ABSTRACT T 01

Cardiovascular imaging in MPS III patients reveals early left ventricular dysfunction

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Introduction:

Mucopolysaccharidosis type III (MPS III, Sanfilippo disease) is characterized by progressive neurocognitive decline with limited somatic disease. However, sudden unexpected death has been reported in patients with MPS III. As cardiovascular disease (CVD) has been reported in a few isolated cases, we aimed to investigate the presence of CVD among MPS III patients in the Netherlands, and to compare the myocardial function of MPS III patients with those of healthy controls. **Methods:** In this cross-sectional study, echocardiographic studies including Speckle-tracking echocardiography (STE) and left ventricle ejection fraction (LVEF) were performed in 30 MPS III patients (21 patients < 18 years of age, 9 patients > 18 years of age) between 2016 and 2017. Results were compared to data from age and BSA matched controls. **Results:** The mean global longitudinal strain (GLS) on STE, a marker for early left ventricle (LV) dysfunction, was decreased in pediatric MPS III patients (-15.1) compared to healthy pediatric controls (-18.7) (mean difference 4.3, 95% CI 2.53-6.07, p< .001), indicating a reduced myocardial deformation. The mean GLS of adult MPS III patients (-14.4) was also decreased compared to adult controls (-16.2) (mean difference 1.78, 95% CI .29-3.26, p=.021). The mean LVEF was lower in adult patients compared to healthy controls (48.7 vs. 56.1%, p=.003). LVEF in pediatric MPS III patients did not differ significantly from controls. **Conclusion**: STE among both pediatric and adult MPS III patients shows signs of early LV dysfunction confirming cardiovascular involvement in MPS III. As a number of disease modifying treatment options are now in trial, including different modes of gene therapy, this may become clinically important with increasing age of MPS III patients. Further studies are needed to assess a potential link with sudden death in MPS III.

ABSTRACT T 02

Clinical, neuroimaging, biochemical and genetic findings in isolated Sulfite Oxidase Deficiency

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Abstract

Isolated sulfite oxidase deficiency (ISOD) is a life-threatening, autosomal recessive disease characterized by severe neurological impairment. As no long-term effective treatment is available for ISOD, distinction from other treatable diseases, such as molybdenum cofactor deficiency type A, should be made.

We reviewed 47 patients (45 previously reported in the literature). Cases were reviewed for consanguinity, sex, age of onset, death, clinical findings (including spasticity, seizures, psychomotor retardation, feeding difficulties, ectopia lentis, microcephalia), laboratory findings (urinary sulfite, S-sulfocysteine (in plasma and urine), plasma cystine, total homocysteine, uric acid and oxypurines in urine) and radiological findings (including cerebral/cerebellar atrophy, cystic white matter changes, ventriculomegalia). We also aligned the published *SUOX* gene mutations to the reference sequence NM_000456.2.

The onset was mostly during the first 72 hours of life (57%) and within the first year of life in all but 2 patients (96%). All patients presented with neurological abnormalities such as neonatal axial hypotonia and/or peripheral hypertonia (100%), (pharmacoresistant) seizures (84%) or developmental delay (97%). In all patients in whom brain MRI/CT was performed, brain abnormalities were found. Feeding problems were also common. As found in our review, measurement of homocysteine in plasma, amino acids in plasma/urine and sulfite in fresh urine supports the diagnosis of ISOD. Analysis of uric acid (plasma) and oxypurines (urine) is useful to rule out molybdenum cofactor deficiency. The following results are expected in ISOD: low cystine and elevated S-sulfocysteine in urine and plasma, increased sulfite excretion in urine, decreased total homocysteine and normal methionine in plasma, normal uric acid levels in urine and plasma, and normal xanthine and hypoxanthine in plasma and urine. Sulfite has to be determined on fresh urine to avoid false negative results.

ABSTRACT T 03

An *in vitro* model for cartilage defects in MPS VI based on induced pluripotent stem cells

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Mucopolysaccaridosis (MPS) VI is a severe metabolic disease caused by deficiency of arylsulfatase B, which results in lysosomal accumulation of glycosaminoglycans. Current enzyme replacement therapy (ERT) is only partially effective. In particular, cartilage defects that impact growth, hand function and mobility are insensitive to ERT. This warrants the development of novel therapies to address these symptoms. To test these therapies, in vitro disease models based on human cells are required. To this end, we have generated patient-derived iPS cells and performed gene correction using CRSPR/cas9-mediated gene editing to generate isogenic controls. iPS cells were differentiated to chondrogenic cells by mimicking embryonic development into mesendoderm, inhibition of the endodermal lineage, and further differentiation into the mesodermal lineage . Immunofluorescent staining of the key chondrogenic transcription factor Sox9 showed robust expression in >90% of cells. RT-qPCR analysis showed expression of chondrogenic factors including Aggrecan, Collagen II, Collagen XI, MATN3, Sox5 and Sox9 . For the generation of gene corrected iPS cells, we have developed a generic method using CRISPR/Cas9 with high efficiency. With this method we achieved supra physiological enzymatic levels that corrected arylsulfatase B deficiency. This in vitro cell model from human patients provides a tool for the development and testing of personalized medicine for MPS VI and other cartilage disorders.
This project is funded by the WE Foundation.

5 keywords
Cartilage, CRISPR, gene editing, induced pluripotent stem cells (iPSC), mucopolysaccharidosis VI, Maroteaux-Lamy syndrome (MPS VI)

ABSTRACT T 04

A change of focus: determining phenotypic specificity facilitates understanding of pathophysiology in ultra-rare genetic disorders

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Abstract

Data scarcity impedes progress in recognizing, understanding and treating the rapidly growing group of ultra-rare genetic disorders. We hypothesized that looking beyond frequencies of phenotypic descriptions, into the specificity of a disease phenotypic feature, will facilitate recognition and - based on the principle that clinical similarities may be indicative of shared pathophysiology – will provide unsuspected insights in the underlying pathophysiology.

We explored this strategy by studying subunit deficiencies of the Conserved Oligomeric Golgi (COG) complex, a subgroup of Congenital Disorders of Glycosylation (CDG). Prioritization based on the frequency of phenotypic features alone was non-informative. In contrast, prioritization based on phenotypic specificity was highly informative. It captured not only phenotypic features commonly associated with CDG, but also a phenotypic feature associated with GPI-anchoring pathway (in line with the involvement of COG complex in this subset of glycosylation) and phenotypic features not seen in any other CDG. These features possibly hint at presently underappreciated functions of the COG complex. One of these features, accounting for the highest phenotypic specificity in COG-CDG, is episodic fever. Interestingly, the COG complex is implicated in the autophagy pathway, as are more than half of the genes underlying diseases that present with episodic fever. This suggests that whereas many COG-CDG phenotypic features are caused by disrupted glycosylation, episodic fever might be caused by disruption of the COG complex function in autophagy.

In conclusion, we demonstrate that despite data scarcity, our strategy focusing on phenotypic specificity can facilitate progress in understanding underlying pathophysiology of ultra-rare genetic disorders.

ABSTRACT T05

Mutations in SELENBP1, encoding a novel human methanethiol oxidase, cause extraoral halitosis

Selenium-binding protein 1 (SELENBP1) has been associated with several cancers, although its exact role is unknown. We found that SELENBP1 is a methanethiol oxidase (MTO), related to the MTO in methylotrophic bacteria, that converts methanethiol to H_2O_2, formaldehyde, and H2S, an activity not previously known to exist in humans. We identified mutations in SELENBP1 in five patients with cabbage-like breath odor. The malodor was attributable to high levels of methanethiol and dimethyl-sulfide, the main odorous compounds in their breath. Elevated urinary excretion of dimethylsulfoxide was associated with MTO deficiency. Patient fibroblasts had low SELENBP1 protein levels and were deficient in MTO enzymatic activity; these effects were reversed by lentivirus-mediated expression of wild-type SELENBP1. Selenbp1-knockout mice showed biochemical characteristics similar to those in humans. Our data reveal a potentially frequent inborn error of metabolism that results from MTO deficiency and leads to a malodor syndrome. The recent paper on these findings describes a novel biochemical pathway not known to occur in humans and a novel inborn error of metabolism adding a new chapter to the genetic causes of malodor syndromes.

ABSTRACT T06

GAA deficiency in Pompe disease is alleviated by exon inclusion in iPSC-derived skeletal muscle cells

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Pompe disease is a lysosomal storage disease caused by a deficiency of the enzyme acid α-glucosidase (GAA), which results in the accumulation of glycogen in many tissues and organs. A complete lack of the enzymatic activity causes classic infantile Pompe disease, and is characterized by an enlarged heart and generalized skeletal muscle weakness. Without treatment, these patient die within their first year of life. Whenever some residual enzymatic activity is still present, Pompe patients present with a more slowly progressive phenotype that is mainly confined to skeletal muscle weakness. Enzyme replacement therapy (ERT), in which the missing enzyme is given intravenously, is the only treatment currently available. Although beneficial, drawbacks remain, including heterogeneous response and antibody formation. This warrants the development of alternative treatments. We have developed a method to restore GAA enzymatic activity in the majority of Caucasian Pompe patients that share the same mutation, termed IVS1. This mutation affects pre-mRNA splicing. This process is critical for the production of the GAA enzyme. The method uses small molecules termed antisense oligonucleotides (AONs) that correct the effect of the IVS1 mutation. We first identified the AONs using cells derived from skin biopsies obtained from Pompe patients. Because skeletal muscle cells are the relevant cell type in Pompe disease, we developed a protocol for the generation of skeletal muscle cells from skin biopsies. Using these cells we showed that the AONs are able to almost completely restore the defect caused by the IVS1 mutation by restoring the normal production of GAA enzyme. We are currently testing these AONs in a new animal model for Pompe disease. This should pave the way for further clinical development of this innovative therapy.

ABSTRACT T 07

SALIVARY α-IDURONIDASE ACTIVITY AS A NEW BIOMARKER FOR THE DIAGNOSIS AND MONITORING OF THERAPY IN NON-HEMATOLOGICAL TISSUES IN MUCOPOLYSACCHARIDOSIS I

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ABSTRACT

Although disease progression in Mucopolysaccharidosis I (MPS-1) can be attenuated by hematopoietic cell transplantation (HCT), it is increasingly recognized that residual disease is substantial. Biomarkers that would allow us to evaluate the efficacy of HCT (and upcoming new therapies) in non-hematological tissues are needed. Current biomarkers, including the iduronidase (IDUA) activity in leukocytes, are not suitable for this purpose as they are assessed in tissues of hematological origin and may not reflect enzyme availability in non-hematologic tissues. Saliva is a non-hematological body fluid which can be collected easily and non-invasively. We hypothesized that the extent of recovery of IDUA activity in saliva after HCT could provide more insight in what happens in non-hematological compartments. This study in 20 MPS-1 patients shows that the measurement of IDUA activity in saliva is possible and allows diagnosis of IDUA deficiency ($p<0.0001$), with values a magnitude further deviating from the normal range than when assayed in corresponding dried blood spots (DBS). Furthermore, it could possibly differentiate between phenotypes ($p=0.045$). Interestingly, patients exhibit strikingly low values of IDUA in saliva after HCT, far below the normal range of controls ($p=0.013$), contrasting the normal IDUA levels in DBS. We postulate that the limited recovery of donor-derived IDUA activity in saliva after treatment reflects the situation in poorly responding non-hematological tissue compartments unveiling enzyme delivery as a weak spot of the current therapy. Salivary IDUA activity could be used as a biomarker for the evaluation of the effect of new therapies in well vascularized non-hematological tissues.

ABSTRACT T 08

Internet-based onderwijs en zelfmanagement tools in de zorg voor patienten met erfelijke stofwisselingsziekten. Corrie Timmer, diëtist. AMC, Amsterdam

Inleiding
Het gebruik van internetopties voor informatievoorziening, scholing (e-learnings/ webinars) en patiëntenvoorlichting (e-health) neemt steeds meer toe. Ook binnen de zorg voor patienten met een erfelijke stofwisselingsziekten (IEM) zijn internet tools in opkomst. Het doel van deze rapportage is om een overzicht te geven van beschikbare tools in Nederland.

Methoden
Er werd een inventarisatie gemaakt van internet-based tools met focus op zelfmanagement apps voor patienten en praktische informatie/e-learnings voor professionals. Op basis van expert kennis en internet search Zoektermen: (inborn error of metabolism OR PKU OR GSD OR keto) AND (App OR online course OR e-learning) wordt een overzicht gepresenteerd.

Resultaten
Zelfmanagement apps:
Op internet zijn internationaal veel zelfmanagement apps te vinden (tientallen), waarvan veel niet gevuld/ geupdate of onafhankelijk. Nederlandse Apps zijn er 2: PKU (zonder eiwitgetallen) en PKU kenner (PKU vereniging ism MODAZ: https://pkukenner.nl/). De App PKUkenner wordt door PKU patiënten steeds meer gebruikt voor het bijhouden van de eiwitinname. Een tweede App (voor non-PKU aminozuur-stofwisselingsziekten) is in aanbouw. Voor GSD wordt een App gekoppeld aan een uitgebreider dossier, inclusief een koppeling met een glucosesensor (https://www.stofwisselingsziekten.nl/gsd-app-ontwikkeling/). Dit vraagt extra veiligheidseisen vanwege het delen van gevoelige informatie via internet. Patiënten die een ketogeen dieet gebruiken voor hun metabole ziekte moeten veel rekenen, waarvoor nu een ketoCalculator App wordt ontwikkeld, gebaseerd op de huidige (exel based) ketocalculator. Er is daarnaast een website die wordt verbeterd (met filmpjes en recepten): www.ketogeenmenu.nl. Voor PKU wordt door enkele centra gebruik gemaakt van "mijnpku.nl": een zelfmanagement platvorm waarin eenvoudig fenylalanine-waarden en korte berichten gedeeld kunnen worden tussen behandelaren en patiënten (ten Hoedt et al, Orphanet J Rare Dis. 2011)

Praktische informatie en e-learnings voor professionals:
De internisten voor volwassenen met erfelijke stofwisselingsziekten hebben een nieuwe website gelanceerd, waarbij onder andere het snel raadplegen van een ziektespecifiek noodprotocol mogelijk is: www.investof.nl. Van zulke naslagwerken zijn internationaal ook diverse te vinden (7 stuks).
E-learnings zijn internationaal beschikbaar: 13 stuks, 5 vanuit industrie, 2 gesponsord, 2 niet online, 2 betaald, 2 gratis. Nationaal zijn ze niet vindbaar. Recent is in Nederland een e-learning online gegaan over het belang van dieetmaatregelen bij IEM. Doelgroepen zijn startende behandelaren en onderzoekers en behandelaren in de eerste en tweede lijn die patiënten met IEM tegenkomen in hun werkveld. Deze nascholing, volledig gebaseerd op casuïstiek en voorzien van achtergrond informatie, behandelt de belangrijkste elementen van dieet en voeding bij verschillende erfelijke stofwisselingsziekten. Op deze site zijn al langer e-learnings beschikbaar over de ziekte van Gaucher en Fabry. De e-learnings worden kosteloos aangeboden vanuit het AMC en zijn geaccrediteerd (http://zz-academie.nl).

Conclusie: internet neemt een steeds belangrijkere plaats in bij onderwijs en bij zelfmanagement van patienten. Bekendheid met deze mogelijkheden is van belang om er optimaal gebruik van te kunnen maken. Inzicht in de kwaliteit van de geboden informatie (up-to-date houden, onafhankelijkheid, betrouwbaarheid) is een vereiste. In Nederland zijn enkele goede initiatieven met een mooi eindproduct voor scholing van zorgverleners en zelfmanagement ondersteuning van patiënten met erfelijke stofwisselingsziekten.

ABSTRACT T 09

Ana Coelho

Zebrafish model for classic galactosemia: new insights on damage onset

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We have developed a zebrafish model for classic galactosemia (CG) that mimics the human biochemical and clinical phenotypes (neurologic and fertility impairments in the absence of exogenous galactose). We have used this model to gain new insights on damage onset of brain and gonadal impairments, particularly if it begins prenatal. For this purpose we have crossed our CG line with the reporter lines that carry brain- and gonadal-specific promoters driving GFP expression (*mbp*:GFP and *vasa*:GFP, respectively).

Brain impairments were evaluated by motor activity, histological analysis and myelination pattern using the *mbp*:GFP *galt* line. Motor activity was examined in WT and KO fish throughout development: larval stage (5 days old), juvenile stage (4 weeks old) and adulthood (3 and 9 months old). KO and WT larvae showed similar activity, whereas KO fish showed a decreased motor activity from juvenile stage onwards. Histological analysis (H&E staining) of juvenile and adult fish (4 weeks and 1 year old, respectively) revealed no major anatomic abnormalities of KO fish. Myelination pattern in early stages of development revealed a decreased length in a specific tract at 10 days in KO fish.

Ovarian impairments were evaluated by macroscopic, histological and fertility analysis. Macroscopic examination of adult fish revealed significant differences between WT and KO. Histological analysis (H&E staining) of juvenile and adult fish (4 weeks and 1 year old, respectively) revealed gonadal abnormalities: total number of follicles was significantly decreased in KO fish and, whereas follicles in the early developmental (ED) stage were decreased, follicles in the early vitellogenic (EV) stage were increased in KO fish. Fertility was evaluated by a series of crossings (mass matings) of WT and KO fish at key time points. KO fish presented a lower number of eggs earlier in development than WT fish. Additionally, using the *vasa*:GFP *galt* line, we could evaluate primordial germ cells (PGCs) migration pattern and number in early stages of development. Number of PGCs does not seem to be significantly affected in KO fish. Migration pattern however is more frequently abnormal than in WT fish, with KO fish often presenting PGCs of ectopic location.

Overall, these findings suggest that there are early postnatal abnormalities in CG. This observation suggests that therapy should be initiated early in life so that it can effectively prevent the development of long-term complications

ABSTRACT T 10

The redox modulating small molecule KH176: from drawing table towards clinical phase 2 trials

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In recent years, there has been substantial progress on many fronts in our understanding of diseases affecting mitochondrial oxidative phosphorylation. Based on this knowledge various new therapeutic intervention strategies like those with small molecules are under development. I will review the state of the art of development of Khondrion's proprietary small molecule library with KH176 as a prototypic example.

KH176 is an orally bio-available small molecule developed to relief mitochondrial patient reported symptoms and stop disease progression. The compound is a member of a new class of drugs essential for the control of oxidative and redox pathologies. Phase 1 clinical trials, performed in healthy male volunteers, consisting of single ascending and multiple dosing arms both randomized, placebo controlled and double-blinded, deemed that KH176 is well tolerated and had the preferable pharmacokinetic profile for a twice daily dosing. Tolerability, safety and efficacy of orally supplemented KH176 is currently being evaluated in a proof of concept study, the KHENERGY study, in adult patients harbouring the m.3243A>G mutation. The headline results of this Phase 2 study and the next steps will be presented.