APS 2022

35th Annual Conference and Seminar

APS ARBEITSGEMEINSCHAFT FÜR PÄDIATRISCHE STOFFWECHSELSTÖRUNGEN

KASSEL /// 2022

October 19-22, 2022
Kongress Palais Kassel

Content

Welcome

Welcome to Kassel!
Welcome to the 35th Annual Meeting of the APS!

This year's scientific program has its focus on hepatic glycogen storage diseases, a group of inborn errors of metabolism with impaired build-up or breakdown of glycogen in the liver.

We have invited national and international experts to share their scientific and clinical experiences. The various scientific sessions will highlight the clinical phenotypes, insights into pathophysiological mechanisms, new therapeutic approaches and the reality of patients living with a hepatic glycogen storage disease.

We are looking forward to lively discussions and an intensive scientific exchange!

Prof. Dr. med. Sarah Grünert
Prof. Dr. med. René Santer

Co-Presidents of APS 2022

Schedule

	Wednesday, October 19, 2022	
18:30-20:00	Satellite Symposium - supported by Sanofi-Aventis Deutschland GmbH	**Gesellschaftssaal**
19:00-20:00	Satellite Symposium - supported by Vitaflo Deutschland GmbH	**Bankettsaal**
from 20:00	Get Together with Poster Walk	**Festsaal**
	Thursday, October 20, 2022	
08:30 - 15:00	**APS Annual Conference**	**Blauer Saal**
15:30 - 17:00	APS General Meeting	**Blauer Saal**
17:15 - 19:15	Social Event (City Tour)	**-**
from 19:30	APS Dinner	**Herkules Terrassen**
	Friday, October 21, 2022	
08:30-13:20	**APS Annual Conference**	**Blauer Saal**
13:30-14:20	Junge Stoffwechsel-Medizin	**Blauer Saal**
14:30-19:15	APS Seminar	**Blauer Saal**
	Saturday, October 22, 2022	
08:30 - 15:15	APS Seminar	**Gesellschaftssaal**

Program

Wednesday, October 19, 2022

18:30-20:00 | Gesellschaftssaal

Satellite Symposium
- supported by Sanofi-Aventis Deutschland GmbH

sanofi

30 Jahre Erfolgsgeschichte der Enzymersatztherapie (ERT)
Chair: Claus Niederau, Oberhausen

18:45-19:05 Ursache unklarer Symptome? ASMD - Eine weitere Indikation im Portfolio einer seltenen Erkrankung
Natalie Weinhold, Berlin

19:05-19:40 Erste kausale Therapie mit Olipudase alfa
Eugen Mengel, Hochheim

19:40-20:00 Gemeinsame Diskussion & Ausblick

in parallel with

19:00-20:00 | Bankettsaal

Satellite Symposium
- supported by Vitaflo Deutschland GmbH

Vitaflo
Enhancing Lives Together

Ketotische Glykogenosen: Grundlagen und Behandlung
Ulrike Steuerwald, Tórshavn/Färöer

from 20:00 Get together with poster walk
Festsaal

Notes

Program

Thursday, October 20, 2022

Blauer Saal

08:30-08:40 **Welcome**
Sarah Grünert, Freiburg

08:40-10:10 **Hepatic GSDs: Clinical overview**
Chair: Gwendolyn Gramer, Hamburg & Chris Mühlhausen, Göttingen

08:40-09:15 The phenotypic spectrum of hepatic GSDs in children: from symptom to diagnosis
René Santer, Hamburg

09:15-09:45 Aging with a hepatic GSD - - - complications in adulthood
Monika Williams, Chapel Hill, NC, USA

09:45-10:10 Continous glucose monitoring in patients with hepatic GSDs
Terry Derks, Groningen, NL

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

10:40-12:30 **Understanding pathophysiological mechanisms**
Chair: Eva Thimm, Düsseldorf & Stefan Kölker, Heidelberg

10:40-11:10 Glycogen metabolism and its genetic defects
Emile van Schaftingen, Brussels, B

11:10-11:40 Pathophysiological mechanism of neutropenia in GSD Ib
Maria Veiga da Cunha, Brussels, B

11:40-12:05 Discovering new pathways in GSD type 1
Maaike Oosterveer, Groningen, NL

12:05-12:30 Assessment of endogenous glucose production in glycogen storage disease type I using stable isotopes
Alessandro Rossi, Naples, I

12:30 - 13:45 **Break with Poster-Lunch | Industrial Exhibition**

Program

Thursday, October 20, 2022

13:45-15.00 **Free Communications**
Chair: Ute Spiekerkötter, Freiburg & Ralf Husain, Jena

Blauer Saal

FC01-01 First stereotactic application of eladocagene exuparvovec into the putamen of a 3-year-old AADC-patient in Germany
Stine Christ, Heidelberg

FC01-02 *Rosa canina L.* extract can normalize the lipid profile and protein trafficking of various Niemann-Pick C1 gene mutations
Dalande Wanes, Hannover

FC01-03 Pathomechanism of CALFAN syndrome
Tal Dattner, Heidelberg

FC01-04 Subdural hematoma in glutaric aciduria type 1: High excreters are prone to incidental SDH despite newborn screening
Nikolas Boy, Heidelberg

FC01-05 Analysis of emotional & cognitive resources of patients with hyperphenylalaninemia (HPA)
Anne Tomm, Leipzig

FC01-06 Impact of pregnancy planning and preconceptual dietary training on metabolic control and offspring's outcome in phenylketonuria
Sven Garbade, Heidelberg

FC01-07 Changes in the care of adult PKU patients due to the COVID-19 pandemic: a retrospective review of the past 2 pandemic years.
Jan-Philipp Köhler, Düsseldorf

15:00-15:30 **Coffee Break | Posters | Industrial Exhibition**

15:30-17:00 **APS General Meeting**

17:15-19:15 **Social Event (City Tour)**

from 19:30 **APS Dinner**
Herkules Terrassen

Program

Friday, October 21, 2022

08:30-09:45 **Free Communications II**
Chair: Amelie Lotz-Havla, München & Peter Freisinger, Reutlingen

Blauer Saal

FC02-01 aRgus: a versatile tool for variant visualization and advanced prediction score modeling in inherited metabolic diseases
Julian Schröter, Heidelberg

FC02-02 A network medicine approach identifies key TCA cycle enzymes as potential therapeutic targets in organic acidemias
Zina Piper, Hamburg

FC02-03 Sudden neonatal death in individuals with medium-chain acyl-coenzyme A dehydrogenase deficiency, 2005-2021 in Germany: limit of newborn screening
Ulrike Mütze, Heidelberg

FC02-04 Feasibility of glycosylation analysis from newborn screening cards: a case series
Julien H. Park, Münster

FC02-05 Metabolic profiling and mitochondrial function in hepatic glycogen storage diseases- a fibroblast study
Jule Theimer, Freiburg

FC02-06 Heterozygosity for glycogen storage disease type IIIa might add to the risk for developing type 2 diabetes
Ulrike Steuerwald, Tórshavn, Faroe Islands

FC02-07 Evaluation of vascular dysfunction and risk of atherosclerosis in patients with glycogen storage disease type I
Johannes Schmitt, Freiburg

09:45-10:15 **Coffee Break | Posters | Industrial Exhibition**

Program

Friday, October 21, 2022

10:15-11:15 | **Living with a hepatic GSD**
Chair: Dorothea Haas, Heidelberg &
Monika Williams, Chapel Hill, NC, USA

Blauer Saal

10:15-10:45 | Challenges and opportunities of living with a hepatic GSD
G. K., Stuttgart

10:45-11:15 | Priorty setting partnership for glycogen storage diseases: cooperation of doctors and patients
Ute Stachelhaus, Gelsenkirchen
Terry Derks, Groningen, NL

11:15-11:45 | **Coffee Break | Posters | Industrial Exhibition**

11:45-13:05 | **Treating Hepatic GSDs: new approaches**
Chair: Ulrike Mütze, Heidelberg & Johannes Häberle, Zurich, CH

11:45-12:10 | Starch treatment in hepatic glycogen storage disorders
Helen Mundy, London, UK

12:10-12:35 | SGLT2 inhibitors in neutropenia of GSD1b
Saskia Wortmann, Salzburg, A

12:35-13:05 | The different types of gene therapy in hepatic GSDs
Priya S. Kishnani, Durham, NC, USA

13:05-13:20 | **Prizes, Farewell, Invitation for APS 2023**

13:30-14:20 | **Junge Stoffwechselmedizin (JSM)**
Blauer Saal

from 14:30 | **APS Seminar**
Blauer Saal

Programm APS Stoffwechselseminar

Freitag, 21. Oktober 2022

Blauer Saal

Vorsitz: R. Santer, Hamburg

14:30 **Eröffnung**
R. Santer, Hamburg

14:30 **Die neuen Konsensus-Empfehlungen zur Vitamin B6-abhängigen Epilepsie**
B. Plecko, Graz, A

15:00 **Update Mitochondriopathien**
F. Distelmaier, Düsseldorf

15:30-16:00 **Kaffeepause**

Vorsitz: P. Freisinger, Reutlingen

16:00 **Fallseminar „Der interessante Stoffwechselfall"**

17:15 **Gruppenarbeit POL-Fall 1**
P. Freisinger, Reutlingen
S. Grünert, Freiburg
U. Mütze, Heidelberg
R. Santer, Hamburg

18:30 **Evening Lecture: Impact of CoViD-19 on patients with metabolic disorders**
M. Scarpa, Udine, I

19:15 **Ende Tag 1**

Programm APS Stoffwechselseminar

Samstag, 22. Oktober 2022

Gesellschaftssaal

Vorsitz: S. Grünert, Freiburg

08:30 **Langzeit-Verlauf von Patienten mit im Neugeborenen-Screening identifizierten angeborenen Stoffwechselstörungen**
U. Mütze, Heidelberg

09:00 **Augenbefunde bei angeborenen Stoffwechselstörungen**
S. Dulz, Hamburg

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

10:00 **Gruppenarbeit POL-Fall 2**
P. Freisinger, Reutlingen
S. Grünert, Freiburg
U. Mütze, Heidelberg
R. Santer, Hamburg

11:15 **Update Glykogenosen**
S. Grünert, Freiburg
S. Rosenbaum-Fabian, Freiburg
R. Santer, Hamburg

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

13:15 **Patienten-Seminar: Glykogenspeicherkrankheiten**
Gruppenarbeit
P. Freisinger, Reutlingen
S. Grünert, Freiburg
U. Mütze, Heidelberg
R. Santer, Hamburg

14:15 **Präsentation der Gruppenarbeit mit Fallvorstellung und Diskussion**
Moderation: *S. Grünert, Freiburg & R. Santer, Hamburg*

15:15 **Schlussbemerkungen und Verabschiedung**
R. Santer, Hamburg

15:20 **Ende Tag 2**

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 October 18, 2022 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.

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 (including dinner and Program)

Registration for the APS Annual Conference	**by October 1st**	**from October 2nd**
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.

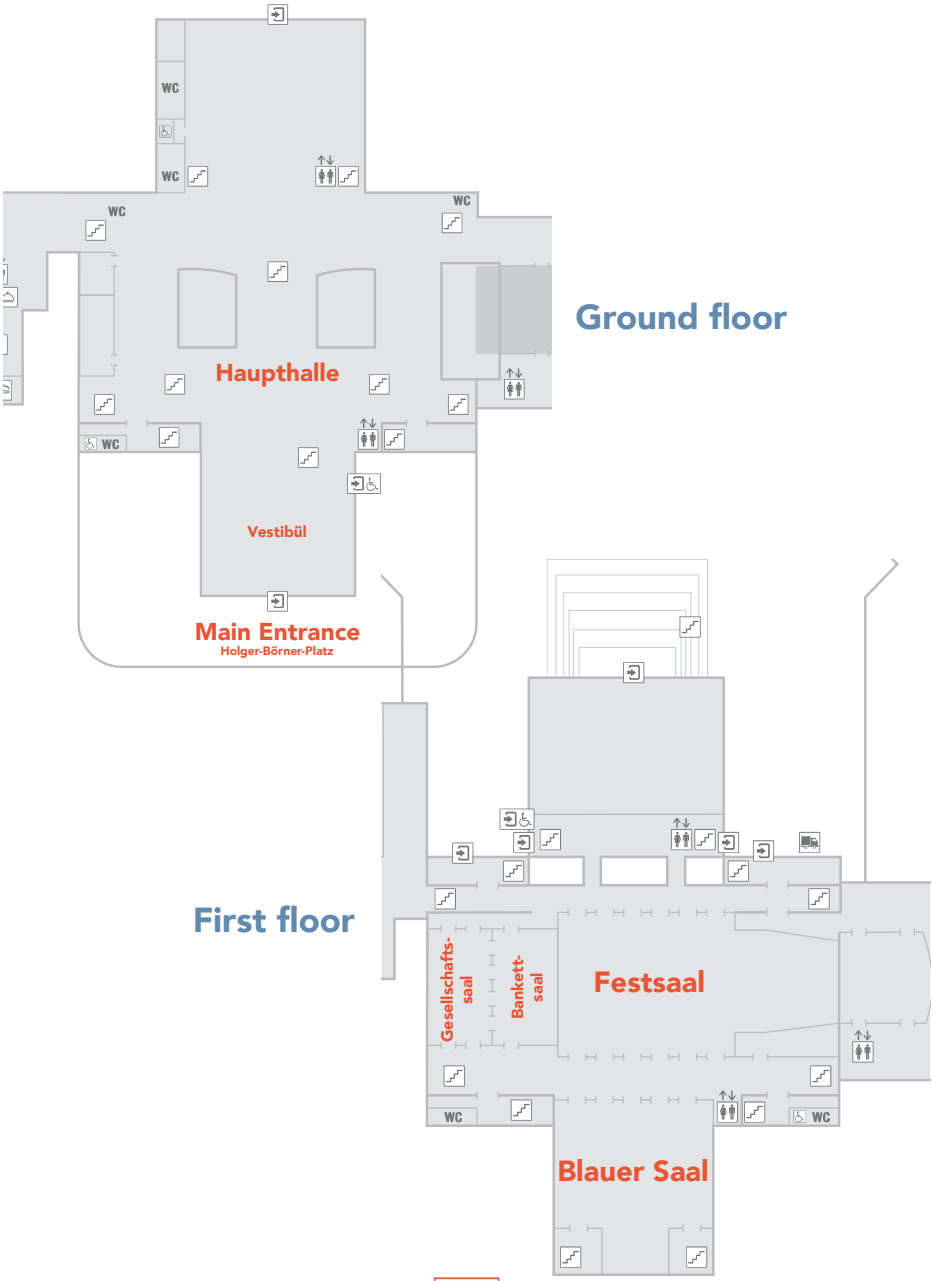
Please register online at www.events.aps-med.de.

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

Wilhelmshöhe train station to Kongress Palais

Tram 4 in the direction of Kaufungen-Papierfabrik
4 min, 3 stops to Kassel Kongress Palais/Stadthalle
Alternatives every 15 minutes
Obligation to wear a mouth-nose-covering

Site map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Festsaal
WC
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Blauer Saal

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	Summe	137.000,-

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)

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Training points

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

Abstracts

Free Communications

FC01-01

First stereotactic application of eladocagene exuparvovec into the putamen of a 3-year-old AADC-patient in Germany

Stine Christ[1], Oya Kuseyri Hübschmann[1], Elena Schnabel[1], Kathrin Jeltsch[1], Georg Friedrich Hoffmann[1], Karl Kiening[2], Thomas Opladen[1]

[1]*University Hospital Heidelberg, Children´s hospital, Division of Child Neurology and Metabolic Medicine*

[2]*University Hospital Heidelberg, Clinic for Neurosurgery, Germany*

Introduction: Aromatic L-amino acid decarboxylase deficiency (AADC) is a very rare autosomal-recessive inherited neurotransmitter disorder. In most cases it results in severe neurologic and vegetative impairments due to the impaired synthesis of dopamine and serotonin. The clinical effect of standard drug therapy consisting of dopamine agonists, monoamine oxidase inhibitors and vitamin B_6 is still very limited. The intracerebral application of eladocagene exuparvovec, an adeno-associated virus-2 (AAV-2) based gene therapy, is the first causal therapeutic approach.
Patient(s) and Methods: We present clinical and biochemical data of a 3-year-old girl with AADC deficiency, who was treated as the first patient in Germany with an intracerebral application of eladocagene exuparvovec within the framework of an individual healing attempt.
Results: The patient was diagnosed at the age of 6 months. She presented a severe phenotype with striking muscular hypotonia, lack of head control, very limited spontaneous movements, recurrent oculogyric crises, no active speech, feeding and sleeping disorders, excessive salvation and sweating as well as nasal congestion. In September 2021 eladocagene exuparvovec was administered bilaterally into the putamen by stereotactic surgery. Postoperative MRI scans showed correct placement of the vector and no indication for any perioperative complications. Two weeks after the intervention the patient developed dystonia and uncontrolled movements, requiring the administration of midazolam despite the reduction of the standard medication (apart from vitamin B_6). Regular monthly follow-ups revealed constant neurological progress. 4 months after application the child shows significant more and better coordinated spontaneous movements, has gained head control for 20 seconds, can lift the head in prone position and is more awake. Vegetative symptoms including sleeping disorders have improved while oculogyric crises and nasal congestion still appear nearly unchanged.
Conclusion/ Discussion: The gene therapy vector was safely administered in our patient. Regular follow-ups document significant neurological improvements. Gene therapy might be a milestone in the treatment of AADC deficiency. Treatment response is age-dependent, emphasizing the need for early diagnosis. Approval of eladocagene exuparvovec in the European Union is expected during 2022.

Free Communications

FC01-02

Rosa canina L. extract can normalize the lipid profile and protein trafficking of various Niemann-Pick C1 gene mutations

Dalanda Wanes[1], Sherin Al Aoua[1], Friederike Walters[1], Hadeel Shammas[2], Anibh M. Das[2], Hassan Y. Naim[1]

[1]*Department of Biochemistry, University of Veterinary Medicine Hannover*
[2]*Department of Paediatrics, Hannover Medical School*

Introduction: Niemann NPC1 or NPC2 gene mutations cause Pick type C (NPC) illness, an autosomal recessive lysosomal storage disorder. The NPC1 protein, which is primarily in charge of intracellular cholesterol mobilization, is essential for maintaining lipid homeostasis. Defective cholesterol mobilization and a buildup of unesterified cholesterol are linked to mutations in NPC1. N-butyldeoxynojirimycin or Miglustat is one of the few available treatments for NPC, and it is widely used in Europe. However, Miglustat's effectiveness varies across NPC patients, and it also has a number of adverse effects. The current study's objective is to identify an alternate therapy with fewer side effects. It has been demonstrated that Rosa canina L. methanol extract (RCME) improves protein trafficking and upholds cholesterol homeostasis.
Patient(s) and Methods: To evaluate the effects of RCME on the trafficking of NPC1 and cellular cholesterol contents, skin-derived fibroblasts from healthy donors or patients carrying homozygote, heterozygote, or compound heterozygote mutations, wild type Chinese hamster ovary (CHO-WT) cells, and NPC1 knocked out CHO (CT43) cells were used. Either RCME (100 g/ml), Miglustat (100 M), or both treatments were applied to the cells. Endoglycosidase H treatment was used to evaluate the trafficking of NPC1 between the endoplasmic reticulum (ER) and the Golgi, and HPLC was used to assess the total cholesterol level.
Results: Our findings showed that NPC1 mutant trafficking between the ER and the Golgi was significantly improved after RCME treatment. Significantly, the elevated cholesterol levels found in the patients' fibroblasts are significantly lowered after receiving RCME treatment, whereas the wild type cells maintained similiar cholesterol levels. Additionally, the RCME reduced or eliminated the cholesterol buildup seen in CT43 cells.
Conclusion/ Discussion: The adverse consequences of NPC1 gene mutations, including as defective NPC1 trafficking and increased cholesterol levels, can indeed be reversed by RCME. Together, these factors make quercetin and other RCME components promising therapeutic agents for NPC.

Free Communications

FC01-03
Pathomechanism of CALFAN syndrome

Tal Dattner[1], Sabine Jung-Klawitter[1], Petra Richter[1], Stefan Kölker[1], Georg F. Hoffmann[1], Christian Staufner[1], Dominic Lenz[1]

[1]Division of Child Neurology and Metabolic Medicine, Center for Pediatric and Adolescent Medicine, Heidelberg University Hospital, Heidelberg, Germany

Introduction: Recurrent acute liver failure (RALF) is a rare, but life-threatening event. In recent years, various "new" causes for RALF have been identified due to the growing accessibility of whole exome sequencing. One of these is CALFAN syndrome (cholestatic acute liver failure and variable neurodegeneration), caused by variants in SCYL1 presenting with fever triggered episodes of liver failure with onset in infancy. SCYL1 is known to play a role in intracellular trafficking and Golgi homeostasis, but so far, little is known about the disease pathomechanism in patients with pathogenic SCYL1 variants.
Patient(s) and Methods: Four patient fibroblast cell lines with different SCYL1 variants were available for comparison with two control fibroblast cell lines. We applied Western Blot to detect changes in protein level of SCYL1 and markers of the endoplasmic reticulum (ER) stress pathway. Immunofluorescence was used to examine protein (co-)localization of Collagen1-α1 with markers of various cellular compartments. Using Electron Microscopy, changes in the microstructure of cellular compartments were studied. To induce ER stress, temperature (40°C) as well as a chemical stressor – Tunicamycin blocking the n-glycosylation of proteins - were applied, respectively.
Results: Collagen1-α1 was retained in the ER of the patient cells. When studying the colocalization of Collagen1-α1 with various compartments of the autophagic pathway, we could not detect a clearance by autophagy; however patient cells showed increased levels of lysosomal vesicles. The microstructure of the Golgi-apparatus was changed, whereas the macrostructure appeared to be intact. When challenged by ER stress, patient cells showed an early activation of the IRE1 pathway, and cell death occurred at an earlier timepoint.
Conclusion/ Discussion: The observed Collagen1-α1 retention confirms a defect of cellular trafficking in CALFAN syndrome, potentially contributing to increased stress responses. Elevated temperature (mimicking fever) leads to a severe ER stress response and eventually apoptosis. We hypothesize that this may be the mechanism underlying hepatocytolysis (and thereby acute liver failure) during febrile infection in patients with CALFAN syndrome.

Free Communications

FC01-04

Subdural hematoma in glutaric aciduria type 1: High excreters are prone to incidental SDH despite newborn screening

Nikolas Boy[1], Alexander Mohr[2], Sven F. Garbade[1], Peter Freisinger[3], Jana Heringer-Seifert[1], Angelika Seitz[2], Stefan Kölker[1], Inga Harting[2]

[1]Division of Child Neurology and Metabolic Medicine, Centre for Child and Adolescent Medicine, University Hospital Heidelberg, Germany

[2]Department of Neuroradiology, Heidelberg University Hospital, Heidelberg, Germany

[3]Children's Hospital Reutlingen, Reutlingen, Germany

Introduction: Background: Glutaric aciduria type 1 (GA1), a neurometabolic disorder of L-lysine metabolism, is characterized by accumulation of neurotoxic metabolites and *acute-* or *insidious-onset* of striatal injury. Two biochemical subtypes (high and low excretors) have been arbitrarily defined. Incidence of subdural hematoma (SDH) was reported in up to 30% of symptomatic patients. A recent retrospective study found SDH in 4% of patients, but not in individuals identified by newborn screening (NBS).

Patient(s) and Methods: In order to investigate localization, frequency, age distribution, additional MR and clinical findings and potential risk factors of SDH in GA1, we systematically analyzed MRI scans in a cohort of GA1 individuals, of which 38 were prospectively followed after identification by newborn screening (NBS), while n=27 were diagnosed by targeted metabolic screening (TMS) and n=4 by high-risk family screening.

Results: A total of 168 MRIs of 69 patients (54 high and 15 low excreters; age at MRI 9 days – 73.8 years, median 3.2 years), were systematically reviewed. SDH was observed in eight high-excreting patients (NBS: n=6; TMS: n=2) imaged between 5.8 and 24.4 months, namely space-occupying SDH in two patients after minor accidental trauma and SDH as an incidental finding in six patients without trauma. In patients without trauma imaged at 3 to 30 months (n = 36, 25 NBS, 27/9 high/low excreters), incidence of SDH was 16.7% (16% in NBS). SDH was more common after acute (33.3%) than insidious onset of dystonia (14.3%) or in asymptomatic patients (5.9%). It was only found in patients with a high excreting phenotype and associated with wide frontoparietal CSF spaces and frontotemporal hypoplasia. High excreters were over-represented among patients with SDH (6/27 vs 0/9 low excreters), acute onset (10/12), and wide frontoparietal CSF spaces (16/19).

Conclusion/ Discussion: Incidental SDH occurs in approximately one in six patients with GA1 during a vulnerable period of late infancy and early childhood despite early identification by NBS and treatment. Greater risk of high excreters is morphologically associated with more frequent enlargement of external CSF spaces including frontotemporal hypoplasia, and may be furthered aggravated by more pronounced alterations of cerebral blood volume and venous pressure.

Free Communications

FC01-05

Analysis of emotional and cognitive resources of patients with hyperphenylalaninemia (HPA)

Anne Tomm[1], Alena G. Thiele[1], Wieland Kiess[1], Skadi Beblo[1]

[1]Hospital for Children and Adolescents, Centre for Pediatric Research Leipzig (CPL), Department of Women and Child Health, University Hospital, University of Leipzig, Germany

Introduction: Today the long-term outcome of early diagnosed and treated patients with hyperphenylalaninemia (HPA) is almost inconspicuous. Nevertheless, problems with implementation of therapy and accompanying increased blood phenylalanine (Phe) concentrations beyond the target range may become apparent, with negative consequences such as behavioral problems, nervousness and lack of concentration especially in adolescence. These in turn interact with each other demanding a conjoined consideration of all sub-areas. Patient-oriented approaches (analysis of executive functions, psychological distress/needs) are indispensable for generating a comprehensive idea of the holistic well-being of the patient and for taking preventive action.
Patient(s) and Methods: In this pilot study, 19 patients with HPA (10 f, 9m, age 10-17 years) could be included so far. We measured subjectively perceived resources (FRKJ/ FERUS), impairment by physical and psychological symptoms (CBCL, YSR, SCL-90, EDI2) and executive functions (convergent problem solving, working memory, flexibility, divided attention, Go/NoGo and incompatibility (TAP, ToL)) and compared it to normative data. Additionally, we collected sociodemographic data as well as biochemical and dietary parameters.
Results: Results of all patients are comparable with the normative data, but patients' individual test scores showed marked variability, especially in ToL (SD 21, range P2-P75%) and divided attention (SD 12, range T28-T66). A negative correlation between concurrent and long-term Phe-concentration and performance in ToL and divided attention could be revealed (ToL concurrent Phe r = -0.61, p =0 .01, long-term Phe r = -0.54, p = 0.03; divided attention concurrent Phe r=-0.53, p=0.04, long-term Phe r=-0.66, p=0.01). No relationship between concurrent or long-term Phe-concentration on global scales of emotional resources (concurrent Phe p=0.33, longterm Phe p=0.17) or mental stress (concurrent Phe p=0.51, longterm p=0.88) could be revealed.
Conclusion/ Discussion: The data show that long-term and concurrent metabolic control in patients with HPA exert influences on psychological and cognitive functions in very particular ways, which are not mirrored in global scales. Further data from a larger and age-differentiated cohort is required to unravel all aspects of long-term outcome in HPA. Unfortunately, patients with mental and physical disabilities or language barriers could not be included, which biases the data.

Free Communications

FC01-06

Impact of pregnancy planning and preconceptual dietary training on metabolic control and offspring's outcome in phenylketonuria

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Introduction: Pregnancies in women with PKU bear a risk for severe phenylalanine-induced embryofetopathy (maternal phenylketonuria syndrome, MPKUS). Good metabolic control in terms of low phenylalanine concentrations (target range 120-360 µmol/L) during pregnancy is generally recommended. We evaluated the feasibility and effectiveness of current recommendations and identified factors influencing maternal metabolic control and children's outcome. **Patient(s) and Methods:** Using filed historical data and interviews of 85 women from 12 German metabolic centers, we investigated first pregnancies ending with childbirth, from the pre-conceptional phase until birth. Children's outcome was evaluated by standardized IQ tests and parental rating of child behavior. **Results:** Of all 85 women 74% started treatment before conception, and 64% reached the phenylalanine target range before conception. Pregnancy planning resulted in earlier achievement of the phenylalanine target (18 weeks before concep-

tion planned vs. 11 weeks of gestation unplanned, p<0.001) and lower plasma phenylalanine concentrations during pregnancy, particularly in the first trimester (0-7 weeks of gestation: 247 µmol/L planned vs. 467 µmol/L unplanned, p<0.0001; 8-12 weeks of gestation: 235 µmol/L planned vs. 414 µmol/L unplanned, p<0.001). Furthermore, preconceptional dietary training increased the success rate of achieving the phenylalanine target before conception compared to women without training (19 weeks before conception with vs. 9 weeks of gestation without training, p<0.001). Mode of nutrition before pregnancy showed no clear advantage, and maternal educational level had no apparent effect on target achievement. The majority (93%) of children had normal IQ (mean 103, range 69-132, median age 7.3 years); however, IQ decreased with increasing phenylalanine concentration during pregnancy. **Conclusion/ Discussion:** This study demonstrates that pregnancy planning has a major impact on the achievement of target phenylalanine levels during pregnancy and is a prerequisite for normal intrauterine development and cognitive functions of offspring. Preconceptional dietary training is also very helpful for reaching target phenylalanine levels during pregnancy. In contrast, lifelong diet and the educational level of women with PKU seem less important for reaching therapy targets. Key points remain the careful education about MPKUS and the harmful high phenylalanine concentrations with the necessity of consistent contraception.

Free Communications

FC01-07

Changes in the care of adult PKU patients due to the COVID-19 pandemic: a retrospective review of the past 2 pandemic years.

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Introduction: Phenylketonuria (PKU) is one of the most common inborn errors of metabolism and is caused by a monogenetic mutation in the phenylhydroxylase gene. The lifelong therapy in most patients consists of a low-protein diet. For metabolic adjustment, regular laboratory determination of phenylalanine in serum (PHE) and outpatient presentation is necessary. The COVID19 pandemic has led to major changes in the lives of many people through various measures such as lockdown, contact restrictions etc. It has also significantly changed the care of patients with chronic diseases. How the COVID19 pandemic has changed the care and metabolic adjustment of adult PKU patients in Germany will be shown by this work for the first time.
Patient(s) and Methods: Medical records of 190 PKU patients presenting to our outpatient clinic from 02/2018 to 02/2022 were retrospectively analyzed. Patients who became pregnant during the period (22), started a new drug therapy (6), lost to follow up after outbreak of the pandemic (26) or presented only after onset of the pandemic (33) were excluded. The records of 115 patients were included (range 19-66 years, W:M 66:49) and retrospectively analyzed for the number of outpatient presentations, dry blood chart (DBC) submissions and their metabolic adjustment before and after the outbreak of the COVID pandemic.
Results: Comparing the two years before the outbreak of the COVID pandemic (02/2018 - 02/2020) with the two years after, the number of outpatient admissions remained almost the same (654 vs 667 presentations). However, the number of additional DBCs sent increased significantly after the outbreak of the COVID pandemic (2.6 vs 4.1 DBCs per patient; p=0.049). Metabolic control of patients deteriorated significantly, especially in the first year of pandemic (PHE before the Pandemic 726µmol/l vs 810 µmol/l in the 2 years after the pandemic; p<0,0001).
Conclusion/ Discussion: Although the number of outpatient presentations has remained the same and the number of DBCs sent has significantly increased, the metabolic control of most patients has deteriorated. It can be assumed that the social changes due to the pandemic, especially in the first year, are the cause of this. Further research, e.g. with patient surveys, is necessary.

Abstracts

Free Communications

FC02-01

aRgus: a versatile tool for variant visualization and advanced prediction score modeling in inherited metabolic diseases

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Introduction: The increasing application of high-throughput sequencing techniques for diagnosis of inherited metabolic diseases (IMDs) generates an expanding number of variants of uncertain significance and novel candidate genes. For many IMDs, no biochemical markers exist or *in-vitro* variant assessment is intricate. A variety of scoring algorithms and tools have been developed for *in-silico* prediction of functional variant effects but the majority of these data are abstract and hardly accessible without advanced bioinformatic understanding. We therefore developed the user-friendly online tool *aRgus* for exploitation and visualization of complex genetic and predictive information.
Patient(s) and Methods: *aRgus* is a stand-alone R/shiny web server application for compilation and visualization of multilevel gene, protein, variant, and *in-silico* prediction data from the publicly available databases ENSEMBL, dbNSFP, gnomAD, Simple ClinVar, and UniProt.
Results: *aRgus* automatically determines the canonical transcript based on the user-supplied HGNC gene symbol and gathers all relevant data. The user can choose from a panel of six visualizations: 1.) unspliced transcript plot; 2.) protein plot; 3.) and 4.) the mutational constraint plots of pathogenic and likely pathogenic ClinVar variants, as well as tolerated gnomAD variants, respectively; 5.) a polynomial regression model with position-coded heatmap depiction of all annotated prediction score values; and 6) groupwise statistical comparison of scores as violin plots. An interactive table shows the retrieved ClinVar variants and annotated non-synonymous single nucleotide variants with color-coded prediction score values.
Conclusion/ Discussion: *aRgus* enables gene- and position-specific prediction score modeling for assessment of proteins and identification of regions susceptible to missense variation up

to single amino acid resolution. In previous studies on metabolic conditions such as mevalonic aciduria, SSADH deficiency, and LARS1 deficiency, we could show that the *aRgus* workflow represents a powerful tool within the scope of enhanced variant interpretation in IMDs. It can be applied for interpretation of new variants in well-described IMDs as well as variants in poorly described genes or candidate genes associated with suspected IMDs. Additionally, *aRgus* can be used for the design of *in-vitro* experiments including knockout models due to the facilitated identification of protein regions with putative functional importance.

Free Communications

FC02-02

A network medicine approach identifies key TCA cycle enzymes as potential therapeutic targets in organic acidemias

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Introduction: Organic acidemias (OAs) are an important class of inherited metabolic disorders (IMD) arising due to defect in intermediary metabolic pathways of carbohydrate, amino acids, and fatty acid oxidation. Current treatment is mainly based on special diet, but patients still develop chronic organ dysfunction, such as kidney disease in glutaric acidemia type 1 (GA1). In search for causal intervention, increased lysine acylation of proteins may be involved in the OAs pathomechanism. To define such mechanisms in an unbiased manner, i.e., not from canonical pathways, relevant proteins and genes including those from disease-disease relationships are networked based on the protein-protein interactome (PPI) and graph theories to novel so-called disease modules.

Patient(s) and Methods: Here we incorporate six proteomics data sets, studying lysine acylation in GA1, hydroxy-methylglutaryl (HMG)-CoA-lyase deficiency and malonic acidemia, to generate the glutarylome, HMGylome and malonylome modules. Intersecting these acylomes resulted in a common network of acylated proteins connected via PPI, the combined-acylome (CA). Network-based centrality measures were then applied to determine targets for *in-vitro* validation via enzymatic activity, functional in-gel activity assay and complexome profiling.

Results: The CA module consisted of 80 proteins that were acylated in all OA. Of these, 21% appeared to be highly modified and form the core-combined-acylome (CCA). The network analysis suggested central roles for dihydrolipoyl dehydrogenase (*DLD*), malate dehydrogenase (*MDH2*) and succinate dehydrogenase flavoprotein subunit a (*SDHA*). Moreover, results revealed that three alpha-ketoacid dehydrogenase complexes, and OXPHOS complexes I, II and V were affected. In-vitro validation experiments in GA1 fibroblasts under acylating conditions showed indeed decreased activity of MDH2.

Conclusion/ Discussion: Thus, unbiased network medicine is a novel approach to decipher previously unrecognized common pathomechanisms of OA. The identification of the CA and CCA adds mechanistic insights into affected protein complexes. Future research will focus on in vivo and clinical validation as well as expanding the CA by more OA and applying drug-repurposing or nutraceutical strategies on their target proteins.

Free Communications

FC02-03

Sudden neonatal death in individuals with medium-chain acyl-coenzyme A dehydrogenase deficiency, 2005-2021 in Germany: limit of newborn screening

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Introduction: Medium-chain acyl-coenzyme A dehydrogenase (MCAD) deficiency leads to hypoketotic hypoglycemia, hepatopathy and often fatal outcome in undiagnosed individuals. Introduction of tandem mass spectrometry-based newborn screening (NBS) programs significantly reduced morbidity and mortality in MCAD deficiency; however, severe hypoglycemia and neonatal death in newborns with early disease manifestation may still occur.
Patient(s) and Methods: Retrospective case collection (Long-term observational study NGS2025) of neonatally deceased infants with MCAD deficiency in Germany from 2005-2021.
Results: Eight individuals with MCAD deficiency died neonatally (median at age 3.5days) in a metabolic decompensation with severe hypoglycemia before NBS result was available. All were born at term, with normal birth weight and postnatal adaption. For 80% poor feeding was reported. 50% were still at maternity hospital. Confirmatory genetic analysis revealed homozygosity for the classic pathogenic *ACADM* variant c.985A>G (Lys329Glu) for all tested patients (n=7), revealing a neonatal mortality rate of 1.3% for this genotype despite NBS.
Conclusion/ Discussion: Early fatal neonatal metabolic decompensations occurring in the first days of life cannot be prevented by NBS, however, we recommend sampling of NBS very early in the time frame recommended by national specifications. The common pathogenic *ACADM* variant c.985A>G is a major risk factor. Algorithms to prevent, diagnose and treat hypoglycemia in neonates in maternity and neonatal units should be optimized. Systematic post-mortem diagnostic protocols are needed for sudden neonatal deaths.

Free Communications

FC02-04

Feasibility of glycosylation analysis from newborn screening cards: a case series

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Introduction: Newborn screening programs have transformed metabolic medicine and allow early targeted treatment of previously untreatable and often fatal disorders. Among inborn errors of metabolism, Congenital Disorders of Glycosylation (CDG) represent an ever-growing group of severe diseases, some of which are amenable to either symptomatic or causative treatment. So far, early diagnosis has been hindered by the fact that defective glycosylation can be absent in the early postnatal period. Here, we present a series of retrospective glycosylation anaylses performed from dried blood spots (DBS) derived from newborn screening programs allowing, in principle, early postnatal diagnosis of CDG.
Patient(s) and Methods: Eight patients who were later diagnosed with various type I and II CDG were included in this study following informed consent. Dried blood spots obtained as part of the German newborn screening program were collected and analysed. After water-based elution with agitation overnight at 4°C, samples were analysed using conventional glycosylation analyses using isoelectric focusing of serum transferrin.
Results: Dysglycosylation was readily detected in DBS obtained shortly after birth from all patients. Follow-up analyses showed marked deterioration of transferrin glycosylation over the following weeks. Generally, patients in whom dysglycosylation was found in DBS samples exhibited more severe phenotypes.
Conclusion/ Discussion: In contrast to previous studies, we found that early postnatal diagnosis of CDG from DBS is possible. However, all cases presented here exhibited severe phenotypes and showed worsening glycosylation over time. This might indicate that dysglycosylation is only seen in more severe cases. In principle, early screening for CDG might be possible although more detailed analyses and controlled studies using alternative methods of analysis might be needed.

Free Communications

FC02-05

Metabolic profiling and mitochondrial function in hepatic glycogen storage diseases- a fibroblast study

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Introduction: Hepatic glycogen storage disease (GSD) subtypes I and III are autosomal-recessive disorders that alter cellular energy metabolism by impairing the break down of glycogen into glucose. Abnormal mitochondrial function has been described in murine GSD 1a hepatocytes, yet significantly less research is available in human cells and ketotic GSDs.We hypothesized that impaired glycogen metabolism results in distinct metabolic phenotypes in the extra- and intracellular compartments that may play a role in the pathogenesis of these disorders.
Patient(s) and Methods: In this study, we investigated cultured human GSD fibroblasts (GSD Ia, GSD Ib, and GSD III) in comparison to healthy controls. We performed mitochondrial function tests by measuring the oxygen consumption rate and lactate production of the cultured fibroblasts. Mitochondrial organization and mitochondrial content were examined in live cells by spinning-disk confocal microscopy. Additionally, we profiled extra- and intracellular metabolites by targeted LC-MS/MS.
Results: Mitochondrial content and network morphology of cells of all 3 GSD subtypes were comparable to that of healthy controls. Likewise, we did not observe significant differences in the basal oxygen consumption rates between healthy controls and GSD cells. Targeted metabolomics followed by principal component analysis (PCA) and hierarchical clustering (HC) uncovered metabolically distinct poises of healthy controls and GSD subtypes. Metabolic profiling was compatible with dysfunctional energy production (glycolysis, Krebs cycle, succinate), and showed reduced creatinine export in GSD Ia and GSD III, as well as reduced antioxidant defense of the cysteine and glutathione systems.
Conclusion/ Discussion: Although we did not observe impairment of mitochondrial content and network morphology in GSD fibroblasts, we could show that extra- and intracellular metabolite profiles distinguish GSD subtypes from healthy controls. Research on human GSD hepatocytes is needed to further elucidate disease mechanisms and to help optimize nutritional and pharmacological treatment for these diseases in the future.

Free Communications

FC02-06

Heterozygosity for glycogen storage disease type IIIa might add to the risk for developing type 2 diabetes

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Introduction: Some genetic conditions are diagnosed frequently in the Faroe Islands, e.g. type IIIa glycogen storage disease (GSD IIIa) caused by mutations in the *AGL* gene coding for the debrancher, the enzyme which is necessary for a complete breakdown of glycogen. Type 2 diabetes (T2D) may occur in affected persons. We hypothesized that being *heterozygous* for GSD IIIa might impair glucose-homeostasis and thus increase the risk for developing prediabetes or manifest T2D.
Patient(s) and Methods: DNA of 850 participants of the Faroese Diabetes Project [Veyhe AS et al. Diabetes Res Clin Pract. 2018] were analyzed for the presence of the Faroese mutation in the *AGL* gene (c.1222C>T, p.R408X): 382 healthy controls, 232 pre-diabetic individuals and 236 persons with confirmed T2D.
Results: A total of 29 (3.4%) participants were identified being heterozygous for R408X. Gender and age as well as BMI and waist-hip-ratio did not differ significantly between GSD-wild type individuals and GSD-heterozygotes. However, risk ratio for abnormal glucose metabolism defined as being pre-diabetic or suffering from T2D was slightly higher in R408X-heterozygotes (RR=1.03 with a 95% CI 0.45 – 2.35).
Conclusion/ Discussion: Thus, we found a 3% higher risk of developing impaired glucose metabolism in those who carry the R408X-mutation. Despite small sample numbers, this study provides clues for an additional factor that increases the risk for pre-diabetes and T2D in this population.

Free Communications

FC02-07

Evaluation of vascular dysfunction and risk of atherosclerosis in patients with glycogen storage disease type I

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Introduction: GSD I is an inborn error of metabolism with impaired glycogenolysis and gluconeogenesis that is clinically characterized by hepatomegaly and recurrent hypoglycemia. Hyperlipidemia with elevated concentration of both triglycerides and cholesterol is a common laboratory finding in patients with GSD I. Hyperlipidemia is a known risk factor for atherosclerosis. However, the cardiovascular risk in GSD I is still not known, and previous studies have shown contradictory results.

Patient(s) and Methods: We investigated vascular dysfunction in a cohort of 32 GSD I patients [26 Ia/6 Ib; mean age 20.7 (4.8-47.5) years] compared to 32 healthy controls matched for sex, age, and BMI. In addition to the lipid profile, we measured sulfur-containing metabolites, so-called aminothiols to evaluate oxidative stress as well as hsCRP and Lp PLA2 as parameters of vascular inflammation. Determination of intima media thickness, retinal vessel analysis, and 24-h blood pressure measurement were performed to evaluate endothelial function.

Results: In addition to the expected atherogenic lipid profile, GSD I patients showed an increased burden of oxidative stress. This was reflected by increased concentrations of oxidized cysteine, oxidized glutathione, and increased ratios of oxidized/reduced aminothiols. Moreover, both inflammatory parameters, hsCRP and Lp PLA2, showed elevated levels in GSD I patients, confirming vascular inflammation. Despite this risk constellation, no evidence of vascular end-organ damage could be detected in the functional-structural examinations: Retinal vessel analysis showed no differences between the two cohorts, and intima-media thickness measurements even yielded a significantly thinner intima media in the GSD I cohort. The 24-h blood pressure analysis also showed no clear differences except for single blood pressure values; above all, pulse wave velocity and pulse pressure as markers of arterial stiffness did not differ.

Conclusion/ Discussion: Our results show no evidence of vascular dysfunction in patients with GSD I up to the age of at least 20 years. This suggests that protective mechanisms exist to protect patients from early atherosclerosis and its subsequent complications. Further studies are needed to uncover these protective mechanisms and to investigate the influence of other factors such as dietary measures, medication, disease complications, and genetic predisposition.

Abstracts

Posters

P01

„Acht auf einen Streich - Achtung Gangliosidosen!"- erste Daten einer patientenorientierten, industrieunabhängigen Registerstudie

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Introduction: Gangliosidosen gehören zu den angeborenen neurodegenerativen lysosomalen Speicheerkrankungen. Die Patienten zeigen progressive Makrozephalie, Entwicklungsverzögerung und eine Regression, die entsprechend der Verlaufsform mit einer frühen Morbidität und Mortalität einhergehen. Eine objektive Charakterisierung des natürlichen Verlaufs der Erkrankungen kann die klinische Forschung insbesondere im Hinblick auf die Entwicklung von neuen Therapien voranbringen.

Patient(s) and Methods: Bei diesem gemeinsam mit der Patientenorganisation Hand in Hand gegen Tay-Sachs und Sandhoff e.V. entwickelte Projekt handelt es sich um eine Register-Studie zur Erfassung der klinischen Manifestationen von 8 Gangliosidosen (GM-2-Gangliosidosen (M.Tay-Sachs, M.Tay-Sachs-Variante B1, M. Sandhoff), GM2-Activator Mangel, GM-1-Gangliosidosen, M. Morquio B (Mukopolysaccharidose Typ IV B), Sialidosen und Galaktosialidosen) NCT04624789). Es wurde eine Querschnittsanalyse der Baseline-Daten bei 26 Patienten durchgeführt. Der primäre Endpunkt ist der Schweregrad der Erkrankung anhand des neu konzipierten 8 in 1-Scores. Sekundäre Endpunkte waren das erstmalige Auftreten neurologischer Zeichen und Symptome, die von Eltern und Ärzten beobachtet wurden sowie die zeitliche Verzögerung in der Diagnosestellung und die phänotypische Charakterisierung der Patienten. Tertiärer Endpunkt waren die Ergebnisse der neurologischen Untersuchungen (Entwicklung, Ataxie, Geschicklichkeit) und die körperlichen und kognitiven Einschränkungen.

Results: Der 8 in 1-Score erfasst quantitativ den Schweregrad der Erkrankung. Die Eltern erkennen das Erstsymptom, akustische Startles, deutlich früher als die behandelnden Ärzte, die dann die Entwicklungsstörung und Hypotonie sehen. Im Median betrug die zeitliche Verzögerung bis zur Diagnosestellung 3.16 [IQR 0.69 … 6.25] Jahre. 8 Patienten zeigten eine spät-infantile Verlaufsform.

Conclusion/ Discussion: Die Daten dieses Registers sensibilisiert behandelnde Ärzte, Therapeuten, Betreuer über diese seltenen und schwer verlaufenden Erkrankungen, um eine frühe Diagnose und eine fachliche Beratung der Eltern frühzeitig zu ermöglichen. Des Weiteren dienen die Daten dazu bessere, quantitativ zu erfassende Endpunkte für zukünftige klinische Studien zu bestimmen. Die bisherigen Daten zeigen eine genauere Charakterisierung der Phänotypen insbesondere wird der bisher kaum beschriebene spät-infantile Phänotyp charakterisiert. Die Erhebung longitudinaler Verlaufsdaten ist geplant.

Posters

P02

Multisystemic manifestations of a leukodystrophy: Aicardi-Goutières syndrome caused by *IFIH1* variant

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Introduction: Pathogenic autosomal dominant gain of function *IFIH1* variants are known to cause the leukodystrophy Aicardi-Goutières syndrome (AGS), an autoinflammatory Type I interferonopathy with variability in disease expression. Type I interferonopathies are characterized by an aberrant and uncontrolled activation of the IFN-alpha pathway often leading to exuberant and uncontrollable inflammatory processes with multisystemic involvement within the first years of life. Leukodystrophy with basal ganglia calcifications, cerebral atrophy, and cerebrospinal fluid findings of chronic lymphocytosis and highly elevated interferon-alpha (INF-alpha) are frequently found. Neurologic and extra neurologic manifestations lead to severe progressive disabilities and premature death. To date treatment of AGS can only rely on supportive care to limit subsequent sequelae. However, recent studies have indicated that the use of Janus Kinase (JAK) inhibitors may be effective in controlling the course of interferonopathies.
Patient(s) and Methods: We report on a 5-year-old girl born with AGS in which an individualized therapeutic attempt with Ruxolitinib, a JAK inhibitor, was initiated at 2.5 years of age. The patient initially presented with an intrauterine growth retardation, primary microcephaly, neonatal anemia and thrombocytopenia. Increased crying occurred after a CMV infection at the age of 3 months and loss of gained abilities after a vaccination at the age of 7 months followed by delayed dentition, failure to thrive, severe psychomotor retardation with tetraspastic tetraparesis, epileptic seizures, hearing loss, reduced visual abilities, autoimmune hepatitis, arterial hypertension with cardiac septal hypertrophy and daily episodes of shivering and discomfort. A de novo missense alteration in IFIH1 (p. Ala719Val) was identified.
Results: Ruxolitinib was started at 0.2 mg/kg/d and slowly increased to a target dose of 0.5 mg/kg/d. A significant decrease of the initially measured hyper-expression of IFN-stimulated genes (so called “IFN-signature”) was evident after three months of treatment. A remarkable improvement of the neurological picture was evident with a reduction of asthenia and irritability, better fine motor skills and balance competencies and a considerable decrease in the frequency of seizures. Furthermore, the autoimmune hepatitis alleviated.
Conclusion/ Discussion: Overall, the treatment of patients Aicardi-Goutières syndrome with JAK Inhibitor Ruxolitinib can result in a substantial improvement in clinical multisystemic symptoms and quality of life.

Posters

P03

Pulmonary fibrosis and hyperinflammation in heme oxygenase 1 deficiency

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Introduction: Homozygosity for pathogenic variants in *HMOX1* leads to heme oxygenase 1 deficiency, disrupting the rate-limiting step of heme degradation. Subsequent oxidative damage causes chronic inflammation with a severe and ultimately fatal disease course. Allogenic stem cell transplant has been proposed as a curative treatment with no other causative treatment options available. We present a case of HMOX1 deficiency and characterize HMOX1 dysfunction as well as oxidative damage.
Patient(s) and Methods: The patient is the first son of non-consanguineous parents of German origin. Hemolytic anemia with low to normal bilirubin was present throughout childhood. Pulmonary fibrosis with bulla formation was detected at the age of five years. Following a respiratory infection, a severe hyperinflammatory phenotype with liver failure developed, that only responded partly to high-dose steroid treatment. After transient stabilization, the patient experienced fatal pulmonary hemorrhage at the age of 5 years. Trio-exome sequencing was performed on the patient and both parents. EBV-transformation of patient-derived B-cells was used to establish a HMOX1-deficient, patient-derived cell model. Hemin challenge was used to simulate heme arising from hemolysis in vitro. Cell viability was analyzed in addition to protein carbonylation, which served as a correlate of oxidative damage to protein. HMOX1 expression in patient and control cells was studied by immunoblotting following $CdCl_2$ stimulation.
Results: Exome sequencing identified the pathogenic variants c.55dupG (p.Glu19Glyfs*14); c.262_268delinsCC (p.Ala88Profs*51) in *HMOX1*. HMOX1 was absent from patient cells, thus establishing the diagnosis. Hemin challenge resulted in severely reduced cell viability in patient-derived LCL, while protein carbonylation was significantly increased compared to controls.
Conclusion/ Discussion: Deficiency in HMOX1 results in a severe, ultimately fatal phenotype characterized by impaired heme metabolism and subsequent oxidative damage. Our findings support the presence of pulmonary involvement as a relevant phenotypical feature of HMOX1 deficiency. Further research is needed to establish specific therapies, while currently bone marrow transplant has the potential to salvage the phenotype of the disorder.

Posters

P04

Characterization of oxidative and mitochondrial stress in X-linked adrenoleukodystrophy fibroblasts

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Introduction: X-linked adrenoleukodystrophy (X-ALD) is an inherited metabolic disorder caused by *ABCD1* gene mutations, leading to a dysfunctional ABCD1 protein. ABCD1 is a peroxisomal transporter crucial for fatty acid transport and β-oxidation of very-long-chain fatty acids (VLCFA). *ABCD1* mutations lead to VLCFA accumulation in body fluids and tissues. Clinical presentation is heterogeneous and ranges from asymptomatic carriers to rapidly progressing childhood cerebral ALD, distinct pathophysiological mechanisms are still unclear. Several studies show elevated oxidative stress parameters and mitochondrial dysfunction in X-ALD cells and tissues, while detailed processes and correlation to clinical presentation need further investigation.
Patient(s) and Methods: This study aimed to analyze oxidative stress and mitochondrial dysfunction in 10 X-ALD fibroblast cell lines from 5 families and two healthy control cell lines. Quantification of cellular reactive oxygen species (ROS) was performed using the 2',7'-dichlorofluorescein diacetate (DCFDA) assay; tert-butyl hydroperoxide (TBHP) was used for stress induction. Mitochondrial function was assessed by measuring the oxygen consumption rate (OCR) using the Seahorse XFe24 extracellular flux analyzer.
Results: Our results show significantly elevated ROS in X-ALD cell lines compared to healthy controls with dose dependent aggravation after application of TBHP. Mitochondrial function is impaired in X-ALD fibroblasts with significantly reduced basal respiration and spare respiratory capacity. **Conclusion/ Discussion:** Our study shows consistent results regarding elevated oxidative stress levels and mitochondrial dysfunction in a panel of X-ALD fibroblasts. Application of the DCFDA assay and the Seahorse XFe24 extracellular flux analyzer delivers reliable results, making them promising tools for further investigations, including high-throughput biomarker and drug screenings. The findings expand the current knowledge about potential pathogenic mechanisms in X-ALD and lead the way for identification of biomarkers predicting the clinical phenotype as well development of new treatment strategies.

Posters

P05

Correlation of therapy regimen, biochemical monitoring and in vivo brain Proton MR-Spectroscopy in a patient with GAMT deficiency and normal neurocognitive development

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Introduction: *GAMT* codes for guanidinoacetate methyltransferase (GAMT) which catalyzes the final step of creatine synthesis. Creatine serves as an essential energy shuttle facilitating manifold functions in neurometabolism. GAMT deficiency is a rare autosomal recessive disease and patients suffer from intellectual disability, seizures, speech and movement disturbances. Treatment consists of daily creatine supplementation to increase cerebral creatine and strategies to reduce toxic guanidinoacetate (GAA) levels.
Patient(s) and Methods: Case study: Our patient was followed over 14 yrs starting at the age of 15 mo. Developmental milestones, brain MRI, quantitative single voxel ^{1}H MRS and biochemical analyses were assessed. Molecular genetic studies confirmed the diagnosis.
Results: GAMT deficiency was diagnosed by characteristic brain MRI, ^{1}H MRS and biochemical findings at age 15 mo, prompting initiation of treatment with creatine/ornithine supplementation. Genetic testing revealed compound heterozygosity for a *GAMT* frameshift mutation (c.442dupC, p.Gln148ProfsX43) and a null allele. Doses of creatine/ornithine were adapted to body weight (100-400 mg/kg per day). Follow-up examinations documented close to normal neurocognitive development, resolution of brain MRI alterations, significant increase of cerebral creatine concentration and improvement of metabolite changes.
Conclusion/ Discussion: Our study presents the first long term follow-up over 14 yrs that provides clinical data, biochemical and multimodal neuroimaging results. It allows for correlations of therapeutic regimen with clinical course, biochemical data and brain ^{1}H MRS creatine levels. The results reveal insights into the dose dependent effects of creatine/ornithine supplementation and expand the phenotypic spectrum of GAMT deficiency. This is the second report of a patient with normal neurocognitive development after initial symptomatic clinical presentation including developmental delay. Early start of supplementation and strict dosing regimen might be important factors contributing to the extremely favorable outcome.

Posters

P06

Metabolic neuropathies in children and adolescents with LCHAD/MTP deficiency: Insights from in-vivo magnetic resonance neurography

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Introduction: In peripheral nerve disorders, the diagnostic gold standard is the clinical examination, supplemented by electrophysiological measurements. Magnetic resonance neurography (MRN) is a novel in vivo method for highly sensitive and non-invasive detection of peripheral nerve disorders. So far, it is mainly used for adults and there is little data about the sensitivity and possible diagnostic advantages of MRN for children and adolescents with suspected neuropathy. Patients with long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency (LCHADD) and mitochondrial trifunctional protein deficiency (MTPD) are known to develop neuropathies, but no data is available on morphological changes of peripheral nerves, especially at early stages. Therefore, we assessed morphological and functional peripheral nerve changes in a small patient cohort with LCHADD and MTPD.

Patient(s) and Methods: Four patients with LCHADD and four with MTPD from 6-18 years of age were examined. Six presented with clinical and/or electrophysiological signs of neuropathy. Each patient underwent imaging of the sciatic nerve at the thigh consisting of a T2-weighted turbo spin-echo and a single-shot diffusion tensor imaging (DTI) sequence. Total T2 nerve lesion load was calculated and the DTI parameters fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD) and radial diffusivity (RD) as well as the nerve cross-sectional area (CSA) were assessed after manual nerve segmentation. Subsequently, results were compared to six healthy controls, who were matched to age, height, and bodyweight.

Results: Compared to controls, patients with LCHADD and MTPD showed hyperintense T2 nerve lesions in the examined nerve sections. Moreover, mean FA of the sciatic nerve (tibial portion) was significantly decreased (0.46 ± 0.05 vs. 0.61 ± 0.08; P=0.013), indicating functional changes in peripheral nerves. This was mainly a result of an increased RD (758.5 ± 186.3 x 10^{-6}

mm^2/s vs. 524.7 ± 131.9 x 10^{-6} mm^2/s; *P*=0.04). There was no significant difference in nerve CSA between patients and healthy controls.
Conclusion/ Discussion: In this preliminary study, MRN was feasible to detect (early) neuropathic changes in a small patient cohort with LCHADD and MTPD. Therefore, it may serve as an important additional tool to help detecting and monitoring peripheral neuropathy in young patients.

P07
Intracellular localization of glycine N-acyltransferase-like protein 1 (GLYATL1)

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Introduction: The phase 2 enzyme Glycine *N*-acyltransferase-like Protein 1 (GLYATL1; EC 2.3.1.68) is an acyltransferase which transfers an acyl group to the *N*-terminus of glutamine and can use phenylacetyl-CoA as an acyl donor. GLYATL1 contributes to the elimination of compounds such as phenylacetate, which can serve as an alternative vehicle for waste nitrogen excretion and is formed from prodrugs which are administered in urea cycle deficiencies. While there is considerable evidence for GLYATL1 being a mitochondrial protein, it has also been suggested to be distributed primarily in the cytoplasm or in the endoplasmatic reticulum. This has prompted us to study its intracellular localization as well.
Patient(s) and Methods: Following stable transfection with eGFP-pcDNA3.1(+) or GLYAT-eGFP-pcDNA3.1(+), HEK293 cells were stained with DAPI and MitoTracker™ Orange CMTMRos or following use of TOMM20 antibody, and studied by confocal laser scanning microscopy. In addition, human liver homogenate and fractions of mitochondria and cytosol were analyzed by gel electrophoresis (SDS-PAGE) and subsequent immunoblot analysis.
Results: The immunoblot yielded the most prominent GLYATL1 signal for the mitochondrial liver fraction, while much less GLYATL1 was noted in the homogenate and none in the cytosol. Confocal laser scanning microscopy of HEK293 cells transfected with eGFP-pcDNA3.1(+) indicated wide distribution of free GFP. In contrast, the localization of the fusion protein GLYATL1-eGFP suggested in particular mitochondrial association as shown by overlay images following MitoTracker™ staining or incubation with TOMM20-specific antibody.
Conclusion/ Discussion: Our study supports the view that GLYATL1 is a mitochondrial enzyme.

Posters

P08

Severe citrullinaemia type I with atypical amino acid pattern

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Introduction: Introduction: Citrullinaemia type I is a severe autosomal recessive urea cycle defect, with a defect in argininosuccinate synthetase (ASS1). Patients usually present during the first days of life with hyperammonemia, lactic acidosis, and very high concentrations of plasma citrulline. However, the severe form of pyruvate carboxylase (PC) deficiency also presents in the first days of life with a similar biochemical trait including elevated plasma citrulline.
Patient(s) and Methods: The index patient was a newborn male, who was transferred on the third day of life from the postnatal ward to the NICU because of respiratory distress and lethargy. A dried blood sample (DBS), plasma, and cerebrospinal fluid (CSF) were taken on day 4. The baby had hyperammonemia (2004 µmol/L) , lactic acidosis (94 mg/L), mild cardiac dysfunction, and convulsions. He died on day 6 of multi-organ failure.
Results: Amino acids in DBS, plasma, and CSF were highly suggestive of PC deficiency as in addition highly elevated to citrulline (1406 µmol/L), the patient had elevated plasma levels of alanine (2813 µmol/L), proline (756 µmol/L), glycine (804 µmol/L), and lysine (854 µmol/L). Genetic analysis revealed homozygosity for the c.470G>A [p. (Arg157His)] mutation in the ASS1 gene. No variants in the PC gene were detected.
Conclusion/ Discussion: According to literature, the amino acid profile was highly suggestive of PC deficiency. We also compared it to the amino acid profiles in DBS from 16 previously diagnosed cases of citrullinaemia type I "which showed a different amino acids pattern". We conclude that the amino acid profile from DBS samples taken in the first days of life cannot reliably distinguish between citrullinaemia type I and PC deficiency.

Posters

P09

Retrospective monocentric analysis of pregnancies with phenylketonuria over the last 15 years

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Introduction: Phenylketonuria (PKU) is one of the most common inborn errors of metabolism and is caused by a monogenetic mutation in the phenylhydroxylase gene. The lifelong therapy in most patients consists of a low-protein diet. For metabolic adjustment, regular laboratory determination of phenylalanine in serum (PHE) and outpatient presentation is necessary. However, high phenylalanine levels in pregnancy lead to a high risk of miscarriage and embryopathy, which shows the relevance for a low-phenylalanine diet in pregnancy. While current European guidelines recommend a target value at least of < 360 µmol/l, this study retrospectively analyses the influence of a target value of 120-240 µmol/l on the course of pregnancy, the quality of life during pregnancy and the foetus.
Patient(s) and Methods: Data sets of 43 pregnancies of 37 PKU patients (28,9 Jahre ± 1) from the period 2007-2022 were retrospectively analysed. The averaged PHE and tyrosine values during the pregnancy were determined, as well as the birth weight, height and head circumference of the children. All results are presented as Mean±SEM.
Results: 39 of the 43 pregnancies were successfully co-attended until birth. In 4 pregnancies there were miscarriages in early pregnancy. One child died immediately postpartum due to severe malformations in a not sufficiently treated maternal PKU. The mean PHE value of the attended pregnancies was 191 ± 13 µmol/l. The mean tyrosine level was 109 ± 4 µmol/l. The children weighed 2951 ± 108 g at birth, were 50 ± 1 cm tall and had a head circumference of 34 ± 1 cm. There was no evidence for the presence of a “small for gestational age” syndrome. There was no correlation between the PHE concentration and the recorded birth parameters.
Conclusion/ Discussion: Outcome is strongly dependent on close follow-up in a metabolic centre. The measured mean PHE values were mostly below 240 mol/l and thus within the target range of the European guideline, whereby embryopathies could be successfully avoided. In order to be able to make specific statements about the quality of life in the pregnancies, further data must be collected and analyzed, e.g. through different questionnaires.

Posters

P10
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 a mouse model. GCDH is a mitochondrial enzyme of the L-lysine, -hydroxylysine, and -tryptophan catabolism. This depletion leads to a neurotoxic accumulation of glutaric acid and related metabolites. Current treatment consists of a low lysine diet, arginine, and carnitine supplementation. Thus, we have chosen AASS and AADAT upstream of GCDH in the L-lysine degradation pathway as potential therapeutic targets since their deletion causes benign or no phenotype.
Patient(s) and Methods: Furthermore, to evaluate this aim, the GA1 mouse model ($GCDH^{-/-}$), the GA1 rescued mouse models ($GCDH^{-/-}/AASS^{-/-}$, $GCDH^{-/-}/AADAT^{-/-}$), and control wild-type mice will be analyzed. Mass spectrometry will be used to screen for metabolite changes in body fluids. Western blots will be performed on extracted organs, and immunohistochemistry 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, through the western blot technique, we show a lack of GCDH protein concentration in diseased mice compared to the control mice in the brain.
Conclusion/ Discussion: Ultimately, we envisage rescuing the phenotype in GA1 mouse models. We hope to translate these insights into a potential therapeutic approach for GA1 patients.

Posters

P11

Mosaicism of the de novo deletion Xq28 X:153779747-153811749 as a cause for SSR4-CDG

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Introduction: SSR4-CDG is a rare subtype of the continuously growing group of inherited glycosylation disorders. As a condition with X-linked recessive inheritance, males are disproportionately affected. Mutations in *SSR4* cause disruption of the eponymous subunit of the translocon-associated protein complex, resulting in impaired translocation and consequently altered glycosylation, typically in a type I pattern of dysglycosylation. Here, we report on a case of SSR4-CDG caused by mosaicism for a de novo deletion.
Patient(s) and Methods: The patient is the first-born son of non-consanguineous parents of German origin. He presented with developmental delay, failure to thrive, muscular hypotonia and marked dysmorphisms. In addition, hypermobility of the joints was noted. Serum samples were used for glycosylation analyses using HPLC, conventional IEF, and MALDI-TOF MS based glycome profiling. The patient and parents underwent exome sequencing followed verification by conventional Sanger sequencing. In addition, two skin biopsies as well as buccal swabs and hair root collections were performed in order to generate material for further genetic analyses.
Results: Glycosylation analysis identified mild dysglycosylation corresponding to a type I pattern of transferrin glycosylation. Trio-exome sequencing identified an X-chromosomal deletion Xq28 X:153779747-153811749 encompassing *SSR4* as the underlying cause of disease. Targeted PCR was not able to amplify *SSR4* in DNA from blood and skin samples, whereas *SSR4* could be amplified in DNA samples prepared from hair roots as well as buccal swabs.
Conclusion/ Discussion: Our findings indicate mosaicism for a de novo deletion encompassing *SSR4* as the cause of our patients phenotype. The mild glycosylation abnormalities reflect partial presence of functional SSR4. The clinical findings suggest connective tissue abnormalities as a key phenotypical feature of SSR4-CDG.

Posters

P12

Interaction between the α-glucosidases, sucrase-isomaltase and maltase-glucoamylase, in human intestinal brush border membranes and its potential impact on disaccharide digestion

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Introduction: The two major intestinal α-glycosidases, sucrase-isomaltase (SI) and maltase-glucoamylase (MGAM), are active towards α-1,4 glycosidic linkages that prevail in starch. These enzymes share striking structural similarities and follow virtually identical biosynthetic pathways. It has been hypothesized that starch digestion can be modulated via "toggling" of activities of these mucosal α-glycosidases. Together this suggests a possible interaction between these two enzyme complexes occurring in the intestinal brush border membrane (BBM). This study addresses the potential interaction between SI and MGAM in detergent extracts of human intestinal BBM and proposes concepts for the implication of this interaction in intestinal starch digestion.
Patient(s) and Methods: BBMs were solubilized in buffers containing Triton X-100 or Triton X-100 and sodium deoxycholate (DOC) and then immunoprecipitated with mAb anti-SI followed by Western blotting with mAb anti-MGAM or vice versa. Further, enzymatic activities in the solubilized membranes towards sucrose and maltose were measured.
Results: The reciprocal immunoprecipitations with either mAb revealed by Western blotting interactions between MGAM and SI concomitant with a hetero-complex assembly of these proteins in the BBM. The inclusion of DOC into the solubilization buffer resulted in a reduction of the enzymatic activities likely due to alteration in the quaternary structure of either enzyme.
Conclusion/ Discussion: In view of their interaction, SI and MGAM regulate the final steps in starch digestion in the intestine, whereby SI assumes the major role by virtue of its predominant expression in the intestinal BBM, while MGAM acts in auxiliary supportive fashion. These findings will help understand the pathophysiology of carbohydrate malabsorption in functional gastrointestinal disorders (FGIDs), particularly in irritable bowel syndrome, in which gene variants of SI are implicated.

Posters

P13
Idiopathic pathological ketotic hypoglycemia and celiac disease

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Introduction: A diagnosis of idiopathic pathological ketotic hypoglycemia (IPKH) is made if recurrent symptomatic events of (mild) hypoglycemia and ketosis occur in the absence of acute infections and after exclusion of endocrine disturbances (such as growth hormone or cortisol deficiency) and metabolic disorders (such as glycogen storage disease type 0, III, VI and IX). Recently we identified several children fulfilling the criteria for IPKH who have an additional diagnosis of celiac disease. **Patient(s) and Methods:** Three patients diagnosed with celiac disease continued to have poor growth and symptoms consistent with IPKH despite full compliance with gluten-free diet and negative transaminase antibodies and gliadin peptide IgG. Because of the high frequency and awareness of IPKH in the community, glucose and beta-hydroxybutyrate were evaluated with a point-of-care device and found to be abnormal with early ketosis. Growth hormone and thyroid hormone deficiency were ruled out. Because of the finding of hepatomegaly, a clinical diagnosis of mild GSD-like condition was made and treatment with uncooked cornstarch (UCCS) and high-protein diet was implemented. UCCS was administered at night at a dose of 0.7 to 2g/kg sufficient to prevent morning ketosis. High-protein diet was commenced with a goal of achieving total protein levels in the blood of 70g/L and pre-albumin levels of 0.20g/L.
Results: After starting a dietary treatment, significant subjective and objective improvement was noted in all patients. Improved growth and body mass index, normalization of liver size and decreased echogenicity of liver were demonstrated. Patients reported feeling more energetic with higher activity level and better endurance.
Conclusion/ Discussion: The co-incidence of IPKH and trisomy 21 has been described (Drachmann et al, JIMD reports 2021). We describe a series of patients with IPKH and celiac disease. The key clinical feature was failure to correct the abnormal clinical signs and growth pattern once celiac disease was adequately treated. With institution of dietary treatment for IPKH there was clinical and biochemical improvement. Parents and patients reported an improvement in Quality of Life. We recommend screening for IPKH in patients with celiac disease who do not respond to adequate dietary therapy in communities with high prevalence of IPKH.

Posters

P14

Cytosolic phosphoenolpyruvate carboxykinase deficiency: genotypic and phenotypic spectrum

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Introduction: Cytosolic phosphoenolpyruvate carboxykinase (PEPCK-C) deficiency is a rare disorder of gluconeogenesis caused by pathogenic biallelic variants in the gene *PCK1*. Patients present with hypoglycemia, lactic acidosis, and hepatopathy. To date, there has been no systematic analysis of its phenotypic, biochemical, and genetic spectrum.
Patient(s) and Methods: All currently published cases and a novel patient with genetically confirmed PEPCK-C deficiency were included. Clinical, biochemical, and genetic characteristics were analyzed. Protein and in-silico prediction score modeling was applied to analyze potential variant effects.
Results: 32 individuals from 25 families were found, including one previously unreported patient. Symptom onset usually occurred in infancy with a broad range from neonatal age to adulthood. The typical biochemical pattern was hypoglycemia triggered by fasting or illness, increased urinary concentrations of tricarboxylic acid cycle metabolites, mildly elevated hepatic transaminases and lactate concentrations in serum. Plasma glutamine concentrations were elevated in some patients and may be a suitable marker for newborn screening. With adequate treatment, biochemical abnormalities usually normalized after a hypoglycemic episode. Regardless of the genotype, a broad clinical spectrum was found for different phenotypes. To date, eight genotypes with nine different *PCK1* variants were identified, of which alleles with the recurrent variant c.925G > A; p.(Gly309Arg) are predominant and appear to be endemic in the Finnish population. Protein modeling suggests altered manganese- and substrate-binding as superordinate pathomechanisms.
Conclusion/ Discussion: Based on the biochemical pattern, PEPCK-C deficiency is a recognizable cause of childhood hypoglycemia. Newborn screening for PEPCK-C deficiency may identify at least a sub-cohort of affected individuals through elevated glutamine concentrations in dry blood and should be pursued. Environmental factors appear to be the main determinant for phenotypic differences in patients with biallelic variants in *PCK1*. Since it is a treatable disorder of gluconeogenesis, early diagnosis is crucial to prevent metabolic derailment and morbidity.

Posters

P15
Corneal involvement in glycogen storage disease type IV

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Introduction: Apart from extremely rare cases of retinopathy in myophosphorylase deficiency (glycogen storage disease type V, GSD V) and generalized lysosomal storage in (treated) Pompe disease (GSD II) patients, ocular involvement has not been described in GSDs. This includes corneal disease, which is rather surprising because the corneal epithelium contains remarkable glycogen stores, both the enzymatic system for synthesis and degradation of glycogen, and GLUT1 as the major glucose transporter. Since glucose supply to the cornea is a diffusive process, as the cornea is and must remain an avascular structure to prevent vascular formation from interfering with light transmission and thus vision, glycogen metabolism is tightly regulated by the c-kit/ FIH-1/Akt/GSK3-β pathway.
Patient(s) and Methods: Here, we present for the first time the case study of a now 14-year-old boy with congenital neuromuscular form of GSD IV and binocular perforating corneal dystrophy.
Results: Patient presented prenatally with polyhydramnion, showed muscular hypotonia and contractures at birth, developed progressive neuromyopathic scoliosis treated with growing rods (age 13) and before surgical correction of multiple contractures. Minor liver involvement (increased echogenicity), minimal mitral regurgitation, normal mental development. At age 10, diagnosis of GSD IV based on detection of compound heterozygosity for *GBE* c.691+2T>C (splice site) und c.708G>C (p.Gln236His) by multiple parallel sequencing. A corneal infiltrate was first observed at age 6 which developed into thinning and ulceration that eventually required penetrating keratoplasty of both eyes at ages 11 and 12 respectively.
Conclusion/ Discussion: This is the first report of corneal involvement in a patient with GSD IV. The latter diagnosis is unequivocal because two variants were detected that have been repeatedly found in patients with a similar myoneuropathic course of branching enzyme deficiency. Despite highly suggestive, the causality for corneal involvement has not been established with absolute certainty, albeit no other causes, particularly infectious, have been found. Massive glycogen deposition in the epithelium was not detected, however as in cases with liver involvement, it is the atypical amylopectin-like glycogen rather than the absolute amount that could trigger an inflammatory response. Limbal stem cells could also be involved, but this would likely result in a different clinical presentation. Finally, neurovascular factors could also be involved in the pathomechanism.

Posters

P16
Unexpected high stature in young adults with GSD type IIIa

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Introduction: Glycogen storage disease type IIIa (GSD IIIa) is caused by biallelic pathogenic changes in the *AGL* gene coding for the glycogen debranching enzyme [OMIN 232400]. Typical manifestations include hepatomegaly, myopathy, fasting ketotic hypoglycemia, short stature and more. We reviewed records of five young Faroese GSD IIIa adults and found an unexpected good growth.
Patient(s) and Methods: Out of seven young Faroese GSD IIIa patients, records of five of them were included in this report (one moved abroad, one just entered puberty). All are homozygous for c. 1222C>T (p.R408X) leading to a truncation in exon 11 and thus affecting both enzymatic activities of the debranching enzyme.
Results: Height with last control (age 22 to 28 years) was 0.8 to 16.5 cm above parental target height (PTH) (ratio height/PTH 1.0 to 1.1). No severe overweight (BMI 20.0 to 27.9) or hepatomegaly (1.0 to 4.2 cm below costal margin) were observed. Creatinine kinase was normal in all of them, liver enzymes slightly elevated in most patients (ALAT max. 203 U/L). Total protein and pre-albumin surpassed target range (>69 g/L resp. >0.19 g/L) in four patients. Uncooked cornstarch at bedtime was used by two patients, before school by one; protein supplements before/around sports by two. All of them are exercising regularly, up to 10 hours per week.
Conclusion/ Discussion: There are several possible explanations for the unexpected good growth in these patients: 1) Our observation describes the normal tend of a generational effect on height. 2) Suboptimal growth of obligate carrier parents caused a lowered final height (also in heterozygous sibs of patients ratio of final height to PTH was lower than in patients themselves). 3) Traditional Faroese diet leads to a high-protein intake (1.5-2.0 g/kg/day protein), which became even higher after re-enforcing high protein intake since patients were about 14 years old. However, compliance with recommended diet was limited. Thus, recurrent mild (nocturnal) hypoglycemia might have occurred and stimulated excessive release of growth hormone. With availability of sufficient protein, this might have caused extra growth.

Posters

P17

SGLT2 inhibition in pediatric and adult GSD Ib patients – a monocentric experience

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Introduction: GSD Ib is caused by variants in the *SLC37A4* gene coding for glucose-6-phosphate translocase. The genetic defect results in impaired glycogenolysis and gluconeogenesis plus neutropenia and neutrophil dysfunction. In addition to hypoglycemias, patients suffer from recurrent infections, oral ulcers and inflammatory bowel disease, which are not sufficiently controlled by GCSF. Recently, the SGLT2 inhibitor empagliflozin has been shown to reduce accumulating 1,5-anhydroglucitol-6-phosphate in GSD Ib patients resulting in an increased neutrophil count with improved function.
Patient(s) and Methods: We describe the clinical course of 6 patients (2 children and 4 adults, age 9 months to 37 years) with GSD Ib receiving empagliflozin (0.27 to 0.58 mg/kg bw/d) for 1 to 20 months.
Results: All patients showed significant improvement of neutropenia. Those treated with GCSF (5 patients) were able to stop (3/5) or reduce (2/5) this medication. Frequency of infections, oral ulcers and bowel movements decreased in all patients. An infant had abdominal wall phlegmona after infection of gastrostomy despite GCSF treatment requiring surgical intervention. No more gastrostomy infections occurred while on empagliflozin. Symptomatic hypoglycemia was the most frequent adverse effect of empagliflozin. The youngest patient had fluctuating glucose levels and experienced two hypoglycemia-associated seizures. Blood glucose stabilized after reduction of empagliflozin dosage. In one adult patient there was a slight increase of albuminuria, overall renal function remained stable in all patients.
Conclusion/ Discussion: Neutropenia and neutrophil dysfunction in GSD Ib patients can be effectively treated with the SGLT2 inhibitor empagliflozin. The most frequent adverse effects are symptomatic hypoglycemias, requiring an effective monitoring and, in some patients, dosage reduction.

Posters

P18

Glycogen storage disease type Ib, SGLT2 inhibitors and liver transplantation: lessons to learn

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Introduction: In the past, the indication for liver transplantation (LTx) in patients with glycogen storage disease type Ib (GSD1b) has been markedly reserved. This is due to neutropenia and granulocyte (PMN) dysfunction, which result in higher propensity for infection and fear of wound healing problems or fistula formation. The widespread use of SGLT2 inhibitors in GSD1b and their impressive effect on PMN counts is now well documented [1]. We report the complicated clinical course of two GSD1b patients who received LTx that eventually led to normal glucose homeostasis. Here, we focus on PMN counts before and after use of an SGLT2 inhibitor.
Patient(s) and Methods: Patient 1 is a 3-year-old girl with typical signs of GSD1b (*SLC37A4* c.1042_43delCT homozygous) including oral aphtosis, frequent infections, and otorrhea at first referral. Parents rejected tube feeding and reasonably satisfactory glucose homeostasis was only achieved with extreme dietary measures unacceptable for parents. Therefore, LTx was considered and off-label treatment with the SGLT2 inhibitor empagliflozin (Empa, 5 mg/d) was started to improve PMN number and function before this intervention. **Patient 2** is a now 10-year-old girl with a syndromic neurodevelopmental disorder (recently elucidated as PAN2 deficiency [2]) and concomitant GSD1b (*SLC37A4* c.1015G>T homozygous) for whom parents in 2015 (before SGLT2 inhibitors were considered) requested LTx to better care for their disabled child. Post-LTx, chronic graft failure, cirrhosis, and hypersplenism with *pan*cytopenia developed. At this time, Empa (20 mg/d) was first introduced, resulting in normal PMN counts for the first time after partial splenic embolization. Re-LTX (on Empa) was uncomplicated, but omission of Empa thereafter again resulted in neutropenia, and only after reintroduction of Empa did PMN numbers normalize. Concentration of 1,5-anhydrogucitol (1,5-AG) in plasma (the accumulating glucose analogue responsible for neutropenia in GSD Ib) was determined by UPLC-MS/MS.
Results: In the first patient, 1,5-AG decreased from 160 to 20 µmol/l on Empa with a parallel increase of PMN number. Post-LTx concentrations leveled off around 10 µmol/l. In patient 2, first LTx had no effect on 1,5-AG and PMN number, Empa reduced 1,5-AG concentration from 200-250 µmol/l to around 30 µmol/l and most recently, after reintroduction of Empa, 1,5-AG and PMN counts have normalized.
Conclusion/ Discussion: Empa may normalize 1,5-AG concentration and PMN numbers in GSD1b patients, lowering the risk for perioperative complications and facilitating the indication for LTx in this disorder. SGLT2 inhibitor treatment is also necessary after LTx.
[1] Grünert et al, Genet Med 2022 [2] Reuter et al, Eur J Hum Genet 2022

Posters

P19

Elevated plasma vitamin B 12 in patients with hepatic glycogen storage diseases

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Introduction: In hepatic glycogen storage diseases (GSDs), the breakdown or synthesis of glycogen in the liver is affected due to different gene mutations. Increased plasma vitamin B_{12} concentrations were observed as part of routine diagnostics in patients with hepatic GSDs. As a cofactor of methylmalonyl-CoA mutase and methionine synthase B_{12} plays an essential role in hepatic energy supply. The objective of our study was to assess vitamin B_{12} status in a large cohort of hepatic GSD patients.

Patient(s) and Methods: Plasma vitamin B_{12}, methylmalonic acid and total homocysteine (tHcy) concentrations were measured in 44 hepatic GSD patients and compared to 42 healthy gender- and age-matched controls. Dietary intake of B_{12} was recorded by a questionnaire. B_{12} status was calculated using the combined B_{12} index. The effect of BMI and disease markers of GSDs (triglycerides or hepatic enzymes) were also studied.

Results: Plasma B_{12} was significantly increased in GSDs patients compared to healthy controls ($p = 0.0002$) irrespective of BMI or transaminases. Transaminases were significantly elevated in ketotic GSD compared to the GSD-I patients. Normal concentrations of plasma tHcy and methylmalonic acid excluded a functional deficiency of B_{12}. Plasma B_{12} concentrations in GSD patients correlated negatively with triglyceride concentrations ($p = 0.008$).

Conclusion/ Discussion: Elevated vitamin B_{12} plasma concentration is a common finding in hepatic GSD patients irrespective of dietary intake. Triglycerides are elevated in GSDs and show a negative association with vitamin B_{12}, suggesting an influence of metabolic control on the B_{12} status of hepatic GSDs patients. Further studies are required to evaluate potential consequences and clinical significance of chronically elevated Cbl concentrations in GSDs. Mechanistic studies to investigate how defective glycogen metabolism impacts intra- and extracellular vitamin B_{12} pathways in hepatic cells are warranted.

Posters

P20

Early diagnosis of neonatal vitamin B12 und cblG deficiency: arguments for newborn screening in Germany

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Introduction: Newborn screening (NBS) including second-tier strategies measuring homocysteine (HC), methylmalonic acid (MMA), and methylcitrate (MC) based on first-tier markers like methionine (Met) and propionylcarnitine (C3) is feasible to identify vit. B_{12} deficiency, organic acidurias, remethylation and cobalamin disorders, but a national NBS program for these disorders does still not exist in Germany.
Patient(s) and Methods: Here we report 3 of those cases, two of them with early diagnosis following NBS in a pilot study and one later in the symptomatic phase.
Results: First case isa now 19-months-old female . NBS showed C3 of 5 µmol/l (<5), in recall C3 2.1 µmol/l and in the context of a pilot study MMA 17.8 µmol/l (<2.5), MC 1.4 µmol/l (<1) and HC 13 µmol/l (<13) were measured. Subsequently low vit. B_{12} (176 ng/l, >211) and holotranscobalamin (HTC) (24.7 pmol/l, 37.5-188) was found. Vit. B_{12} of the mother was 222 ng/l (>211), HTC 30 pmol/l (37.5-188), HC 18.76 (<13.9) and anti-parietal cell antibodies 1:1280 (<1:80) were shown. Initial muscular hypotonia and breastfeeding difficulties of the newborn responded well to oral vitamin B_{12} substitution. Normal development and weight gain so far.
Second case is a 6 months old breastfed female with normal national NBS (but retrospectively slightly elevated C3/C2) presenting with seizures and developmental delay. Metabolic workup showed C3 of 10 µmol/l, HC 203 µmol/l, MMA in urine 290 mmol/mol Krea, vit. B_{12} 165 ng/l, HTC 4.2 pmol/l and low maternal vit. B_{12} (94 ng/l) as cause of vit B_{12} deficiency.
Third case is a 5 months old female with IUGR and microcephaly and consanguineous parents. NBS in the context of a pilot study showed Met 4.2 µmol/l, HC 58.7 µmol/l, MMA 0.4 µmol/l, MC 0.2 µmol/l. Vit. B12 was 216 ng/l. WES showed a homozygous duplication in *MRT*and confirmed cbl G deficiency. Hyperexcitability and opisthotonus improved rapidly under treatment with betaine, folinic acid and hydroxocobalamin. Met reached a constantly normal level but HC remained moderately increased (< 50 µmol/l). Low but growing head circumference (-5,2 z), no significant loss of developmental milestones so far.
Conclusion/ Discussion: These cases indicate that vitamin B_{12} and cbl G deficiency, both conditions with a (more) favorable outcome if the treatment starts early, should be included in the national NBS in order to prevent the manifestation of irreversible neurologic symptoms of affected newborns und to avoid recurrence of vitamin B_{12} deficiency in future pregnancies.

Posters

P21

Lipid nanoparticle-mediated delivery of plasmid DNA for re-applicable, long-term gene therapy independent of pre-existing neutralizing antibodies

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Introduction: Adeno-associated viral vectors (AAV) have achieved tremendous success in clinical trials demonstrating safety and efficacy in delivering a functional copy of a defective gene. However, application is limited by exclusion of patients with pre-existing neutralizing antibodies (NAbs), wide patient-to-patient variation of expression levels and restriction to a single application.
Lipid Nanoparticles (LNP) enable non-viral delivery of nucleic acids independent of NAbs and thereby application and re-administration in all patients. In contrast to AAV, LNP do not deliver their payload to the nucleus but release it in the cytoplasm. This limits their application to RNA-based approaches, such as the clinical trial for GSD1a mRNA-LNP therapy. In addition, duration of gene expression from mRNA is restricted and frequent administrations are necessary to achieve long-term therapeutic effects. Together with Acuitas Therapeutics, we developed novel DNA vectors delivered with LNP, capable of translocating DNA to the nucleus to enable long-term gene therapy for all patients with the option of re-administration.
Patient(s) and Methods: To enable nuclear localization of LNP-delivered DNA, we equipped a luciferase (luc)-expressing plasmid DNA (pDNA) vector with DNA-nuclear targeting sites, which represent binding-sites for transcription factors that shuttle the DNA through the nuclear pores. To reduce the innate immune response to the pDNA payload, we take advantage of a CpG-free pDNA backbone and an LNP-incorporated Dexamethasone-prodrug (Integrated Nanotherapeutics, Vancouver, BC). Acuitas Therapeutics formulated the pDNA in liver-specific LNP.
Results: LNP-pDNA injected BALB/c wt mice showed efficient expression 7 days post-injection (p.i.), which declined by the 1-month time-point. Re-stimulation of isolated splenocytes from these mice with a luc-peptide in an anti-Interferon-γ ELISPOT revealed a transgene-specific T-cell response as limitation for long-term expression. In contrast, immuno-deficient NSG mice showed stable expression until the endpoint 6-months p.i.
Conclusion/ Discussion: In these initial proof-of-concept experiments, we could demonstrate efficient non-viral delivery of pDNA and expression of a reporter gene *in vivo*. Long-term expression was limited by an adaptive immune response against cells expressing the xeno-transgene luc. We aim to investigate whether a similar immune response will develop against more physiological proteins and explore approaches to induce immune tolerance against expressed transgenes.

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