A 10-month old girl, first child of non-consanguineous parents, with two previous miscarriages, was admitted to the PICU due to respiratory syncytial virus pneumonia requiring ventilatory support. She had a previous history of laryngomalacia, impaired growth (since 5 months of age), psychomotor developmental delay, progressive muscle stiffness, retroflexion of the neck and strabismus. On day 6 after admission dexamethasone was started to improve respiratory symptoms. Around day 12, she developed persistent fever, marked progressive hepatosplenomegaly, thrombocytopenia, anemia, hypofibrinogenemia, hypertriglyceridemia, severe hyperferritinemia, elevated liver enzymes and bilirubin. Soluble CD25 was normal and there was no CD8+ T cells activation. Bone marrow showed rare images of hemophagocytosis but no other relevant findings or abnormal cells. There were bilateral symmetrical white matter lesions on cranial MRI with peri-ventricular, central and subcortical distribution with a reduced N-acetylaspartate peak in spectroscopy. Gama-globulin, cyclosporin A and alemtuzumab were started based on the assumption of secondary HLH. Despite intensive therapeutic intervention the infant died due to multiorgan failure after 45 days. Pending results known post-mortem showed a very low beta-glucosidase activity, corroborating type 2 Gaucher's disease (GD) diagnosis. Conclusion: Associations between HLH and inborn errors of metabolism, namely GD, have rarely been reported in the literature. The underlying process in GD appears to be inflammation subjacent to glucocerebroside accumulation. This inflammatory response could be the link between HLH and GD.

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A NEW PORTUGUESE PATIENT WITH LYRM7 MUTATIONS – EXPANDED MRI FINDINGS

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Text body: Background:LYRM7 (LYR motif containing 7) gene mutations are a cause of mitochondrial complex III deficiency. Few patients were described so far. Recently a distinct MRI pattern of progressive leukoencephalopathy with multifocal cavitations in the periventricular and deep cerebral white matter was described related with LYRM7mutations.Case Report:An 11-month-old girl, born to consanguineous parents, was referred to our neurometabolic clinic for investigation of global developmental delay, sensorineural deafness and low visual acuity. At 2-months of age she was admitted with respiratory distress and an unexpected metabolic acidosis with raised lactic acid was noticed. She also had macrocytic anaemia and transient hyperglycaemia with ketonaemia. Initial metabolic investigation revealed abnormal redox imbalance, markedly raised urinary lactic acid (moderate elevation of adipic, 3-hydroxysuberic and 3-hydroxydodecanoic acids) and a minor elevation of alanine. Ammonia was normal. Biotinidase deficiency and pyruvate dehydrogenase deficiency were excluded. At 7 months of life she started having seizures. CT scan at that time showed discrete hypodensities in the right corona radiata and bilateral pontocerebellar hypodensity. Brain MRI revealed a bilateral restricted diffusion from the cervical spinal cord until the posterior subependymal areas. The biochemical analysis of mitochondrial respiratory chain in muscle biopsy revealed an increased activity of citrate synthetase and complex II associated with a decrease activity of II-III complex. Complex III activity was reported as normal. Muscle morphology was normal. Mitochondrial DNA copy number was 30%, suggesting a secondary depletion. Mitochondrial DNA sequencing revealed two alterations in heteroplasmy in MT-TD and MT-CYB genes. NGS gene panel for nuclear genes associated with mitochondrial disorders revealed the variant c.73G>A in LYRM7 gene in homozygosity, not previously reported in healthy controls. This variant appears to be located in a functional domain and was previously described in two Portuguese patients. The child deceased at 14-months with respiratory failure and irreversible lactic acidosis. Conclusion: The authors described the third patient in Portugal with LYRM7 mutation, in particular the unexpected MRI pattern since it lacks the major stigmata associated with this gene. We hypothesize that additional mitochondrial DNA variants of MT-TD and MT-CYB genes could explain the diversity of phenotype.

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INFLUENCE OF AGE, GENDER AND POLYMORPHISMS ON PLASMA BIOMARKERS OF HOMOCYSTEINE METABOLISM

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Text body: Background: Hyperhomocysteinemia associates with several pathological conditions, namely vascular and neurodegenerative diseases. Its causes are multifactorial and include shortage of B-vitamins. Despite apparent adequate intakes, dietary surveys reveal a widespread prevalence of suboptimal folates and tCbl plasma levels in various age groups, what raises special concern at young ages, in which it relates to developmental delay and irreversible neurological damage. Aims: To evaluate the impact of age, gender and genotype on Hcy-related metabolism biomarkers. Methods: A healthy population of children (9-yo) and adolescents (17-yo) was studied. Immunoassays and GC-MS-SIM-mode quantified plasma levels of biomarkers. PCR-RFLP/qPCR assays assessed common polymorphisms in related genes (MTHFR 677, MTHFR 1298, MTR 2756, MTRR 66, TCN2 776, TCN2 67). Results: A pediatric population was stratified according to age and gender and results revealed that age, but not gender, impacts almost all metabolic biomarkers. Indeed, when comparing 9 and 17-yo groups, tHcy plasma levels presented a significant increase whereas those of folate, tCbl and Holo-TC showed a significant decrease. However, gender is an important factor in the 17-yo group, since tHcy levels were significantly higher in males than in females. Interestingly, MMA plasma levels seem to be influenced by age and gender, because only older women presented statistically lower levels. When analyzing individuals altogether significant negative linear associations were observed between plasma levels of tHcy and those of folate, tCbl and Holo-TC. Plasma MMA levels were significantly correlated with tCbl and Holo-TC levels, but only in the older group. All genotype frequencies were comparable to those reported for other European populations and the results revealed that plasma concentrations of metabolic markers are not affected by the presence of these genes' variants, except in the 17-yo group, where MTHFR677TT and MTR2756GG genotypes are associated with significantly higher levels of tHcy and lower levels of tCbl, respectively. Conclusions: The present study adds new information concerning Hcy metabolism in two pediatric populations, children and adolescents, and reports the influence of genetic variants on plasma concentrations of several metabolic biomarkers thus allowing a better knowledge of native phenotypes. Nevertheless, larger studies are needed for the implementation of disease prevention measures.

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PROTEINURIA IN A PATIENT WITH A LATE DIAGNOSIS OF PHENYLKETONURIA IN ADULTHOOD

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Text body: Phenylketonuria (PKU) is one of the most common inherited metabolic disorders. Adult patients' follow-up is somewhat controversial namely regarding optimal metabolic targets and the management of potential comorbidities that may appear. It is described the case of a 38 years-old female with learning difficulties since childhood. Besides a previous history of lithiasic pancreatitis at 28 years-old, she had no other significant medical background. Following the birth of a child with a global psychomotor development delay and microcephaly, the hypothesis of maternal toxicity was raised and the patient was diagnosed with PKU at the age of 33 years-old. After a first attempt of therapeutic intervention, the patient voluntarily abandoned the outpatient clinic for about 4 years. Later on, she returned, was re-evaluated and a therapeutic plan was implemented, although with difficulties in reaching target levels due to poor adherence (PHE: 1045--1262umol/L; TYR:36-61umol/L). Additionally, high blood pressure, peripheral oedema and a significant proteinuria of 1.6g/24h were identified. Renal function analysis, immunological study with serum protein electrophoresis and renal echography were all normal. A renal biopsy was requested and showed a pattern suggestive of minimal lesions versus focal segmental glomerulosclerosis. Treatment with angiotensin converting enzyme inhibitor was implemented allowing to progressively control blood pressure. Proteinuria also decreased progressively during follow-up (to 0.28g/24h) with no further renal function deterioration. This cases illustrates an important comorbidity that appeared during follow-up of an adult female patient with a late diagnosis of PKU. It is known that arterial hypertension is present in one fourth of PKU patients, reflecting an important secondary health problem in these patients. Protein intake and proteinuria are involved in the pathophysiology of renal injury in PKU patients, but the present patient had no restricted diet for most of her life. Nonetheless, these patients constitute a high risk group for the development of chronic kidney disease.

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MOLYBDENUM COFACTOR DEFICIENCY

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Text body: Background Molybdenum cofactor deficiency (MCOD) is a rare inborn error of metabolism associated with neonatal seizures, severe progressive encephalopathy, delayed development and coarse dysmorphisms. We present a neonate with a diagnosis of MCOD admitted in our unit. Case Report A male neonate was delivered vaginally with breech presentation at 40 weeks of gestational age to a 33-year-old gravida and a young related father. The pregnancy, a second gestation after a healthy 5-year-old infant, was uneventful. The Apgar score was 10, 10 and 10 at 1, 5 and 10 minutes, respectively, and the birth weight was 4010 g. At 6 hours of life, he started neonatal seizures - characterized by anomalous limb movements - refractory to phenobarbital. The first head ultrasound (TFUS) was normal. Sepsis workup and basic metabolic profile were negative. He was transferred to our unit at day 8. Continuous electroencephalographic monitoring confirmed epileptiform activity at the left parieto-occipital region, with correlation to the clinical findings. TFUS at day 10 revealed bilateral cystic lesions, and magnetic resonance imaging at day 13 of life showed bilateral multicystic leukomalacia (extending to thalamus and basal ganglia) and hypogenesis of the corpus callosum. These findings (progressive cystic lesions and refractory seizures) were very suggestive of MCOD. High levels of urinary sulphite, associated with hypouricemia and hypohomocysteinemia, corroborated the hypothesis of MCOD. The result of genetic analysis is on hold. Despite the escalation of antiepileptic drugs - including levetiracetam, lidocaine and midazolam perfusions - there was a partial seizure response associated with a progressive clinical worsening with loss of feeding autonomy, general hypotony and poor reflexes. The patient remains under palliative care. Conclusion Although a rare disease, MCOD diagnosis should be considered in progressive cystic lesions associated with refractory seizures. Simple laboratory tests can help achieving the diagnosis. However, despite early diagnosis, the presence of extensive brain damage in this patient made any therapy futile.

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BRIEF COGNITIVE EVALUATION IN ADULT-ONSET LEUKODYSTROPHIES

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Text body: Background: Leukodystrophies, despite rare, are an important group of disorders with an increasing number of adult-onset forms, due to a better phenotypic and genotypic understanding. Patients with adult--onset typically present slowly progressive forms that can include various degrees of cognitive impairment. The evaluation of cognitive involvement in this group of patients can be challenging and further information is needed regarding its assessment. Objective: We aimed to describe the cognitive function in patients with adult-onset leukodystrophy. Methods: We prospectively included patients followed in our centre with a genetic diagnosis of adult-onset leukodystrophy. Patients who were deemed unable to collaborate in cognitive evaluation were excluded. Demographic and clinical data was collected and cognitive function was assessed with the Mini Mental State Examination (MMSE) or the Montreal Cognitive Assessment (MoCA). Results: We included six patients (two with Krabbe disease, three with cerebrotendinous xanthomatosis and one with X-linked adrenoleukodystrophy), four females and two males, with mean age of 42.66 (± 8.40) years and mean disease duration of 20.66 (± 14.16) years. Mean educational level was 7.83 (± 6.24) years. Only one patient was illiterate, did not performed the MoCA and had a total MMSE score of 19. The remaining patients had a mean MoCA score of 19.8 (± 6.06). The results of all patients were abnormal after adjustment for age and educational level. The cognitive domains more frequently involved were short-term memory/delayed recall and visuospatial ability, with preservation of orientation in all patients. Discussion: The data presented adds further evidence of widespread cognitive decline in adult patients with leukodystrophies. Brief cognitive evaluation tests can be an important screening tool for cognitive involvement in these patients and should be considered in routine follow-up. Accurate and early diagnosis of mild cognitive impairment and dementia is essential, due to their psychosocial impact and the need of personalized interventions in this group of patients.

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FATIGUE AND QUALITY OF LIFE IN ADULT-ONSET LEUKODYSTROPHIES

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Text body: Background: Leukodystrophies are a group of progressive metabolic and genetic disorders characterized by white matter abnormalities in the brain and spinal cord, occasionally with peripheral nerve involvement. Despite individually rare, their prevalence and clinical burden in adult patients are being increasingly recognised. However, there are few publications concerning health-related quality of life (HRQOL) in these patients. Objective: To study clinical variables related to HRQOL in adult patients with leukodystrophy. Methods: We included 8 adult patients with a diagnosis of leukodystrophy followed in our centre. Patients with severe cognitive impairment or unable to answer the questionnaires were excluded. Demographics and clinical data were collected and HRQOL was assessed using the Portuguese version of the Medical Outcomes Study Short Form Health Survey 36 Item (SF-36). Possible associated variables were assessed with the Modified Fatigue Impact Scale (MFIS), the Pittsburgh Sleep Quality Index (PSQI) and the Hospital Anxiety and Depression Scale (HADS). Results: We included 2 patients with Krabbe disease, 2 patients with cerebrotendinous xanthomatosis, 2 patients with X-linked adrenoleukodystrophy and 2 patients with vanishing white matter disease. Four of the patients were female, with a mean age of 42.63 (± 10.65) years and a mean disease duration of 24 (± 17.67) years. The mean disease severity EDSS score was 4.62 (± 2.01). We found a significant negative correlation between the psychosocial subscale of MFIS and better SF-36 mental ($r=-0.84$, $p=0.008$) and physical ($r=-0.71$, $p=0.048$) scores. We also found a significant positive correlation between the physical subscale of MFIS and disease duration ($r=0.72$, $p=0.042$). We found no significant correlations between SF-36 mental/physical scores and disease duration, EDSS, PSQI and HADS scores, as well as MFIS total, physical and cognitive scores. Discussion: The psychosocial impact of fatigue appears to be more influential on HRQOL of adult patients with leukodystrophies than disability, physical or cognitive burden. A larger disease duration seems to impact the physical but not the psychological fatigue burden. These findings could help improve patient care, paying more attention to HRQOL, specifically focusing on social dynamics and integration of these patients. However, due to the small sample studied, further investigations are needed to confirm this hypothesis.

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PROVING PATHOGENICITY OF A GLA NOVEL MUTATION IN A FEMALE PATIENT

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Text body: Background: Fabry disease (FD) is an X-linked lysosomal storage disorder caused by mutations in the GLA gene. More than 1000 GLA gene mutations have been described and associated with FD, most of them unique ("private mutations"). When faced with a novel mutation it is paramount to prove its pathogenicity, which may be harder in female patients.
Case report: we present the case of a 76 year old female patient with chronic kidney disease (CKD) stage G3a/A2 (KDIGO) who, in a Fabry disease screening from the nephrology department, presented a not previously described GLA mutation – heterozygote variant c.650C>G (p.Thr217Arg). On her clinical evaluation, she complained of hypoacusia and tinnitus. She did not show any other symptoms or signs of central or peripheral nervous system, cardiac, respiratory, gastrointestinal, dermathological or rheumatologic involvement. In the additional investigation it was noted: mild left ventricular hypertrophy, diastolic dysfunction grade 1 and mild left atria dilatation in the echocardiogram, absence of late gadolinium enhancement in cardiac MRI, cerebral vasculopathy with periventricular white matter lesions in brain MRI, bilateral moderate sensorineural hearing loss in audiogram and slight signs of cornea verticillata in eye exam. With no definitive findings compatible with FD we proceed with biomarkers, tissue and pedigree analysis; her plasma globotriaosylsphingosine levels in dried blood spots were within the normal range, skin biopsy did not show Gb3 inclusions and kidney biopsy was not performed due to presence of small kidneys. The pedigree analysis was remarkable for the history of hypoaccusis in several members (but not with an X-linked inheritance pattern), one brother with CKD and another brother with ischemic cardiomyopathy; however, the GLA gene sequencing of the possible affected men did not show the presence of the described variant.
Analysis of the urine sediment showed possible lipid inclusions in urinary sediment cells, proving the variant's pathogenicity. Remarkably, software analysis was inconsistent: Polyphen-2 and MutationTaster suggest this is probably a pathogenic variant and SIFT and Align-GVGD suggest it is probably benign.
Conclusion: this case report shows how difficult it can be to prove the pathogenicity of a GLA gene mutation not previously described, mainly in families without identifiable affected males. We also want to highlight the importance of urine sediment evaluation in this situation.

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NEUROPAD® AS AN INSTRUMENT TO EVALUATE SUDOMOTOR FUNCTION IN FABRY DISEASE – A PROOF OF CONCEPT STUDY –

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Text body: Background: Fabry Disease is an X-linked lysosomal storage disorder characterized by the absence or deficiency of α-galactosidase A activity. Hypohidrosis is a common and early symptom and, additionally, a cause of morbidity in these patients. Sudomotor functions tests may play a role in the diagnosis and follow--up of the disease as well as in monitoring the response to therapy. Neuropad® is a simple and affordable test that gives a qualitative result about sudomotor function, through color change. Sudometrics® is an image analysis algorithm that allows to make the Neuropad® a quantitative and reproducible method.
Aim: This study aims to determine if Neuropad® can constitute a method to evaluate the sudomotor dysfunction and whether the obtained results correlate with the survey of autonomic symptoms and also with demographic and disease severity.
Methods: In this prospective and cross-sectional study we recruited 15 patients, in whom Neuropad® and the survey of autonomic symptoms were applied. Sudometrics® estimated the percentage of color change. The remaining variables were determined in routine clinical evaluation.
Results: In this population (33.3% males, with a median age of 56 years), there was a decrease in the sudomotor function, particularly in male, despite the reduced report of dysautonomic symptoms. With aging, there was a tendency for improved hand sudomotor function, as opposed to the feet. In the classical phenotype, the sweat ability was decreased when compared to the attenuated phenotype. The results tend to be lower with the increase in disease severity and the use of enzyme replacement therapy.
Conclusions: Hypohidrosis is a common and debilitating symptom. Therefore there is a need for objective and accessible methods of evaluation of this clinical manifestation. In the future, Neuropad® in combination with Sudometrics® may constitute a tool in the diagnosis and monitoring of Fabry Disease.

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NONKETOTIC HYPERGLYCINEMIA: CASE REPORT

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Text body: Introduction: Nonketotic hyperglycinemia (NKH) is a rare autosomal recessive inborn error of metabolism due to deficient activity of glycine cleavage enzyme system. Prognosis is very reserved because glycine accumulates in tissues including the central nervous system (CNS).

Clinical report: First child of non-consanguineous young couple, with an uneventful pregnancy and term dystocic hospital delivery. He showed feeding difficulties by 16 hours of life and physical examination found axial hypotonia with mild peripheral spasticity, persistent hiccups, myoclonic seizures and hyperexcitability. He was admitted in the neonatal intensive care unit and progressive lethargy led to coma by the 5th day of life with need of invasive ventilation from this day until 22 days of life. Generic blood and urine analysis including ammonia, lactate and organic acids were normal. Plasmatic, urinary and cerebrospinal fluid (CSF) glycine levels were elevated, respectively 1727,2µM [223,8-514,2], 13211,4µM [283-1097] and 321,6µM [3,7-7,6]. Glycine ratio between CSF and plasma were also elevated: 0,19 [<0,04]. Transcranial ultrasound and cerebral magnetic resonance im¬aging (MRI) both showed hypoplastic corpus callosum. Electroencephalogram presented a burst-suppression intermittent pattern consistent with NKH encephalopathy. Molecular diagnosis identified two heterozygous mutations (c.1406G>A and c.2690G>C) on the GLDC gene. He started treatment by the 7th day of life with Sodium benzoate, Dextromethorphan, Calcium pholinate, Pyridoxine, Clonazepam and Phenobarbital. Nowadays, he is 14 months old, with a severe neurodevelopmental impairment and incomplete seizure control and last glycine level (23/11/2018) was 1159.6µM.

Conclusion: This case presents 2 undescribed variants of the GLDC gene associated with a severe classic NKH. Despite optimized treatment with normalization of CSF glycine levels by the 12th day of life, this patient's neurodevelopmental outcome will still be very reserved. Future therapeutic approaches such as stem cell technology and gene therapy are hopped to provide effective solutions for these patients. Key--words: Encephalopathy; GLDC; Glycine; Nonketotic hyperglycinemia

SYMPOSIUM SATELLITE MEETING

MANAGEMENT OF PKU DURING LIFE

Programme

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MANAGEMENT OF PKU DURING LIFE

Coimbra, 16th March 2019

09:00-09:10	Welcome and Introduction	**Paula Garcia (Coimbra)**
	Session I	**Paula Garcia (Coimbra)**
09:10-09:30	PKU European Guidelines – an Overview	Maria Giżewska (Szczecin)
09:30-09:50	Differences to the Portuese PKU Consensus	Patrícia Janeiro (Lisboa)
09:50-10:00	Q&A	
	Session II	**Chair: Júlio César Rocha (Porto) Luísa Diogo (Coimbra)**
10:00-10:20	Management of PKU in Different Stages of Life – an introduction	Júlio César Rocha (Porto)
10:20-10:40	➢ Patients 0-4 Years of Age	Amaya Bélanger (Madrid)
10:40-11:00	➢ Adolescents	Esmeralda Martins (Porto)
11:00-11:20	Coffee Break	
11:20-11:40	Maternal PKU	Paula Sanchez Pinto (Santiago de Compostela)
11:40-12:00	➢ Adults	Arlindo Guimas (Porto)
12:00-12:30	Discussion	
	Session III	**Chair: Elisa Leão Teles (Porto)**
12:30-12:50	Aging of PKU Patients	Álvaro Hermida (Santiago de Compostela)
12:50-13:10	Long Term Follow Up of Cognition and Mental Health in Adult PKU	Rianne Jahja (Amesterdam)
13:10-13:20	Q&A	
13:20-13:30	Conclusions	Elisa Leão Teles (Porto)
13:30	Closing Session	**Paula Garcia (Coimbra)**

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