36th Annual Conference and Seminar

APS 2023

MULTI-OMICS IN DAILY (METABOLIC) LIFE

MAIN PROGRAM

ARBEITSGEMEINSCHAFT FÜR PÄDIATRISCHE STOFFWECHSELSTÖRUNGEN

March 7-10, 2023

Kongress Palais Kassel

www.events.aps-med.de

CONTENT

SCHEDULE

	Tuesday, March 7, 2023	
17:45	Welcome + Evening Lecture	**H4 Hotel, Gartensaal**
19:00	Get Together APS Seminar	**H4 Hotel**
	Wednesday, March 8, 2023	
08:30-17:00	**APS Seminar**	**Gesellschaftssaal**
17:00-18:00	Junge Stoffwechselmedizin	**Gesellschaftssaal**
18:00-19:30	Satellite Symposium - AMRYT PHARMA	**Gesellschaftssaal**
from 19:30	Get Together with Poster Walk	**Festsaal**
	Thursday, March 9, 2023	
07:00-07:45	Early bird yoga	**H4 Hotel, Merz+Longo**
08:30-15:45	**APS Annual Conference**	**Blauer Saal**
15:45-17:00	APS Quo Vadis?	**Blauer Saal**
17:00-18:30	APS Members Meeting	**Blauer Saal**
18:30-19:30	APS Networking	**Haupthalle**
from 20:00	APS Dinner	**Renthof**
	Friday, March 10, 2023	
08:30-13:30	**APS Annual Conference**	**Blauer Saal**

Welcome

Welcome to Kassel!
Welcome to the 36th Annual Meeting of the APS!

Dear Participants,

We are delighted to welcome you to the 36th Annual Conference of the Association for Pediatric Metabolic Diseases (APS)! This year's conference will focus on „Multi-omics in daily (metabolic) life," and offers a unique and exciting opportunity for professionals in the field of pediatric metabolic diseases to gather, share knowledge, and exchange ideas.

As we delve into the latest advancements in the field of pediatric metabolic diseases, we will explore the various omics techniques that are being used to study these complex conditions and how they impact daily life. With experts in this emerging field as keynote speakers reviewing state of the art knowledge and free communication sessions on the newest research accomplished with a poster exhibition, we will provide a comprehensive overview of the latest research and developments in the field.

We hope that you will take advantage of this opportunity to network with your colleagues and make new connections, as well as to learn and grow professionally.

We look forward to a successful and productive conference, and we hope that you will find the 36th Annual Conference of the APS to be a meaningful and rewarding experience.

Warmest regards,

Ao. Univ.-Prof. Dr. med. Saskia Wortmann, PhD

Priv.-Doz. Dipl.-Ing. Dr. Johannes Mayr

Co-Presidents of APS 2023

UNIKLINIKUM SALZBURG
LANDESKRANKENHAUS

Amalia Children's Hospital
Radboudumc

Dienstag, 7. März 2023

H4 Hotel

- Vorsitz: C. Mühlhausen, Göttingen

17:45 **Eröffnung**
- C. Mühlhausen, Göttingen

18:00 **Evening Lecture**
Kommunikationsfallen: wie man sie vermeidet, umgeht, aufstellt und wieder herauskommt
- P. Burgard, Heidelberg

19:00 **Get Together und gemeinsames Abendessen**

Mittwoch, 8. März 2023

Gesellschaftssaal

- Vorsitz: R. Santer, Hamburg

08:30 **Basics der Stoffwechsel-Labordiagnostik mit Befunde-Quiz**
- A.Schumann, Freiburg

09:30-10:00 **Kaffeepause**

10:00 **Gruppenarbeit POL-Fall 1**
- P. Freisinger, Reutlingen
- S. Grünert, Freiburg
- C. Mühlhausen, Göttingen
- R. Santer, Hamburg

11:30 **Update CDG – neue und behandelbare Krankheiten**
- C. Johnsen, Göttingen

12:15-13:30 **Mittagspause**

13:30 **Fallseminar „Der interessante Stoffwechselfall“** Gruppenarbeit
- Teilnehmer-Moderation: R. Santer, Hamburg

15:00 **Dyslipidämien**
- B. Koletzko, München

Mittwoch, 8. März 2023

Gesellschaftssaal

15:45-16:15 **Kaffeepause**

16:15 **Update NCL mit Video-Quiz**
- C. Schwering, Hamburg

17:00 **Verabschiedung und Ende**
- R. Santer, Hamburg & C. Mühlhausen, Göttingen

17:00-18:00 **Junge Stoffwechselmedizin**

18:00-19:30 **Satellite Symposium**
mit freundlicher Unterstützung von AMRYT PHARMA

Ein seltenes Krankheitsbild: viele verschiedene Gesichter – wie differenzieren?

• Mitraten ist gefragt: welche Krankheit versteckt sich hinter den Symptomen (interaktive Fallvorstellungen)?
• Herausforderungen der Diagnostik und Differentialdiagnosen
• Komplexität der Krankheitsbilder- Patientenvorstellung in der Neuropädiatrie oder in der Stoffwechselambulanz?

Es diskutieren mit Ihnen:
- Annette Richter-Unruh (Bochum)
- Clemens Kamrath (Gießen)
-Martin Wabitsch (Ulm)

ab 19:30 **Get together with poster walk**
Festsaal

Thursday, March 9, 2023

07:00-07:45 **Early bird yoga** (please bring your own yoga mat)
- Margarete Eckl - Iyoga, Munich
H4 Hotel, Merz+Longo

Blauer Saal

08:30-08:40 **Welcome**
The future is now: OMICS in daily (metabolic) life
- Saskia Wortmann & Johannes Mayr, Salzburg (AT)

08:40-10:10 **An introduction to OMICS in inborn metabolic diseases**
- Chair: Daniela Karall, Innsbruck (AT), Ulrike Mütze, Heidelberg

All you need to know about OMICS: an introduction to terms and techniques
- Martin Poms, Zürich (CH)

The power of exome sequencing for gene discovery in mitochondrial disease
- Holger Prokisch, Munich

Variant interpretation - the use of OMICS for confirming or discarding VUSses from exome sequencing
- Davor Lessel, Salzburg (AT)

10:10-10:40 **Coffee Break | Posters | Industrial Exhibition**

10:40-12:10 **OMICS: from IMDs to daily life**
- Chair: Skadi Beblo, Leipzig & Nastassja Himmelreich, Heidelberg

How to proceed after negative exome: Multi-omics in diagnostics of mitochondrial disease - the value of muscle and skin biopsy
- Robert Taylor, Newcastle (UK)

Multi-omics in art
- Stepanka Kuckova, Prague (CZE)

Multi-omics in crime investigation
- NN

12:10-13:30 **Break with Poster-Lunch**

Thursday, March 9, 2023

Blauer Saal

13:30 - 14:30 **New avenues to solve old problems?**
- Chair: Ralf Husain, Jena & Corinna Weigel, Erlangen

The future of newborn screening: genomics or metabolomics?
- Jim Bonham, Sheffield (UK)

Epigenetics in IMD: the example of Epi-cblC, an inherited disorder of intracellular B12 metabolism
- Jean-Louis Gueant, Nancy (FR)

14:30-15:20 **Free communications I**
- Chair: Ulrike Steuerwald, Hannover & Natalie Weinhold, Berlin

FC 01-01 Renal phenotype in a hypomorphic murine model of propionic aciduria
- Anke Schumann, Freiburg

FC 01-02 Region-specific lipidomic profiling in brain and spinal cord tissue of X-linked adrenoleukodystrophy mice
- Lara Marten, Göttingen

FC 01-03 mRNA-based approach induces the expression of functional PAH enzyme in vitro
- Daniel Frank, Mainz

FC 01-04 Pathogenic non-functional mutants of intestinal lactase-phlorizin hydrolase form hetero-complexes with the active wild type enzyme and negatively impact its function and intracellular trafficking
- Tammy Stellbrinck, Hannover

FC 01-05 Using induced pluripotent stem cell (iPSC) technology to understand the ultra-rare metabolic disease malate dehydrogenase 2 (MDH2) deficiency (MDH2D) and its potential treatment with triheptanoin
- Alexander Lämmle, Bern (CH)

15:20-15:45 **Coffee Break | Posters | Industrial Exhibition**

Thursday, March 9, 2023

Blauer Saal

15:45-17:00	**APS Quo Vadis?**
17:00-18:30	**APS members‘ meeting**
18:30-19:30	**APS Networking** Haupthalle
from 20:00	**APS Dinner** Renthof

Friday, March 10, 2023

08:30-10:00 **Free communications II**
- Chair: Marianne Rohrbach, Zurich (CH) & Steffi Dreha, Münster

Blauer Saal

FC 02-01 Repurposing Bempedoic acid as a therapeutic option in GSD Type 1: From biochemical principles to first clinical data
- Anibh Martin Das, Hannover

FC 02-02 Mevalonate Kinase Deficiency significantly impairs Glycosylation
- Christian Thiel, Heidelberg

FC 02-03 Isovaleric aciduria identified by newborn screening: Strategies to predict disease severity and stratify treatment
- Ulrike Mütze, Heidelberg

FC 02-04 ACMSD deficiency, a new disorder of tryptophan catabolism responsive to protein restriction
- Clara Köller, Salzburg (AT)

FC 02-05 Machine learning methods improve specificity in newborn screening for isovaleric aciduria
- Elaine Zaunseder, Heidelberg

FC 02-06 / FC 02-09 Complex metabolic disharmony in PMM2-CDG paves the way to new therapeutic approaches / Biotin improved psychomotor abilities in individuals with Congenital Disorders of Glycosylation – a pilot study
- Nastassja Himmelreich, Heidelberg

FC 02-07 Value-based healthcare for glycogen storage disease type IB: Repurposing Empagliflozin
- Clara Köller, Salzburg (AT)

FC 02-08 Psychosocial issues and coping strategies in families affected by long-chain fatty acid oxidation disorders
- Maren Thiel, Freiburg

10:00-10:30 **Coffee Break | Posters | Industrial Exhibition**

Friday, March 10, 2023

Blauer Saal

10:30-12:30 **New techniques for new insights and future treatments**
- Chair: Eva Thimm, Düsseldorf & Sabine Illsinger, Hamburg

tRNA Sequencing - a new technique and metabolic signature
- Melanie Achleitner, Salzburg (AT)

Fluxomics for IMD - a new tool to study complex metabolic pathways
- Laura Steinbusch, Maastricht (NL)

Untargeted metabolomics reveals novel biomarkers and pathomechanisms
- Ron Wevers, Nijmegen (NL)

Bridging OMICS to (personalized) treatment in daily life
- Saskia Wortmann, Salzburg (AT) & Nijmegen (NL)

12:30 **Prizes, Farewell, Invitation for APS 2024**

12:40-13:30 **Break with Poster-Lunch**

GENERAL INFORMATION

Conference venue

Kongress Palais Kassel
Holger-Börner-Platz 1
34119 Kassel
Germany

Phone: +49 561 707702
Email: info@kassel-marketing.de
www.kongress-palais.de

Arrival by car

The Kassel Kongress Palais is located in the middle of Germany and can be reached from all directions in Europe by the shortest route.
Parking is available in the Parkhaus Kongress Palais / Kattenstraße with 109 spaces. Further public parking spaces are available in the immediate vicinity.

Arrival by train

Travel to the APS conference in Kassel (ICE station Kassel-Wilhelmshöhe). With the offer of Kassel Marketing GmbH and Deutsche Bahn you can save money when visiting your congress in Kassel.
https://www.veranstaltungsticket-bahn.de/?event=1099&language=de

Arrival by plane

Frankfurt Airport provides a direct connection to the European air network. German airports are served particularly frequently, and the flight time within Germany is less than one hour. From Frankfurt Airport, you can get directly to Kassel by train in about two hours.

Conference Fee

Registration for the APS Annual Conference	**by February 13th**	**from February 14th**
APS Members	€ 65,-	€ 90,-
Non-Members	€ 100,-	€ 125,-

Students and PhD candidates do not have to pay this fee on presentation of a corresponding certificate when registering.

Please register online at www.events.aps-med.de.

Participation in the „APS Stoffwechsel Seminar“ is free of charge for physicians, dieticians and metabolic lab personell.

Tram 4 in the direction of Kaufungen-Papierfabrik
4 min, 3 stops to Kassel Kongress Palais/Stadthalle
Alternatives every 15 minutes

GENERAL TECHNICAL INFORMATION FOR SPEAKERS

Conflict of interest
We would like to point out that the speakers are required to present in a product and service-neutral manner. Possible conflicts of interest must be announced at the beginning of the presentation.

Conference language
Official language of the APS Annual Meeting is English, the APS Seminar will be held in German.

Compatibility
Please submit your presentation as a PC-compatible file on a data storage device (memory stick). After saving it on the data storage device, please make sure the presentation is running smoothly. Speakers are responsible for their presentation's compatibility.

Media center
Please hand in your data storage device at the "media center" at the registration desk 2 hours before your presentation.

Submission via e-mail
You can also send your presentation in advance as an e-mail attachment to aps@studio12.co.at (by March 6, 2023 at the latest).

MacOS
Mac users are urgently requested to save their presentation on the data storage device in a PC-compatible way and ensure that it will run without issue.

CONTACT INFORMATION

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APS Seminar

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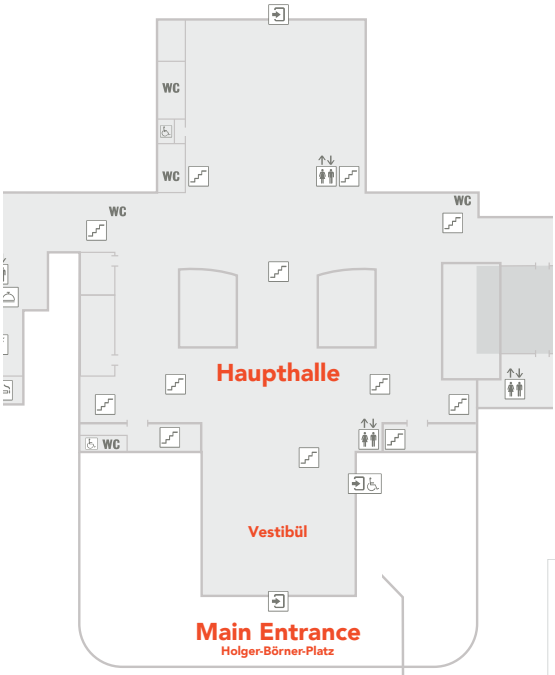
Training points

The recognition of the Annual Conference as a certified event for Continuing Medical Education will be applied for at the Landesärztekammer Hessen.

SITE MAP



Ground floor

First floor

APS 2023

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APS-SEMINAR: Für das Seminar findet kein Sponsoring statt. Die Veranstaltung wird ausschließlich durch die APS selbst finanziert. Höhe der Gesamtaufwendungen: 7.500 EUR.
(Disclosure of sponsorship services in accordance with the FSA Code as part of the expanded transparency requirement for the support of congress events)

Notes

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Free Communications

FC 01-01

Renal phenotype in a hypomorphic murine model of propionic aciduria

Anke Schumann[1], Christoph Schell[2], Anna Laura Kössinger[2], Ainhoa Martinez[3], Eva Richard[3], Lourdes R. Desviat[3], Luciana Hannibal[4], Ute Spiekerkötter[1]
[1]Department of General Paediatrics, Adolescent Medicine and Neonatology, Medical Center-University of Freiburg, Faculty of Medicine, Freiburg, Germany. [2]Institute for Surgical Pathology, Medical Center-University of Freiburg, Faculty of Medicine, University of Freiburg, Freiburg, Germany. [3]Centro de Biología Molecular Severo Ochoa, UAM-CSIC, CIBERER, IdiPaz, Universidad Autónoma, Madrid, Spain. [4]Department of General Paediatrics, Adolescent Medicine and Neonatology, Laboratory of Clinical Biochemistry and Metabolism, Medical Center-University of Freiburg, Faculty of Medicine, Freiburg, Germany

Introduction

Propionic aciduria (PA) is a caused by mutations in the mitochondrial enzyme propionyl-CoA carboxylase (PCC). PCC leads to hampered energy generation from branched-chain amino acids, odd chain fatty acids and cholesterol and the accumulation of disease-specific metabolites (e.g. 3-OH-propionic acid, methylcitric acid). PA patients present with acute life-threatening metabolic crisis triggered by catabolism. Multisystemic long-term complications include neurological and cardiac impairment as well as chronic kidney disease (CKD). Mitochondrial dysfunction and the accumulation of potentially toxic metabolites have been discussed as disease driving mechanisms. We investigated the renal phenotype of a hypomorphic murine PA model (*Pcca*$^{-/-}$) to address possible disease related mechanisms for CKD.

Patients/Methods

Pcca$^{-/-}$ and wild-type kidneys of female mice were analysed using immuno-blotting, LC-MS/MS and histomorphological assessment at different ages.

Results

Creatinine levels were elevated in *Pcca*$^{-/-}$ mouse kidneys pointing to impaired kidney function. We detected a decreased ratio of reduced to oxidized glutathione in kidney lysates, suggesting a need to counteract oxidative stress. Mitochondrial marker proteins (VDAC, COX IV) were up-regulated. Metabolomic profiling showed elevated concentrations of methylcitrate and propionate in *Pcca*$^{-/-}$ mouse kidneys. The analysis of tricarboxylic citric acid cycle metabolites revealed elevated succinate and citrate concentrations while the amino acid profile was comparable to wild-type mice. Investigation of the mitochondrial quality control system revealed a marked reduction of PINK1, an important inducer of mitophagy, while SQSTM1, an autophagy marker, was up-regulated. PGC-1 alpha, a gate-keeper orchestrating mitochondrial biogenesis, mitochondrial quality control and mitochondrial fission/fusion activity, was down-regulated in the kidneys of *Pcca*$^{-/-}$ mice. Drp1, a mitochondrial fission protein, was increased. Interestingly, PGC-1 alpha

expression is positively correlated with activation of the mitophagy pathway and counter acts mitochondrial fission. Morphological assessment of *Pcca*$^{-/-}$ mouse kidneys showed a partial flattening of tubular epithelial cells and at least focal tubular-cystic dilation.

Conclusion/Discussion

Our results suggest that impairment of mitochondrial quality control and disturbed mitochondrial dynamics are important mechanisms for the progression of kidney dysfunction in PA. The identified pathomechanisms point to pharmacologically targetable pathways which will be explored in future studies in this mouse model.

FC 01-02

Region-specific lipidomic profiling in brain and spinal cord tissue of X-linked adrenoleukodystrophy mice

Lara M Marten[1], S S Justus Lattau[2], Dirk Fitzner[2], Stefan Nessler[3], Christine Stadelmann[3], Hendrik Rosewich[1], Jutta Gärtner[1]
[1]Department of Pediatrics, University Medical Center Göttingen, Göttingen, Germany. [2]Department of Neurology, University Medical Center Göttingen, Göttingen, Germany. [3]Institute of Neuropathology, University Medical Center Göttingen, Göttingen, Germany

Introduction

X-linked adrenoleukodystrophy (X-ALD) is an inherited neurometabolic disorder caused by *ABCD1* gene mutations. Dysfunctional ABCD1 protein leads to accumulation of very long chain fatty acids (VLCFA) in blood and tissue. VLCFA toxicity likely contributes in a yet unknown way to phenotypic presentation such as childhood cerebral ALD, adrenomyeloneuropathy (AMN) and asymptomatic carriers, but is insufficient as sole explanation for divergent phenotypes. The abundance of VLCFA and subsequent disproportionation of other lipids has a variety of metabolic consequences, that likely contribute to the course of disease. This study aims to investigate lipid metabolism in different CNS regions via lipidomic analysis in the X-ALD mouse model.

Patients/Methods

Brain (corpus callosum, motor cortex) and spinal cord tissue from male 3- and 12-month-old ABCD1-/0 mice and wildtype litter mates was objected to quantitative shotgun lipidomics. Mass spectrometry-based analysis was performed by Lipotype GmbH. KNIME Analytics Platform was used for data processing. Statistical analyses were performed using R Statistical Software, MetaboAnalystR, lipidr and mixOmics. Lipid species and subspecies are annotated according to their molecular composition as described by LIPID-MAPS.

Free Communications

Results

The lipidomic analysis included over 700 lipid species. Data analysis revealed region-specific clustering for both age groups, shown in principal component analysis and heatmap. Significant differences between X-ALD and wildtype tissues were found in a series of lipid classes and were more profound in white matter versus gray matter tissue. Moreover, these differences increased significantly in the older cohort.

Conclusion/Discussion

Our results revealed for the first time region-specific lipidomic profiles in tissues from X-ALD and wildtype mice. We were able to discriminate brain regions according to characteristic lipid compositions and show aggravation of incorporated VLCFA over lifetime. Notably, the largest discrepancy between X-ALD and wildtype was found in spinal cord tissue from 12-month-old mice, consistent with the X-ALD mouse model characteristics of an AMN phenotype and lack of cerebral manifestation. Our findings provide a detailed insight into lipidomic profiles in X-ALD mouse brain and spinal cord tissue and show how VLCFA accumulation impacts the complex lipid composition. These results provide valuable insight into possible pathophysiological processes in X-ALD and the analyses will now be extended to patient material.

Free Communications

FC 01-03

mRNA-based approach induces the expression of functional PAH enzyme in vitro

Daniel Frank[1], Christine Weinl-Tenbruck[2], Maria Jose Limeres[1], Mansure Abdollah Pasha Famian[1], Nigel Horscroft[3], Fred Zepp[1], Frédéric Chevessier-Tünnesen[2], Stephan Gehring[1], Julia B. Hennermann[1], Maximiliano L. Cacicedo[1]
[1]Children's Hospital, University Medical Center of the Johannes-Gutenberg University, Mainz, Germany. [2]CureVac SE, Tübingen, Germany. [3]Atriva Therapeutics GmbH, Tübingen, Germany

Introduction

Phenylketonuria (PKU) is an autosomal recessive inborn error of metabolism caused by a deficiency in the hepatic enzyme phenylalanine hydroxylase (PAH). Dysfunction in PAH leads to accumulation of phenylalanine (Phe) in blood, CNS, i.a., resulting in severe neurological symptoms. Treatment options include a strict phenylalanine-balanced lifelong diet, treatment with the essential PAH co-factor BH_4 for patients suffering from mild PKU with residual PAH activity, or a daily injection of a pegylated form of phenylalanine ammonia-lyase, which can metabolize phenylalanine, but may cause severe side effects. Thus, there is a high medical need for alternative treatment options. Here we present the in vitro evaluation of a novel mRNA-based therapy for PKU.

Patients/Methods

mRNA constructs were evaluated regarding high expression yield and superior enzymatic activity. HeLa and HepG2 cell lines as well as primary murine hepatocytes were transfected and PAH protein quantity and quality were measured via confocal laser scan microscopy (CLSM), western blot analysis (WB) and enzyme assay.

Results

PAH presence was detected in high amounts 24h after transfection using CLSM and WB in established cell lines. Moreover, expression was sustained over 72h with a decrease over time. Most importantly, produced PAH functionality was assessed by measuring enzymatic activity. Results showed a successful and specific function of the enzyme through the transformation of Phe into tyrosine. This functionality assay allowed the evaluation of PAH in the different cell types and conditions. Changes in enzymatic activity were assessed by challenging the produced PAH to different amounts of its substrate (Phe) and cofactor (BH_4). In correlation with WB results, a peak in enzymatic activity was observed 24h after transfection with a marked decrease with time. Finding of functional PAH expression prepared the basis for further in vivo evaluation of mRNA treatment in a PKU mouse model.

Free Communications

Conclusion/Discussion

mRNA-based therapies have shown to be a potent tool with the capacity to fulfil expectations in various fields. The presented data supports the promising role of mRNA in the future treatment of PKU as an example for protein replacement therapies.

FC 01-04

Pathogenic non-functional mutants of intestinal lactase-phlorizin hydrolase form hetero-complexes with the active wild type enzyme and negatively impact its function and intracellular trafficking

Tammy Stellbrinck[1], Dalanda Wanes[1], Lara Marten[2], René Santer[3], Hassan Y. Hassan Y. Naim[1]
[1]Department of Biochemistry, University of Veterinary Medicine Hannover, Hannover, Germany. [2]Department of Pediatrics and Adolescent Medicine, University Medical Center Göttingen, Göttingen, Germany. [3]Department of Pediatrics, University Medical Center Eppendorf, Hamburg, Germany

Introduction

Congenital lactase deficiency (CLD) is a rare disorder caused by genetic variants in the coding region of the lactase gene (LCT), which encodes the intestinal glycoprotein lactase-phlorizin hydrolase (LPH). LPH is a brush border disaccharidase that digests lactose the main carbohydrate in mammalian milk. CLD patients present with severe malabsorption symptoms such as diarrhea and abdominal pain shortly after birth, when lactose is the sole nutritionally important carbohydrate rendering CLD life threatening for newborns. Several hypomorphic variants of the LCT gene have been identified in homozygotes and compound heterozygotes. The severe impact of these variants on structure and function of LPH has led us to ask whether heterozygotes may also present with malabsorption symptoms. We therefore investigated potential interactions between wild type LPH (LPH-wt) and the pathogenic LPH mutants LPH-E1612*, LPH-G1363S, LPH-R1587H, LPH-S1124L, LPH-S688P, LPH-S1150Pfs*19, and LPH-Y1390*.

Patients/Methods

LPH-wt was co-expressed with LPH mutants in COS-1 cells and their interaction and the generation of hetero-complexes was examined by co-immunoprecipitation. The impact of the mutations on trafficking, cellular localization and digestive function of resulting LPH hetero-complexes was assessed.

Free Communications

Results

LPH-wt interacts avidly with LPH-G1363S, LPH-R1587H, LPH-S1124L, and LPH-S688P. The resulting hetero-complexes are retained in the ER and have massively lost their enzymatic activity. Only the hetero-complex of LPH-wt with LPH-S688P was slightly active. Immunofluorescence images revealed the hetero-complexes predominantly in the ER. Two of the truncated mutants did not interact with LPH-wt, while LPH-E1612* interacted with LPH-wt without affecting the lactase activity.

Conclusion/Discussion

We show that pathogenic LPH mutants negatively impact the activity and impair the trafficking of LPH-wt through formation of heterodimeric-complexes suggesting possible clinical implications for heterozygote carriers of CLD variants. Clinical symptoms could be mild, similar to presentation of adult-type hypolactasia, which has a different genetic background and affects 2/3 of the world population. Presumably, heterozygous carriers might be erroneously assigned to this group or remain undiagnosed when following a diet naturally low in lactose. The biochemical details of hetero-complex formation and how they affect lactose digestion capacity in vivo are important issues for future studies.

Free Communications

FC 01-05

Using induced pluripotent stem cell (iPSC) technology to understand the ultra-rare metabolic disease malate dehydrogenase 2 (MDH2) deficiency (MDH2D) and its potential treatment with triheptanoin

Sophie Koller[1,2,3], Adhuresa Ramosaj[2,3,4], Jean-Marc Nuoffer[2,3], Déborah Mathis[3], Alexander Laemmle[2,3]

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Introduction

Mitochondrial malate dehydrogenase (MDH2) deficiency (MDH2D) is caused by pathogenic variants in the MDH2 gene. MDH2 is part of the tricarboxylic acid (TCA) cycle and the malate-aspartate shuttle (MAS). Patients with MDH2D suffer from early-onset encephalopathy. Their lactic acid levels are elevated in blood and cerebrospinal fluid. To date only five cases of MDH2D have been reported. Currently, there is no cure for this devastating disease. However, our research group recently published a promising drug trial using triheptanoin in a 3-year old girl with MDH2D who responded well to the treatment.

Here, we aimed to better characterize this ultra-rare disease and to improve our understanding of the suggested treatment with triheptanoin.

Patients/Methods

Therefore, we generated a liver disease model using patient-derived human-induced pluripotent stem cells (hiPSCs) differentiated into hepatocytes (hiPSC-Heps).

Results

Characterization of patient-derived hiPSCs and hiPSC-Heps revealed significantly reduced MDH2 expression and activity. As found in patients, MDH2 deficient cells produced more lactate compared to control cells. Interestingly, patient-derived cells bypassed the defective MDH2 enzyme by upregulating alternative pathways including both mitochondrial isoforms of malic enzymes (ME2 and ME3). In addition, MDH2 deficient cells showed a preference for succinate (complex II-dependent) over pyruvate (complex I-dependent) respiration thus implying that the triheptanoin-derived propionyl-CoA fuels the respiratory chain over complex II.

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Conclusion/Discussion

Taken together, our results in patient-derived hiPSC-Heps revealed disease-specific characteristics, provide an explanation why and how MDH2D is compatible with life and serve as basis for on-going experiments with triheptanoin to further unravel its molecular mechanism of action.

FC 02-01

Repurposing Bempedoic acid as a therapeutic option in GSD Type 1: From biochemical principles to first clinical data

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Introduction

Hypoketotic hypoglycaemia is a metabolic and diagnostic hallmark in patients with glycogen storage disease type 1 (GSD 1) leading to cerebral energy depletion during catabolism. Hypoketonaemia is due to elevated cellular levels of malonyl-CoA which blocks the entry of long-chain fatty acids into the mitochondrial matrix for ß-oxidation and subsequent ketogenesis in the liver. In muscle, malonyl-CoA inhibits energy production from fatty acids as energy substrate. Bempedoic acid (BA) as a prodrug is approved for the use in adult patients with dyslipidaemia. This drug is able to lower malonyl-CoA-levels thus increasing fatty acid oxidation and ketogenesis. BA inhibits adenosinetriphosphate-citrate lyase thus reducing lipid synthesis as well as the synthesis of malonyl-CoA. We hypothesized that repurposing of BA is able to improve metabolic control in patients with GSD 1 by improving energetic balance via fatty acid oxidation as well as ketogenesis.

Patients/Methods

We studied the effect of BA at a dose of 180 mg once daily on metabolic stability in three adult patients suffering from GSD 1 with dyslipdaemia.

Results

BA led to an improved metabolic control in terms of stability of glucose levels, carbohydrate requirements, plasma levels of lactate, uric acid and lipids, ketone bodies increased even under random conditions during visits to our outpatient-unit. No side effects of BA were observed in our patient cohort.

Conclusion/Discussion

In a pilot study, BA had a positive effect on metabolic control in patients with GSD 1 without side effects. Therefore, repurposing of BA may be a novel treatment option in patients suffering from GSD 1. Further studies are required in a larger patient cohort supplemented by studies in hepatocytes in vitro.

FC 02-02

Mevalonate Kinase Deficiency significantly impairs Glycosylation

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Introduction

Mevalonate kinase (MVK) is an enzyme in the early polyisoprenoid pathway required for cholesterol, dolichol, hormone and vitamin biosynthesis as well as for energy metabolism. MVK deficiency either leads to hyperimmunoglobulinemia D syndrome (HIDS) or mevalonic aciduria (MVA) which represents the more severe end of the clinical spectrum. Symptoms include recurrent febrile crises, often accompanied by hepatosplenomegaly, lymphadenopathy, arthralgia and skin rashes. MVA patients additionally present with neurologic, ocular and cardiac symptoms. Here, we were interested to find out about the consequences of MVK deficiency on other metabolic pathways, esp. the glycosylation machinery.

Patients/Methods

Complex metabolic studies combined with mass spectrometry-based OMICS analysis were conducted. We here focus on lipidomic and glycomic analysis performed in skin fibroblasts of eleven MVA patients.

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Results

Lipid analysis by NEI-MS/MS revealed a general impairment in lipid homeostasis. Among others, significant reduced levels of cholesterol esters and elevated amounts for ceramide and sphingomyelin were found. The ester linked glycerophospholipid phosphatidylethanolamines was significantly reduced whereas phosphatidylserines were significantly elevated. The ether linked glycerophospholipids alkyl-phosphatidylcholines, alkyl-phosphatidylserines and alkyl-phosphatidylinositols showed significantly raised levels. Notably, total dolichol-phosphate needed for protein glycosylation was significantly reduced. Lectin binding studies and analysis of glycoprotein markers attested an immense impairment in the N-glycosylation pathway. Profound analysis of total N-glycans by xCGE-LIF further revealed a reduction of complex type N-glycans with elevated fucosylated structures and abnormalities within the group of high mannose type glycans.

Conclusion/Discussion

We here demonstrate for the first time that deficient MVK leads to a disturbed lipid homoeostasis followed by a global glycosylation deficiency in MVA patients. Therefore, at least MVA belongs to the disease group of congenital disorders of glycosylation (CDG). Since it can be assumed that also the enzymes following MVK in the polyisoprenoid pathway lead to a glycosylation defect, these should be included in the list of suspected CDG candidates in the context of genetic patient diagnostics. Whether HIDS patients with higher residual enzyme activity show a glycosylation phenotype as well, needs to be elucidated.

Free Communications

FC 02-03

Isovaleric aciduria identified by newborn screening: Strategies to predict disease severity and stratify treatment

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Introduction

Newborn screening (NBS) allows presymptomatic identification of individuals with rare diseases, such as isovaleric aciduria (IVA). Reliable case definition is the pre-requisite to initiate treatment in a timely and severity-adjusted manner.

Patients/Methods

To predict the individual disease severity, NBS and confirmatory data were evaluated through a prospective, observational, multi-centre study of individuals with confirmed IVA identified by NBS between 1998 and 2018 in Germany.

Results

Screening results, metabolic parameters, and genetic and clinical data of 84 individuals with IVA detected by NBS (median age at last study visit 7.8 years) were included. Patients with a symptomatic disease course later in life (metabolic decompensations; symptomatic at last visit) showed higher median isovalerylcarnitine (C5) concentrations

in the first NBS sample (10.6; 10.8µmol/) and initial isovalerylglycine concentration in urine (1,750; 1559 mmol/mol creatinine) than those who remained asymptomatic (both 2.7 µmol/l, P<0.0001; and 180 mmol/mol creatinine, P=0.0003; 180 mmol/mol creatinine, P=0.0004, respectively). Global IQ correlated in trend inversely with C5 (R=-0.255; slope = -0.869; P=0.08704). Genetic prediction scores highly correlated with the metabolic parameters, but not sufficiently with the clinical endpoints.

Conclusion/Discussion

The metabolic parameters of the first NBS sample and the biochemical confirmation are reliable early predictors of the clinical course in IVA and allow a case definition (attenuated or classic). Prediction of the attenuated IVA is supported by genetic testing. On that basis an algorithm was established for newborns with a positive NBS result for IVA aiming for individual risk stratification and reliable therapeutic decision-making.

FC 02-04

ACMSD deficiency, a new disorder of tryptophan catabolism responsive to protein restriction

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Introduction

Inborn metabolic disorders (IMDs) of amino acid metabolism can present with global developmental delay and implicate treatment options with protein restriction. The neuronal excitotoxin quinolinate, an intermediate in the de novo synthesis pathway of nicotinamide adenine dinucleotide (NAD) from tryptophan, is derived from alpha-amino-beta-carboxy-muconate-epsilon-semialdehyde (ACMS). ACMSD encodes amino-carboxymuconate semialdehyde decarboxylase, which is the only known enzyme that can process ACMS to a benign catabolite and thus prevent the accumulation of quinolinate from ACMS. Quinolinate accumulation has been related to (Alzheimer's) dementia, neuroinflammation and psychiatric disease.

Free Communications

Patients/Methods

Exome sequencing of a 6-year-old male with global developmental delay, autistic features and hyperactivity revealed a homozygous deletion in ACMSD involving the promotor/exon1 and predicted to lead to absence of the enzyme. Four-fold increased quinolinate was determined in the patient's serum. One week after implementation of a low-protein (vegetarian) diet the parents reported a clearly improved behaviour with less hyperactivity. Serum quinolinate levels were measured 4 weeks after dietary change and were comparable to those in controls.

Psychological testing (Kaufmann ABC) under normal protein load had shown a below average non-verbal IQ of 70 (85-115) with pronounced deficiencies in memory span and visual processing. Follow up testing after one year of vegetarian diet showed improvement in all investigated subareas, especially in memory span and capacity. This is also reflected by an improved non-verbal IQ of 73 (percentile ranking improved by >1).

Via matchmaking a young adult female presenting with psychiatric disease, progressive loss of skills, diffuse leukoencephalopathy on brain MRI and a homozygous truncating ACMSD variant was found. Her brain biopsy was compatible with encephalitis, further investigations are pending.

Conclusion/Discussion

ACMSD deficiency is a novel IMD presenting as neurodevelopmental disorder with a spectrum encompassing developmental delay, behavioural issues to psychiatric disease with loss of skills. We have shown in one case that dietary protein restriction can limit quinolinate accumulation and seems beneficial for behaviour and possibly also learning and development.

Free Communications

FC 02-05

Machine learning methods improve specificity in newborn screening for isovaleric aciduria

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Introduction

Recently, in medical applications, machine learning methods, a sub-field of artificial intelligence, have been applied successfully in various areas such as cancer research and medical imaging and also improved newborn screening (NBS) programs for several diseases. Isovaleric aciduria (IVA) is part of newborn screening programs worldwide, with huge benefits for severely affected individuals with IVA. However, NBS for IVA also identifies a high number of individuals with an attenuated, possibly asymptomatic, disease variant (so-called “mild” IVA) and is increasingly hampered by a rising number of false positives due to the use of pivmecillinam antibiotics in late pregnancy.

Patients/Methods

For the first time, we examined applying artificial intelligence methods in NBS for IVA as an innovative technique, a *digital-tier strategy*, analogous to a biomarker second-tier method to increase specificity and by this reduce the number of false positives. These methods are applied and evaluated on a data set with more than 2 million NBS profiles screened at the Heidelberg NBS laboratory.

Results

We show that machine learning methods can reduce the number of normal newborns falsely classified as newborns with IVA by nearly 70% from 103 to 31 compared to traditional NBS while maintaining 100% sensitivity in cross-validation. Furthermore, we show that the machine learning methods can accurately predict mild and classic IVA variants solely based on the NBS data. Moreover, the data analysis techniques revealed that besides isovalerylcarnitine (C5), the metabolite concentration of tryptophan (Trp) is important for improved classification of screened false positives.

Conclusion/Discussion

By this, the application of machine learning in NBS for IVA could have a major impact on newborns, as it facilitates early precise detection of true positives, and reduces the harm and psychological stress on newborns and their families. An accurate prediction of new-

borns with mild and classic IVA would allow immediate treatment of all individuals at risk, but would also reduce over-treatment for individuals with the predominantly identified attenuated variant. Altogether the use of ML can be highly beneficial in NBS for IVA and guide directions for future research in this field.

FC 02-06

Complex metabolic disharmony in PMM2-CDG paves the way to new therapeutic approaches

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Introduction

Deficiency of phosphomannomutase 2 (PMM2) leads to PMM2-CDG, the most common type within the Congenital Disorders of Glycosylation (CDG). Clinical symptoms comprise e.g. mental retardation, seizure, hypotonia, cerebellar hypoplasia, ataxia, strabismus, abnormal fat distribution, scoliosis, cardiomyopathy, coagulopathy, and hepatomegaly with elevated liver enzymes. Thus far, no holistic therapy for PMM2-CDG is known and the mortality rate is approximately 20% in the first years of life. Interestingly, clinical symptoms that are common in PMM-CDG are also present in patients suffering from defects in the amino acid synthesis, fatty acid and lipid metabolism, the tricarboxylic acid cycle and lysosomal protein degradation. We here performed profound biochemical studies in patients´ fibroblasts to elucidate whether PMM2-CDG causes aberrations in other metabolic pathways as well.

Patients/Methods

Skin fibroblasts of PMM2-CDG patients (n=7) and controls (n=4) were used to analyse acylcarnitines, amino acids, organic acids, and lipids by mass spectrometry. Abnormalities concerning 21 lysosomal proteins as well as biotinidase and catalase were addressed by activity measurements. Expression of calnexin, calreticulin, PDI and ubiquitinylation of proteins were tested by Western blot.

Free Communications

Results

We found several significantly altered short-chain metabolites like free carnitine (C0), propionylcarnitine (C3), isovalerylcarnitine (C5), Methylcrotonylcarnitine (C5:1) and 3-hydroxyisovalerylcarnitine+β-hydroxymethylbutyrate (C5OH + HMB) as well as the long-chain acylcarnitines octadecanoylcarnitine (C18:1) and octadecadienylcarnitine (C18:2). Furthermore, hyperaminoacidemia associated with higher expression of calnexin, calreticulin and PDI in combination with intensified amounts of ubiquitinylated proteins were detected. Activity of lysosomal enzymes was widely reduced (esp. alpha-L-fucosidase and alpha-glucosidase) and elevated citrate and pyruvate levels indicated mitochondrial confusion. Main lipid classes such as phosphatidylethanolamine, cholesterol or alkyl-phosphatidylcholine as well as minor lipid species such as hexosylceramide, lysophosphatidylcholines or phosphatidylglycerol were abnormal. Furthermore, biotinidase as well as catalase revealed severely diminished activities.

Conclusion/Discussion

Our investigation demonstrated that the PMM2 defect has significant effects on other metabolic pathways. Interestingly, we found that some of the abnormalities identified in the various metabolic pathways are directly biochemically related. We assume that the combination of metabolic disharmony finally resulted in the clinical symptoms known from PMM2-CDG patients. Based on our data we will show new and simple therapeutic approaches for PMM2-CDG.

Free Communications

FC 02-07

VALUE-BASED HEALTHCARE FOR GLYCOGEN STORAGE DISEASE TYPE IB: REPURPOSING EMPAGLIFLOZIN

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Introduction

Neutropenia and neutrophil dysfunction are characteristic phenotypic features of Glycogen storage disease type 1b (GSD1b). Until recently, treatment involved granulocyte-colony-stimulating factor (G-CSF) injections, which improve neutrophil count but not function. In 2019, insight into the underlying pathomechanism prompted successful repurposing of empagliflozin to address both neutropenia and neutrophil dysfunction.

Patients/Methods

We conducted a retrospective multicenter study including six subjects from the Netherlands (NL) and five from Austria (AT) to investigate assets of empagliflozin from a value-based health care perspective. We investigated the four pillars of value based health care.
1) personal value investigating patient rated quality of life and patient reported outcome;
2) allocative value assessing medication costs, total costs including medical contacts, a sensitivity analysis and budget impact analysis;
3) technical value investigating laboratory results and (pediatric) Crohn disease activity index ((P)CDAI) and
4) societal value assessing cost evaluation and indices for burden of disease.

Results

Empagliflozin treatment improved outcomes of all four value pillars.

1) Quality-of-life scores improved by 4.5points (on a scale from one to ten) demonstrating a clear positive evolution of personal value.

2) The medication cost were reduced by 37% (NL) and 96% (AT), total treatment costs

by 47% (NL) and 66% (AT). The one- and three-year economic benefits of empagliflozin likewise showed a significant cost reduction. Further allocative value might lie in empagliflozin's favorable side effect profile compared to G-CSF, especially upon long-term use, but this was not investigated here.

3) Technical value: clinically all patients showed major biomedical improvements concerning neutrophil dysfunctional related findings. Eight of eleven patients showed improved and five of eleven normalized neutrophil counts, G-CSF was reduced in five and stopped in six of eleven patients.

4) Societal value: burden of disease was reduced, archived via a reduction in costs, reduction of required resources and individual prosperity of patients and their families.

Conclusion/Discussion

Our data show that empagliflozin is clearly superior to G-CSF from a value-based health care perspective. Empagliflozin improves major biomedical outcomes, patient-reported outcomes, and is a cost-effective medical intervention. Thus, it should be established and reimbursed as first line therapy in GSD1b neutropenia and neutrophil dysfunction.

Free Communications

FC 02-08

Psychosocial issues and coping strategies in families affected by long-chain fatty acid oxidation disorders

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Introduction

Long-chain fatty acid oxidation disorders (lc-FAODs) are associated with a high disease burden due to both the risk of metabolic decompensation as well as chronic complications in some defects. Little research has been performed on the impact of these disorders on the daily life of parents and caregivers.

Patients/Methods

We performed a web-based questionnaire study among parents/caregivers of patients affected with lc-FAODs in German-speaking countries. The questionnaire specifically focused on different aspects of the disease, including diagnosis, clinical course, dietary management, siblings, job situation, social life, sports, travelling, as well as the parents' attitude towards their child's disease.

Results

Data were collected from parents/caregivers of 63 patients (63% mothers, 36% fathers) with lc-FAODs (mean age of patients 8.1 years, LCHADD 40%, MTPD 14%, VLCADD 41%, CPT2D 5%). The overall disease burden of parents was considered highest during infancy and decreased with increasing age of their child. Although most patients attended a regular school, more than one third of parents were afraid that their child's disease might have an impact on his/her career choice and adult life. Negative effects of the child's disease on the job situation and career development were more commonly reported by mothers compared to fathers. While 44% of parents reported, that their child's disease was a source of conflict within their partnership and in 6% even the cause for separation/divorce, 48% of parents experienced that their child's disorder brought them closer together. Although the majority of parents consider their child's metabolic disorder a severe disease, most parents thought that life with a lc-FAOD is well-manageable.

Conclusion/Discussion

Although a lc-FAOD disorder of a child poses a significant burden on the daily life of parents and caregivers, most parents have a positive attitude towards their child's disease and seem to cope well with their situation.

Free Communications

FC 02-09

Biotin improved psychomotor abilities in individuals with Congenital Disorders of Glycosylation – a pilot study

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Introduction

Congenital Disorders of Glycosylation (CDG) are rare diseases (>170) which usually lead to multisystemic abnormalities. Clinical features comprise e.g. cerebellar hypoplasia, mental retardation, strabismus, muscular hypotonia, peripheral neuropathy, liver dysfunction, fat pads, coagulation defects, failure to thrive and high mortality. Thus far, the vast majority of individuals cannot be treated effectively. Notably, deficiency of the glycoprotein biotinidase (BTD; MIM #253260) leads to CDG mimicking symptoms as e.g. ataxia, epilepsy-like seizures, encephalopathy, hearing and eye problems, weakness, loss of appetite, increased susceptibility to infections, dermatitis and hair loss. We wanted to find out whether a CDG-based hypoglycosylation could lead to a reduction of biotinidase activity and hereby contribute to the clinical symptoms of CDG. Furthermore, it should be clarified whether the oral administration of biotin would have an effect on CDG progression.

Patients/Methods

Biotinidase activity was measured in dried blood spots of six approved CDG cases (3 CDG-I and 3 CDG-II, age 7-14 years). Oral biotin 10 mg/day was given during one year. We here performed an open-labeled-study with not-blinded observers. For evaluation, Adaptive Behavior Assessment System II (ABAS-II) questionnaires were used which were completed by the parents (t0 = before biotin application, t1 = 6 months under biotin treatment, t2 = 12 months under biotin treatment).

Results

Medium enzyme activity in 6 individuals with CDG was 47% (range 12-80%; reference range 20-200%). ABAS-II questionnaires indicated improved skills concerning communication (5/6 individuals), community use (4/6), functional pre-academics (5/6), home and living (5/6), health and safety (6/6), leisure (5/6), self-care (5/6), self-direction (5/6) and social (5/6).

Free Communications

Conclusion/Discussion

Although the biotinidase activity was reduced in individuals with CDG, the medium activity was just above the range of a partial BTD (10-30 %) which normally does not require biotin supplementation in individuals with BTD. However, in case of individuals with approved CDG, biotin administration led to clearly improved psychomotor abilities. As biotin is a safe and cheap dietary supplement and simple to administer, we speculate that it might represent a potential treatment for CDG which is not restricted to a specific CDG type. Currently, an ongoing biotin supplementation study with more individuals (>80) is carried out.

Posters

P01

Recommendations for diagnosing and managing individuals with glutaric aciduria type 1: Third revision

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Introduction

Guideline recommendations for glutaric aciduria type 1, a neurometabolic disorder of L-lysine metabolism with a high risk for striatal injury, have first been published in 2007, followed by two revisions (2011, 2016). The aim of this third revision was to re-evaluate

previous recommendations and formulate revised and—for new topics—new recommendations based on the best evidence available, clinical experience and patient perspectives.

Patients/Methods

Five meetings of the guideline development group (GDG) were conducted with participation of 23 international experts and 13 professional societies as well as a patient support group. Relevant key questions were identified by interdisciplinary consensus procedure. The methodology by SIGN (Scottish Intercollegiate Guideline Network) and GRADE (Grading of Recommendations, Assessment, Development and Evaluation) were used for systematic literature evaluation and grading of recommendations. A structured consensus process guided by moderation was conducted to achieve formal consensus. The manuscript was revised by external experts and legitimised by all participating professional societies as well as the E-IMD consortium (European Network and Registry for intoxication type metabolic diseases).

Results

A total of 24 recommendations on diagnostic procedures (n=4), metabolic maintenance treatment (n=5), emergency treatment (n=2), neurologic complications (n=2), vaccinations (n=1), disease education and transition (n=2) and clinical monitoring (n=9) were outlined. Consensus was achieved for all recommendations and was strong (>95%) in 21/24 of them. None of the previous recommendations has been proven invalid. Six new recommendations (#4,#13,#14,#19,#22 and #24) were formulated and one former 'statement' was changed to a recommendation (#8). All recommendations were classified as [certified (n = 2); modified (n = 15); new (n = 7)] in relation to the previous version.

Conclusion/Discussion

Newborn screening and adherence to treatment recommendations have led to significantly improved outcomes. For this third revision, new research findings, such as increasing evidence for the impact of treatment quality on outcome, evolving phenotypic variability and variant disease courses, long-term outcome, extra-neurological manifestations and the perspective of affected individuals have been implemented, and hopefully will be accepted and practiced. The GA1 guideline process demonstrates how continuous increase of levels of evidence and recommendations is facilitated by concomitant clinical trials and patient registries.

Posters

P02

Occurrence of Hyperprolactinemia and Prolactinoma in Inherited Disorders of Biogenic Amines

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Introduction

Dopamine deficiency in the brain is common to most of the inherited disorders of biogenic amines. Dopamine inhibits prolactin secretion from the lactotroph cells of the anterior pituitary. In dopamine deficiency, elevated serum prolactin level is occasionally used as peripheral marker. We have observed that some patients who presented persistently elevated prolactin levels despite adequate treatment with levodopa had pituitary microadenomas. Here we study the occurrence of pituitary hyperplasia/prolactinoma (PL) or levodopa-refractory hyperprolactinemia (LRHP) in individuals with inherited disorders of biogenic amines.

Patients/Methods

Acquisition of clinical, laboratory and radiological data was performed in the framework of the International Working Group on Neurotransmitter Related Disorders (iNTD). Here, we report the preliminary findings. Individuals with pituitary hyperplasia/prolactinoma or persistently elevated (> 50 ng/mL or >1000 mU/L) serum prolactin despite well-controlled clinical symptoms under therapy were included.

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Results

16 individuals (9 females, n total: 210) were reported having PL/LRHP: nine with 6-pyruvoyltetrahydropterin synthase, five with dihydropteridine reductase, and one each with DNAJC12 and tyrosine hydroxylase deficiency. 10 patients had pituitary hyperplasia/microadenoma in cranial MRI. Eight were treated with cabergoline, markedly decreasing serum prolactin levels. No symptoms related to thyroid or growth hormone deficiencies, or to the mass effect of the lesion were observed, but three female individuals had menstruation irregularities or puberty-related symptoms.

Conclusion/Discussion

We hereby report an increased incidence of PL/LRHP and a disproportionately high occurrence in tetrahydrobiopterin deficiencies, although this may be subject to detection and frequency bias. This observation may be related to long-term dopamine deficiency leading to autonomous lactotroph cells eventually forming a pituitary hyperplasia/prolactinoma. The lesions are often asymptomatic, not requiring specific treatment, but menstrual irregularities are common in females. This study underlines the importance of specific follow-up during puberty with focus on menstrual cycle and endocrinological abnormalities in individuals with biogenic amine disorders, especially in those with tetrahydrobiopterin deficiencies, and questions the relevance of monitoring serum prolactin levels.

Posters

P03

De novo missense variants in CLCN7 may cause a novel lysosomal storage disorder due to hyperacidification of lysosomes

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Introduction

An acidic pH is maintained within lysosomes to ensure proper function of the enzymes of this cell compartment. Key regulators of lysosomal pH are an ATP-driven proton pump and a Cl-/H+ antiporter encoded by CLCN7. Silencing of CLCN7 has been shown to severely impair lysosomal acidification and to result in the clinical picture of osteopetrosis. Only recently, two patients with heterozygosity for the same de novo gain-of-function variant were reported for the first time (Nicoli et al., Am. J. Hum. Genet. 2019) with hypopigmentation, organomegaly, and delayed myelination and development ("HOD").

Patients/Methods

Case studies of patients #3 and #4 with this novel entity.

Results

Patient #3, a blond boy now 5 years old, presented around 8 months of age with strabism, muscular hypotonia, and a primary psychomotor developmental disorder. Over time, he developed massively enlarged organs (liver, spleen, kidney with fully preserved function) due to generalized histiocytic storage of foamy material. Leukocytes also showed extreme vacuolization. Cerebral volume reduction and delayed myelination were seen on cMRI. Most recently, mild thickening of the left ventricular myocardium was observed. Chitotriosidase was extremely elevated (with normal oxysterols and lyso-SM-509); however, in vitro enzymatic studies in dried blood yielded normal results for all lysosomal enzymes studied. The clinical course is progressive (despite treatment with chloroquine known to increase lysosomal pH) and characterized by massively thickened bowel walls causing chronic impairment of intestinal transit with loss of protein and electrolytes, and repeated episodes of enterogenic infections. Diagnosis was established by trio exome analysis and detection of heterozygosity for the novel CLCN7 de novo variant p.(Lys285Thr).

Patient #4 is a boy who had died without diagnosis years ago with a very similar clinical picture. In a DNA sample from stored fibroblasts we detected heterozygosity for CLCN7 p.Tyr715Cys by Sanger sequencing, the variant known from patients #1 and #2.

Conclusion/Discussion

We present impressive clinical and histopathological findings from two independent cases with this novel lysosomal storage disease, which is undetectable by enzymatic assays and can be diagnosed only by targeted or untargeted genetic testing.

P04

ASS1 deficiency is associated with impaired neuronal differentiation in zebrafish larvae

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Introduction

Citrullinemia type 1 (CTLN1) is an autosomal recessive urea cycle disorder caused by deficiency of the cytosolic enzyme argininosuccinate synthetase 1 (ASS1) due to pathogenic variants in the *ASS1* gene on chromosome 9q34.11. Even though hyperammonemic encephalopathy induced by defective hepatic ureagenesis is considered the major pathomechanistic factor for neurocognitive impairment in CTLN1, a relevant subset of individuals presents with a neurodegenerative disease course and cognitive deterioration in the absence of hyperammonemic episodes, implying alternative pathomechanisms of neurological dysfunction.

Patients/Methods

We established a zebrafish model for CTLN1 by injection of translation-inhibiting morpholino (MO) in zebrafish embryos. Since ASS1 deficiency is not associated with accumulation of ammonia in zebrafish larvae, this model enabled the investigation of ammonia-independent effects of ASS1 dysfunction until 3 days-post-fertilization (dpf). Morphological and biochemical analyses were combined with whole mount in situ hybridization (WISH) and MO injection in transgenic zebrafish strains. Co-injection of human ASS1 mRNA served as specificity control.

Results

ASS1 is expressed in the central nervous system with a maximum at 1 dpf. MO-injected zebrafish larvae exhibited disorganized mesencephalic structures with neuronal cell loss due to a neuronal differentiation defect. Neuronal differentiation markers neurod1 and eleval3 were reduced in WISH with almost absent elavl3 expression at 1 dpf in the

transgenic zebrafish strain tg(elavl3:eGFP), while the neuronal transgene expression of tg(NBT/lyn:eGFP) was reduced until 3 dpf. Glial cell lines were not affected as indicated by the unaltered expression of gfap and olig2. Accumulation of L-citrulline did not account for the observed phenotype. Co-injection of the human ASS1 mRNA rescued the morphological and biochemical phenotype, confirming specificity of the obtained results including conserved ASS1 function across species.

Conclusion/Discussion

The present findings imply a novel (moonlighting) function of ASS1 in neuronal differentiation. Further delineation of the molecular effects of neuronal ASS1 dysfunction might open novel therapeutic avenues for CTLN1 in the future.

P05

Mild Hyperphenylalaninaemia (MHP) revisited – Systematic review and meta-analysis

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Introduction

Literature reports insufficient evidence to decide between cut-offs of >360 vs. >600 µmol/l phenylalanine (Phe) in blood for treatment of MHP. The range between >360 and 600 µmol/l was labelled as "grey zone". We aim to analyse evidence regarding the grey zone by comparing outcomes (intelligence, information processing, educational/professional career, clinical neurology, and emotional/behavioural problems) for the ranges ≤ 360 vs. >360 - 600 µmol/l.

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Patients/Methods

Systematic literature search identified 19 original articles (including n=448 subjects). Levels for SIGN evidence and study quality were assigned to original studies.

Results

Ten studies (n=210 subjects: 92 ≤ 360, 125 >360; SIGN levels 2++ to 3; moderate to high quality) report normal outcomes without differences between the two Phe ranges. Results of four studies (n=179: 52 ≤ 360, 65 >360, 12 unclear; SIGN levels 2- to 3; very low to low quality) are predominantly in the normal band, however, show some differences between the two Phe ranges. Four studies (n=100; SIGN levels 2- to 4; very low to moderate quality) do not allow to compare outcomes in the two Phe ranges. Correlation and/or regression coefficients between Phe and outcome variables in 10 studies cluster in two groups. In two studies (2++, moderate; 3, very low) correlations are high (-.69, -.56), in six studies (2+ - 2++, moderate) correlations are low (-.16 to +.01). Regression coefficients (IQ loss/60 µmol/l Phe) are extremely large (-4.7 to -3.0) in four studies (3, 2-, 2++; very low to moderate), but very small (-.3 to +.09) in five studies (2+, 2++; moderate to high).

Conclusion/Discussion

Evidence and quality levels are better for studies showing no differences between Phe ranges than for those reporting differences. Means of minimum and maximum Phe concentrations in regression studies are 216 and 600 µmol/l, excluding that small coefficients are due to reduced variance. The four extremely large coefficients (-4.7 to -3) are much higher than meta-analytic results in classical and mild phenylketonuria (-1.5 IQ points/60 µmol/l), raising doubts on their validity. Data indicate that the “grey zone” and 600 µmol/l as cut-off for treatment of MHP can be judged as safe.

Posters

P06

AICA Ribosiduria Presenting with Chorioretinal Atrophy and Intellectual Disability

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Introduction

Inborn errors of the tightly regulated process of purine metabolism result in severe syndromes of primarily neurological symptoms as well as manifestations in various other organ systems. AICA ribosiduria is caused by pathogenic variants in ATIC with subsequently impaired 5-aminoimidazole-4-carboxamide ribonucleotide formyltransferase / IMP cyclohydrolase, catalyzing the final steps of de novo purine synthesis. So far, only eight cases have been described in the literature, making it an exceedingly rare condition. The exact pathomechanism of the condition is debated, with evidence pointing towards toxic effects of accumulating AICA-riboside.

Patients/Methods

We present the case of 16-year-old boy who is the son of consanguineous parents. He presented with severe, progressive vision loss in addition to intellectual disability and focal seizures. Developmental status and intelligence were assessed using the Wechsler Intelligence Scale for Children – Fifth edition (WISC-V). Exome sequencing was performed in addition to biochemical work-up including analysis of purine metabolites by Liquid chromatography-tandem mass spectrometry (LC-MS/MS).

Results

Exome sequencing identified two variants – c.1277A>G (p.K426R) and c.642G>C (p.Q214H) – in ATIC (NM_004044). LC-MS/MS detected significantly elevated levels of AICA-riboside in multiple samples with a mean excretion of 59.17 ± 3.97 mmol/mol creatinine (reference: < 5 mmol/mol creatinine), confirming the diagnosis of AICA ribosiduria in the patient. Developmental testing revealed substantial intellectual disability with an overall IQ of 44 (90% confidence interval 42-51, percentile rank < 0.1). Ophthalmological examination demonstrated chorioretinal atrophy in optical coherence tomography.

Conclusion/Discussion

The reported patient adds to the phenotypic spectrum of AICA ribosiduria, presenting with a relatively mild manifestation of this ultra-rare condition. Currently ongoing research aims at identifying the underlying pathomechanism, exploring potential therapeutic avenues.

Posters

P07

What is a diagnosis worth? The MitoCope-study on the psychosocial experience of parents of children with a mitochondrial disease

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Introduction

Reaching a genetic diagnosis of a mitochondrial disease in a child is often perceived as "diagnostic odyssey". Additionally, after receiving a diagnosis, the parents face ongoing uncertainty: mitochondrial diseases show a little predictable and relentlessly progressive, individually heterogeneous course with no curative therapies available. Despite the awareness of this burden little is known if and how getting a genetic diagnosis impacts parental psychosocial experience and coping. Additionally nothing is known about the differences between fathers and mothers in this regard. This information however is crucial to improve the holistic management for families affected by mitochondrial diseases.

Patients/Methods

After ethical approval, we conducted a semi-structured interview study. Inclusion criteria: genetically proven mitochondrial disease, both parents available for separate interviews, parents fluent in German. The same interviewer conducted all interviews at a location of the parents' choice. These covered the following topics: demographic data (age, profession, income, distribution of care work) experiences and feelings regarding the diagnosis, changes experienced after getting the diagnosis concerning the topics: everyday life, access to financial support and therapies, connecting with other affected families, interaction with family and friends, attitude to prenatal diagnosis and further desire to have children. All interviews were recorded and transcribed. The data were analyzed manually and descriptive.

Results

Until now 10 families have been interviewed. The majority of parents felt relieved when finally knowing the cause of their child's symptoms but also felt emotionally burdened, since their hope for cure had been destroyed. The lack of treatment guidelines and the unpredictable future of their child continued fueling this uncertainty. Parents reacted and coped differently. Mothers mostly focused on their role as mother and did the majority of the care work. Whereas fathers sought to understand the disease pathomechanism and expressed concerns about the parental relationship.

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Conclusion/Discussion

Reaching a genetic diagnosis makes a difference for the affected families in many areas. Due to the mitochondrial diseases' nature, the parents remain burdened after the longed-for diagnosis. These data enhance our understanding of the families' needs and enable to improve the holistic management of families with (suspected) mitochondrial diseases during their journey.

P08

The interaction between pathogenic variants of intestinal sucrase-isomaltase and the functionally active enzyme results in hetero-complexes with reduced function and impaired intracellular trafficking

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Introduction

Congenital sucrase-isomaltase deficiency (CSID) is a rare genetic disorder characterized by malabsorption of starch and sucrose. CSID is caused by mutations in the SI gene that encodes SI, the major intestinal brush border enzyme, and leads to its dysfunction and impairs its intracellular trafficking. Malfunctioning of SI in CSID elicits symptoms such as severe osmotic diarrhea, abdominal cramps, vomiting and flatulence. Pathogenic SI gene variants (SIGVs) identified in CSID are also associated with irritable bowel syndrome (IBS), a common functional gastrointestinal disorder. In this study, the impact of severe SIGVs found in heterozygote carriers on the function and trafficking of functionally active SI has been investigated.

Patients/Methods

FLAG-tagged SI wild type ($SI^{WT\text{-}FLAG}$) was co-expressed with HA-tagged SI mutants ($SI^{G1073D\text{-}HA}$, $SI^{V577G\text{-}HA}$, and $SI^{R1124X\text{-}HA}$) or HA-tagged SI wild type ($SI^{WT\text{-}HA}$) in COS-1 cells. The interaction was examined in co-immunoprecipitations and the effects of the mutations on the trafficking, function and cellular localization of the resulting SI heterodimers were assessed.

Posters

Results

$SI^{G1073D\text{-}HA}$, $SI^{V577G\text{-}HA}$, and $SI^{R1124X\text{-}HA}$ interacted avidly with $SI^{WT\text{-}FLAG}$ forming heterodimers that revealed altered intracellular trafficking and were ultimately retained in the endoplasmic reticulum (ER) or the Golgi apparatus. Furthermore, the enzymatic activities of the heterodimers were substantially reduced as compared to interacting wild type forms $SI^{WT\text{-}HA}$ and $SI^{WT\text{-}FLAG}$. Immunofluorescence images confirmed the localization of the SI^{WT}/ SI^{mutant} heterodimers in the ER, while $SI^{WT\text{-}FLAG}$/ $SI^{WT\text{-}HA}$ proteins were localized at the cell surface.

Conclusion/Discussion

This in vitro cellular model system of heterozygotes in CSID and IBS shows that SI mutants can negatively impact SI^{WT} by forming dysfunctional heterodimers that are retained in the ER or Golgi apparatus depending on their maturation state. These interactions can be explained by a kin recognition mechanism similar to the Golgi retained glycosyltransferases or due to ER molecular chaperones that bind the SI^{WT}/ SI^{mutant} heterodimers and impair their overall trafficking and function. The current study demonstrates potential for SIGVs to act in a semi-dominant fashion via sequestration of the SI^{WT} copy into an inactive form of the enzymatic heterodimer and provides novel insights into the potential role of heterozygosity in the pathophysiology of CSID and IBS.

Posters

P09

PLPBP variants cause a well-treatable vitamin B6-dependent epilepsy: three cases with a favorable course

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Introduction

PLPBP (formerly referred to as PROSC) encodes a pyridoxal-5′-phosphate (PLP)-binding protein that regulates intracellular PLP homeostasis. Biallelic pathogenic PLPBP variants are a rare cause of early-onset epilepsy (OMIM 617290) readily treatable with vitamin B6, but most patients show delayed psychomotor development.

Patients/Methods

Case series of 3 patients with PLPBP variants, two with early and one with late pyridoxine treatment.

Results

Case 1 is a 21-years-old male from Bosnia with normal motor milestones, moderately delayed speech development, learning difficulties in school age, and an IQ of 85. First seizures were observed at 3 weeks with a burst-suppression EEG pattern and were treated with phe-nobarbital. Later, clusters of focal and generalized seizures occurred without specific triggers. Numerous antiepileptic drugs were used over the years. During adolescence, psychiatric symptoms such as anxiety, confusion and hallucinations appeared. At age 16, propofol, thio-pental, and midazolam were required to treat status epilepticus. Rapid whole exome sequenc-ing (WES) revealed homozygosity for a novel PLPBP missense variant. Pyridoxine treatment resulted in complete recovery; the patient remained seizure-free and without neurological abnormalities with pyridoxine as the only medication, while psychiatric symptoms improved. Brain MRI was always normal.

Cases 2 and 3, a 13-years-old boy and a 15 years-old-girl, are siblings from Syria, born to consanguineous parents. Both had their first seizures during the second week of life and re-sponded well to pyridoxine. Both showed mild development delay at the beginning but no def-icits later on. They suffered from recurrent febrile seizures until school age under pyridoxine monotherapy. Both remained seizure-free for many years and showed an unremarkable brain MRI. Recently, after treatment interruption due to a virual infection with vomiting and diarrhea, the boy had a seizure. WES showed homozygosity for a novel PLPBP variant.

In all 3 cases, pipecolic acid, AASA und P6C in plasma and urine showed normal results.

Conclusion/Discussion

Our three cases underline that PLPBP deficiency is a well-treatable epilepsy. Therefore, it is very important to consider PLPBP variants as a cause of epilepsy and to make a treatment trial with pyridoxine even if metabolic work-up is normal and regardless of the pa-tient's age.

P10

Effect of hexacosanoic acid (C26:0) on survival, mitochondrial function and oxidative stress in X-linked adrenoleukodystrophy fibroblasts

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Introduction

Very long chain fatty acids (VLCFA) accumulation is the major biochemical marker in X-linked adrenoleukodystrophy (X-ALD) and results from dysfunctional peroxisomal ABCD1 protein caused by *ABCD1* gene mutations. The clinical manifestation is variable, ranging from asymptomatic carriers to severe childhood cerebral ALD. Interestingly, there is no correlation between VLCFA plasma levels and clinical presentation, and dietary correction had no effect on clinical course. While the cytotoxicity of VLCFA has been established, the additional factors leading to the onset and progression of clinical symptoms remain unknown. Elevated oxidative stress and signs of mitochondrial dysfunction are present in X-ALD cells and tissues, with yet unclear significance. This study aims to elucidate the interplay of excess VLCFA, mitochondrial function and oxidative stress in X-ALD fibroblasts.

Patients/Methods

Effect of hexacosanoic acid (C26:0) on survival, mitochondrial function and oxidative stress was analyzed in X-ALD and healthy control fibroblasts. Media containing C26:0 in different concentrations was applied for 24 hours prior to experiments. Survival was assessed with the colorimetric MTT assay. Mitochondrial function was analyzed by mitochondrial stress assay with the Seahorse XFe24 flux analyzer. Reactive oxygen species (ROS) were quantified with the 2',7'-dichlorofluorescein diacetate (H_2DCFDA) assay.

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Results

C26:0 treatment causes dose-dependent cell death after 24 hours in all cell lines, with X-ALD fibroblasts being particularly sensitive. ROS levels are elevated, and mitochondrial function is impaired by C26:0 treatment in all cell lines, aggravated at higher C26:0 concentration. However, the effect is less pronounced in X-ALD cell lines compared to healthy control. Spare respiratory capacity increases in all cell lines after C26:0 treatment.

Conclusion/Discussion

The results confirm C26:0 cytotoxicity and the ability to induce oxidative stress. C26:0 impairs mitochondrial function. Surprisingly, this effect was more pronounced in healthy fibroblasts. Whether the lower C26:0 effect on mitochondrial function in X-ALD fibroblasts can be explained by a potential mitochondrial dysfunction, compensatory mechanisms or a preexisting stress condition needs further investigation. Our results extend current knowledge of VLCFA impact on oxidative stress and mitochondrial function in X-ALD and contribute to a better understanding of potential pathogenic mechanisms.

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P11

Prenatal Trio-Exome-Analysis: A routine diagnostic tool with high diagnostic yield

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Introduction

Routine prenatal diagnostic involves NIPT, ultrasound test and cytogenetic investigation after invasive sampling (CNV, amniocentesis) in our days. Recently trio exome analysis is done in addition to find a genetic explanation for ultrasound abnormalities.

Patients/Methods

Prenatal trio exome analysis indicated by worrisome ultrasound findings after exclusion of abnormal karyotype or in parallel to cytogenetic investigation. Reported were pathogenic or likely pathogenic classified variants.

Results

Between August 2021 and November 2022 we performed a total of 310 prenatal trio exome analyses due to sonographic fetal abnormalities with an average turnaround time of 13.2 days. Most frequent leading symptoms were increased nuchal translucency (n=92), heart (n=68), skeletal (n=54) and brain (n=40) abnormalities.

86 cases of 310 trios (27.7%) showed likely pathogenic (class 4) or pathogenic (class 5) single nucleotide variants or small insertions or deletions (n=70) or copy number variants (n=16) as an explanation for the sonographic abnormalities. In several additional cases, likely pathogenic or pathogenic findings were reported which could not explain the phenotype. In 24 cases with increased nuchal translucency (22%), in 17 cases with heart abnormalities (25%), in 20 cases with skeletal abnormalities (37%) and in 9 cases with brain abnormalities (23%) positive results could be given. Most pathogenic variants found were located in structural or regulatory genes. Some genes were reported several times in connection with the ultrasound findings, for example COL1A1 (osteogenesis imperfecta 4x), RAF1 (noonan syndrome 4x), FGFR3 (achondroplasia, 3x). We also found metabolic diseases, for example Morbus pompe (GAA, compound heterozygous).

48 of the variants occurred de novo, 36 were inherited. 60 of the diseases we found were autosomal dominant. Additionally, we detected 22 autosomal recessive and 3 X-linked diseases. We reported 62 heterozygous, 16 homozygous, 5 hemizygous cases and 3 compound heterozygous cases.

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Conclusion/Discussion

Prenatal trio exome analysis is a powerful method that provides a substantial contribution to prenatal diagnostics with an additional detection rate of around 28% to cases with sonographic abnormalities. The high percentage of de novo variants detected here leads to the assumption that many pathogenic variants would probably have escaped detection using singleton instead of trio exome analysis.

P12

Pregnancy, delivery, and postpartum period in NBAS-associated disease

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Introduction

Biallelic pathogenic variants affecting the Sec39 domain of the neuroblastoma amplified sequence (*NBAS*) gene are associated with a primary hepatic phenotype characterized by recurrent acute liver failure, named infantile liver failure syndrome type 2 (ILFS2). Affected individuals experience life-threatening liver failure, most likely triggered by febrile infections. Pregnancy, delivery, and the postpartum period entail an increased risk of fever and are well known triggers of decompensation in different inherited metabolic diseases.

Patients/Methods

In a multidisciplinary team, we developed a strategy for the management of pregnant women with ILFS2 and studied the course of two pregnancies in an affected mother homozygous for the *NBAS* variant c.2708T>G, p.(Leu903Arg).

Results

No complications associated with ILFS2 were observed during both pregnancies. Two healthy boys were born by cesarean section. Prolonged labor, epidural analgesia, and breastfeeding were avoided in order to reduce the risk of fever and febrile infections. Maternal body temperature was closely monitored; in case of elevated body temperature, antipyretic treatment (acetaminophen, metamizole) was given immediately. Alanine and aspartate aminotransferases as well as liver function remained normal throughout the whole observation period.

Conclusion/Discussion

This is the first report on successful pregnancy and delivery in a woman with NBAS-associated disease. Avoidance of potential risk factors, careful medical assistance and monitoring by an interdisciplinary team of gynecologists, anesthesiologists, and metabolic experts enabled safe pregnancy and childbirth in a woman with ILFS2.

P13

Adult neuropsychiatric manifestation of Hartnups' disease with a novel SLCA6A19 variant: a case report

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Introduction

Adults suffering from inborn metabolic diseases are often missed in routine diagnostic procedures due to a low level of awareness that these inherited disorders may present at any age during life.

Patients/Methods

We report a 26-year-old female originally admitted for psychiatric evaluation of an apparent acute exacerbation of an anxiety disorder, previously diagnosed. Over time, the course was consistent with catatonic psychosis, which was treated by electroconvulsive treatment. When she experienced additional rapid somatic deterioration, she was referred to our neurology department. On referral, she presented with reduced level of consciousness, mutism with no targeted movements, obvious anxiety and tetraspasticity; general examination was remarkable for eczema and cachexia (BMI 19.0 kg*m-2). While EEG was non-specifically altered, repeat brain MRI showed progressive atrophy and leukoencephalopathy. EMG/ENG was consistent with lower motor neuron dysfunction. Due to her age and speed of decline, we initially assumed autoimmune encephalitis and performed plasma exchange, followed by high-dose glucocorticoid and intravenous immune globuline therapy. As repeated CSF analyses did not reveal findings compatible with CNS inflammation (absence of pleocytosis, intrathecal immunoglobuline synthesis, CSF specific oligoclonal bands or neuronal autoantibodies), metabolic and genetic testing was performed. Metabolic workup revealed hyperaminociduria while neutral

amino acids in plasma were depleted, and tryptophane was undetectable. Whole-exome sequencing revealed compound heterozygosity in the SLC6A19 gene, with one allele harboring a known pathogenic variant [c.718C>T, p.(Arg240*)] and the other a variant of unknown significance [c.170G>A,p.(Arg57His)]. Assuming Hartnup's disease, we offered a high-protein diet (3 g/kg body weight/d) via a nasogastric tube and supplemented niacine (100 mg twice daily). On this treatment, the patient´s condition improved considerably within one week, i.e. she started to drink from a cup and eat prepared food, speak short sentences with increasing coherency, spending several hours in a rehab chair. Plasma levels of most neutral amino acids rose to the lower range of normal. The further course will be reported.

Conclusion/Discussion

Metabolic workup and whole exome sequencing are strongly recommended in patients with rapidly progressive psychiatric diseases, especially when classic standard treatment fails.

P14

ISCA2 leukencephalopathy in a 3-month-old boy

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Introduction

ISCA2 (iron-sulfur cluster assembly-2) gene defects, first reported in 2015, cause autosomal recessive early onset mitochondrial leukencephalopathy or multiple mitochondrial dysfunction syndrome type 4. Up to now, 24 cases were described, most of them in Saudi Arabia and one from an Italian family. Typically, affected patients have a normal pregnancy and adaptation. The first weeks or months of life they have an adequate development, followed by a rapidly progressing neurological decay. The (eye-)movement disorder (vertical nystagm) and neuroradiology alterations (cystic lesions in brain stem) are pathognomonic for ISCA2. Most patients have died in the first months. Up to now no curative treatment is known. Therapy is limited to alleviate symptoms.

Patients/Methods

We report the first Austrian ISCA2 patient. The boy is the first child of Austrian non-consanguineous parents. Pregnancy and birth were uneventful. First clinical signs (vertical nystagmus, developmental stagnation) were seen at age of three months, and first considered as part of SARS-CoV2-infection (COVID-19). However, symptoms persisted.

Results

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A whole body MRI (to exclude a paraneoplastic syndrome) showed a symmetric leukencephalopathy and no indicator for a tumor or an inflammatory process. Laboratory parameters in blood and cerebral-spinal fluid showed a slight increase in lactate concentrations in blood and cerebral-spinal fluid. The alanine/lysine ratio was also slightly increased, pointing to a mitochondrial malfunction. Exome sequencing searching for the terms: eye movement disorder and leukencephalopathy revealed a homozygous mutation in the ISCA2 gene , both parents are carriers. The patient was in a palliative setting with supportive care and died at age 8 months.

Conclusion/Discussion

We report the first known Austrian patient with leukencephalopathy caused by mutation in ISCA2 gene. However rare, in the evaluation of sudden neurological decay, with eye movement disorder (vertical nystagm) and leukenecephalopathy, ISCA2 leukencephalopathy is a possible diagnosis. This case has prompted us to collect further cases to better characterize the pathophysiology of the disease.

P15

Left and right ventricular dysfunction in propionic acidemia – results of a single-center cross-sectional study

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Introduction

Propionic acidemia (PA) is an organic aciduria caused by deficiency of propionyl-CoA carboxylase. Besides e.g., progressive neuromuscular disease, left ventricular (LV) dysfunction is common, leading to cardiomyopathy or acute heart failure, which strongly contributes to mortality in PA. We sought to assess echocardiographic parameters of left and right ventricular (RV) systolic and diastolic function that indicate early signs of cardiac disease manifestation in PA.

Patients/Methods

This is a cross-sectional single-center study conducted at a Tertiary Medical Care Center. Systolic and diastolic functional parameters of the LV and RV were assessed by echocardiography: LV fractional shortening (FS), LV ejection fraction (EF), mitral annular plane

systolic excursion (MAPSE), LV-global longitudinal strain (GLS), mitral valve (MV) E/A ratio, MV E/e', LV-myocardial performance index (LV-MPI), MV deceleration time (DT-E), tricuspid annular plane systolic excursion (TAPSE), RV-global longitudinal strain (GLS)/-free wall strain (FWS), RV-fractional area of change (FAC), tricuspid valve (TV) S', RV-myocardial performance index (RV-MPI), TV E/A, TV e'/a', and TV E/e'. Besides descriptive analyses we assessed frequency, onset, and combinations of echocardiographic parameters.

Results

N=18 patients with PA were enrolled (mean age at assessment 13.1 years). Abnormal parameters were LV-GLS (72.2%) LV-EF (61.1%), MAPSE (50%), MV E/e' (44.4%), LV-MPI (33.3%), LV-FS (33.3%), MV E/A (27.8%), TV S' (16.7%), TAPSE (11.1%), RV-GLS/FWS (11.1%), TV E/A (16.7%), and TV E/e' (33.3%). The most prevalent combinations of pathological parameters were MAPSE+LV-GLS, LV-EF+LV-GLS, TV E/A+TV E/e', and TAPSE+RV S'. With age, the probability of developing abnormal LV/RV function increases.

Conclusion/Discussion

We demonstrate a high rate of cardiac disease manifestation in PA, higher than in all previous studies regarding LV dysfunction in PA, where only LV-FS was measured (FS abnormal in 9-40%). LV-GLS seems to be a robust parameter to indicate early cardiac disease manifestation, which is shown here for the first time in literature for this disease. In particular systolic LV dysfunction is more often found than RV dysfunction. It remains to be evaluated, whether earlier detection of cardiac disease in PA leads to improved outcome, e.g., by earlier implementation of cardiac therapies or liver transplantation, which can reverse cardiomyopathy in PA.

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P16

Glutaric acidemia type-1: Therapeutic strategies in a mouse model

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Introduction

Glutaric aciduria type-1 (GA1) is a rare inherited disease affecting newborns caused by a deficiency of glutaryl-CoA dehydrogenase (GCDH). Despite dietary treatments, one-third of patients still develop chronic kidney disease and white matter changes. To address this challenge, we aim to target enzymes upstream of GCDH in the L-lysine degradation pathway in a mouse model.

GCDH is a mitochondrial enzyme of the L-lysine, -hydroxylysine, and -tryptophan catabolism. Its depletion leads to a neurotoxic accumulation of glutaric acid and related metabolites. Current treatment consists of a low-lysine diet, arginine, and carnitine supplementation. To improve this treatment, we chose AASS and AADAT upstream of GCDH as potential therapeutic targets since their deletion causes benign or no phenotype.

Patients/Methods

To evaluate this aim, the GA1 mouse model (GCDH-/-), the GA1 rescued mouse models (GCDH-/-/AASS-/, GCDH-/-/AADAT-/-), and control wild-type mice are analyzed. Mass spectrometry is used to screen for metabolite changes in body fluids. Western blots and immunohistochemistry are performed on extracted organs to check for morphological changes.

Results

Our preliminary data confirm the efficacy of the GA1 mouse model, where the concentrations of the analyzed metabolites increased in GCDH-/- mice compared to control mice. Moreover, we show a lack of GCDH protein concentration in diseased mice compared to the control mice in various organs. However, we found a different pattern of GCDH expression while comparing two mice backgrounds.

Conclusion/Discussion

We envisage rescuing the phenotype in GA1 through the additional knock-outs. Ultimately, we hope to translate these insights into a potential therapeutic approach for GA1 patients.

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