

Title: Evaluation of dietary treatment and amino acid supplementation in patients with organic acidemias and urea cycle disorders. Information from a world wide database (EIMD-registry).

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Abstract:

The daily dietary management in organic acidemias (OA) and urea cycle disorders (UCD) is very diverse (1, 2). The major aims of this study are to assess the long-term dietary treatment in OA and UCD in comparison with the guidelines in a large patient cohort and to assess metabolic control by evaluation of plasma amino acids levels. Protein intake was compared to recommended daily allowance (RDA) by WHO 2007 (3) and plasma amino acid z-scores were calculated by comparing plasma levels with the amino acid reference values (4). A total of 630 OA and 460 UCD patients from the European registry and network for intoxication type metabolic diseases (E-IMD, EAHC no. 2010 12 01) were included. In the majority of the patients the amount of natural protein intake exceeded the recommended daily allowance (RDA) (65% in OA and 54% in UCD). Plasma BCAA levels were very low in MMA and PA (mean plasma valine z-score \pm SD: -2.5 ± 1.4 , mean isoleucine z-score \pm SD: -1.9 ± 1.4 and mean leucine z-scores \pm SD: -1.1 ± 2.0) and in UCD (mean BCAA z-score \pm SD: -3.4 ± 4.8). In OTC and CPS1 and HHH those receiving monotherapy L-citrulline had higher plasma arginine z-scores as compared to those receiving monotherapy L-arginine ($F(114)=2.149$, $p=0.034$), while plasma levels did not differ between those receiving monotherapy L-citrulline and those receiving combination of L-citrulline and L-arginine ($F(94)0.147$, $p 0.884$).

We can conclude that, despite a relative high natural protein intake in comparison to guideline recommendations, metabolic control defined by the plasma BCAA levels, in MMA, PA as well as in UCD, is insufficient and more attention in daily practices with respect to patient outcome is required. Furthermore, L-citrulline either or not in combination with L-arginine may be preferable in OTC, CPS, HHH compared to L-arginine monotherapy.

This work was financially supported by Metakids and the Erasmus Medical Center.

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Evaluation of C26:0-lysophosphatidylcholine and C26:0-carnitine as diagnostic markers for Zellweger spectrum disorders

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Introduction: Zellweger spectrum disorders (ZSD) are a group of genetic metabolic disorders caused by a defect in peroxisome biogenesis. This results in multiple metabolic abnormalities, including elevated very long-chain fatty acid (VLCFA) levels. Elevated levels of C26:0-lysophosphatidylcholine (C26:0-lysoPC) have been shown in dried blood spots (DBS) from ZSD patients. However, little is known about the sensitivity and specificity of this marker and C26:0-carnitine, another VLCFA-marker, in ZSD. We investigated C26:0-lysoPC and C26:0-carnitine as diagnostic markers for ZSD in DBS and fibroblasts.

Methods: C26:0-lysoPC levels in 91 DBS from 37 different ZSD patients were determined and compared to the levels in 209 control DBS. C26:0-carnitine levels were measured in 41 DBS from 29 ZSD patients and 97 control DBS. We measured C26:0-lysoPC levels in fibroblasts from 24 ZSD patients and 61 control individuals.

Results: Elevated C26:0-lysoPC levels (>72 nmol/L) were found in 86/91 ZSD DBS ($n=33/37$) corresponding with a sensitivity of 89.2%. Median level was 567 nmol/l (range 28 - 3133 nmol/l). Consistently elevated C26:0-carnitine levels (>0.077 μ mol/L) in DBS were found in 16 out of 29 ZSD patients corresponding with a sensitivity of 55.2%. C26:0-lysoPC levels were elevated in 21/24 ZSD fibroblast lines.

Discussion: C26:0-lysoPC in DBS is a sensitive and useful marker for VLCFA accumulation in patients with a ZSD. C26:0-carnitine in DBS is elevated in some ZSD patients, but is less useful as diagnostic marker. Implementation of C26:0-lysoPC measurement in the diagnostic work-up when suspecting a ZSD is advised. This marker has the potential to be used for newborn screening for ZSD.

New developments and insights into defects of the pentose phosphate pathway

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Introduction

In recent years three defects in the oxidative part of the pentose phosphate pathway (PPP) have been described. Ribose-5-phosphate isomerase (RPI) deficiency, Transaldolase (TALDO) deficiency and very recently Transketolase (TKT) deficiency.

Patients

RPI deficiency: 13 years after the first report a second patient has been diagnosed by genetic panel testing, MR spectroscopy and polyol analysis in urine, giving more insight in the phenotype.

TALDO deficiency: To improve the knowledge of TALDO deficiency we performed a retrospective study of clinical, biochemical and molecular genetic data of 34 patients from 25 families with proven TALDO deficiency.

TKT deficiency: 5 patient from 3 families were diagnosed with TKT deficiency by WES, abnormal polyol analysis and enzymatic testing.

Results

RPI deficiency: The second male patient is now 18 years old, had psychomotor retardation and developed epilepsy at the age of 9 months. From 7 years he regressed neurologically and lost most of his skills, he has visual impairment with retinitis pigmentosa. MRI revealed diffuse, extensive cerebral white matter abnormalities. A novel homozygous missense mutation (c.592T>C; p.Phe198Leu) in exon 6 of the RPIA gene was detected. MR spectroscopy showed a prominent peak between 3.6 to 3.8 ppm which represents arabitol and ribitol. In urine D-arabitol and ribitol were more than 50 times the upper level of normal.

TALDO deficiency: Most of the patients have a normal mental development. Presentation can be divided in early and late onset. In early onset 77% present with hepatic dysfunction, while in late presentation only 33% had liver dysfunction. Overall cardiac and kidney abnormalities were found in 35 and 29%, respectively. Anemia and thrombocytopenia are seen in 66 and 70% of cases. Common dysmorphic features were abnormal skin (69%), cutis laxa (56%) and a triangular face (44%).

TKT deficiency: All patients were small for gestational age, had short stature, and had a delayed development. Congenital heart defects were frequent. Chronic diarrhea and cataracts were noted in the older individuals. TKT enzymatic activity was significantly reduced in all cases. Elevated urinary excretion of erythritol, arabitol, ribitol, and pent(ul)ose-5-phosphates were detected as well as elevated erythritol, arabitol and ribitol in plasma in these patients.

Conclusions

It is important to recognise patients with a defect in the PPP, since they probably are often missed in the diagnostic work-up. Analysis of polyols in urine is an essential test in diagnosing these disorders.

Nucleotide analysis of a gene panel involved in Lysosomal Storage Disease (LSD) in patients with a strong clinical suspicion.

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The diagnostic workup in patients clinically suspected of Lysosomal Storage Diseases (LSD) is often challenging due to the variability in the clinical phenotype and inconsistent genotype-phenotype correlations. The standard sequential workflow of a urine screening, followed by enzymatic testing and a final confirmation by iterated Sanger sequencing is time consuming, not widely available and poorly standardized. To counter these issues, we developed a next generation sequencing (NGS) gene panel for mutations in for 50 LSD-causing genes . Over a period of ten months, we analysed 80 samples from patients with a strong clinical suspicion of an LSD. Our panel was able to determine the molecular cause of the disease in 14 cases (17%), including diseases such as ceroid lipofuscinosis type 6 and 7, Niemann Pick C, Wolmann disease, MPSI, II and IV (Morquio B), cystinosis, mannosidosis type I and II and finally mucopolipidosis type II and III. Most of these patients were missed by multiple rounds of conventional biochemical testing. The NGS-based approach was also able to redirect certain diagnoses: e.g., a patient initially suspected of galactosialidosis was found to be compound heterozygous for pathogenic mutations in the *GNPTAB* gene, causing mucopolipidosis type II or III. Additionally, we identified several patients as carriers of pathogenic mutations in LSD genes, including *GBA*. Carriers of *GBA* mutations have an increased chance of developing early onset Parkinsonism, making early genetic counselling possible. In view of these results, we propose that panel-based NGS should be considered as first-line test in the LSD diagnostic workflow.

Neonatal cholestasis: a metabolic diagnostic odyssey of our times.

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Introduction:

Neonatal cholestasis has many etiologies and is in 25% due to inborn errors of metabolism. The diagnosis is anything but straightforward and requires an extensive, sometimes invasive work-up. The list of differential diagnoses grows continuously.

Patient

A male patient was born at term (birth weight 3.66 kg). Initially, there was unconjugated hyperbilirubinaemia that settled with phototherapy. There was also cutis laxa with excess skin in the neck, axilla and groin and unilateral cryptorchidism. A cardiac murmur led to an ultrasound of the heart that showed a dilatation of the sinus aortae.

At 2 weeks of age he had an UTI with sepsis due to *E. Coli*. At 2 months he developed conjugated jaundice bilirubin direct/total 4.49/13.77mg/d, AST 401 iu/L, ALT 73 IU/L, gammaGT and ALK phos normal, ceruloplasmin 0,03 mg/dL. Stools were pigmented. Liver ultrasound showed normal bile ducts, hyperechogenic liver parenchyma, normal liver size but enlarged spleen (+3.7 stdev). CMV pcr was positive but urinary cultures and CMV PCR on newborn screening were negative. Urinary polyols showed an increased galactitol (227 mmol/mol creat, nl 3-81) but galactose-1-P-urinyl transferase showed a normal activity. TALDO deficiency was excluded.

At the age of 2 months there was a normal psychomotor development with increasing hepatosplenomegaly and improvement of the cutis laxa. Sialotransferrin isoelectric focusing showed a type 2 pattern. A liver biopsy showed micronodular cirrhosis with a ductular reaction. There was also steatosis of the hepatocytes. There were PAS positive globules within the hepatocytes.

At the age of 5 months he presented with a pneumonia. On this occasion on a chest X-ray an anterior diaphragmatic hernia (Morgagni) was documented. CT confirmed precordial herniation of the colon in front of the lungs. This was surgically corrected.

MALDI-TOF showed truncated glycans with mainly desialylation indicating a defect in golgi acidification. Mutation analysis of the *ATP6AP1* (Xq28) showed a new mutation: c.649T>A, p.217Y>N. This is in a highly conserved locus down to zebrafish.

Conclusion

We describe a new case of ATP6AP1-CDG with a novel mutation and expand the phenotype with heart, skin and diaphragmatic involvement. So far 11 cases (3 families) have been described with ATP6AP1-CDG with severe liver involvement as the most prominent feature.

Biomarkers of Oxidative Stress, Inflammation, and Vascular Dysfunction in Inherited Homocystinuria and the impact of Taurine Treatment

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Background: Cystathionine β -synthase deficient homocystinuria (CBS DH) is clinically silent at birth but with significant morbidity over time with excessive clotting, dislocated lenses, scoliosis, osteoporosis, cognitive impairment and seizures. Current treatment is sub-optimal with difficult compliance and has not improved substantially in over 30 years. Data from a CBS DH mouse model implicated oxidative stress and inflammation in pathogenesis, and showed that taurine treatment mitigated these effects and improved clotting abnormalities. To translate this basic laboratory research, a formal human clinical study was designed to investigate first the safety profile and pharmacokinetics of taurine therapy in individuals with CBS DH, and second whether markers of oxidative stress, inflammation and of platelet or endothelial function would be abnormal, and which of these would respond to taurine administration.

Study setup: We enrolled 14 patients (ages 8 – 35 years, 8 males, 6 females) with molecular confirmed CBS DH not fully responsive to vitamin B6 treatment with homocysteine levels $> 50 \mu\text{M}$, and without inflammatory disorder or antioxidant therapy, and 22 matched control subjects. Age groups were prepubertal 27%, teenage 27%, young adult 27%, and adult 14%. At baseline, we determined 5 biomarkers of oxidative stress, 13 markers of inflammation, and 11 disease-related metabolites, and lipid profiles. We measured thromboxane B2 metabolite levels to evaluate platelet activation, and we performed brachial artery flow-mediated dilation (FMD) studies to evaluate endothelial function. Subjects were then treated with taurine for 4.5 days. After two subjects received 25 mg/kg twice daily, the remaining 12 subjects received the intended high dose therapy of 75 mg/kg twice daily. The response to therapy was measured after 4 hours treatment for immediate effect and after 4 days treatment.

Results: Taurine treatment was well tolerated with minor, transient adverse effects of gastrointestinal discomfort (43%) and headache (7%), and elevation of triglycerides most notably in subjects with preexisting hypertriglyceridemia. CBS DH patients had higher baseline taurine levels than controls. Taurine pharmacokinetics were very rapid reaching a maximum at 1.2 hours after dosing, and returning to near normal levels at 12 hours after dosing, but with slow accumulation resulting in elevated predosing levels (190%) after 4 days treatment. Biochemically, patients had elevated homocysteine, SAM, SAH, and taurine levels, but lower levels of betaine (when not betaine treated). Betaine treatment decreased homocysteine, and increased methionine, dimethylglycine, methylglycine and serine. Taurine treatment had no effect on any biochemical parameter other than taurine itself. Taurine treatment increased triglyceride levels ($p=0.01$), but cholesterol levels or Apo-A1 levels did not change, whereas betaine treatment decreased Apo-A1 levels.

There was marginal evidence for inflammation with borderline elevated TNF- α and high sensitivity CRP. The latter decreased slightly after taurine treatment, but a major decrease was observed in betaine treated patients. There was evidence for increased oxidative stress on 2,3-dinor-5,6-dihydro-isoprostane F2 α -III and superoxide dismutase levels but not on TBARS or dityrosine levels, and no impact of taurine. Thromboxane B2 metabolites were normal indicating no activation of platelet aggregation. FMD studies showed a treatment

improvement with taurine for patients with high homocysteine levels (n=6,+53%) and particularly when pretreatment FMD was depressed (<10mm) (n=8, +65%, p=0.01). Finally, of 4 patients with elevated Lipoprotein a levels (>30 mg/dL), 2 had experienced a thrombotic event, whereas of 8 patients with low Lp(a) levels none had a thrombosis.

Conclusion: This exploratory study confirms mild levels of inflammation and oxidative stress with limited response to taurine intervention. It identified a positive effect of taurine treatment in patients with abnormal endothelial function and suggests that the relation of Lp(a) levels to abnormal clotting events should be further investigated. High dose taurine was found to be a safe treatment with rapid kinetics but with a long-term accumulation effect. Future studies of taurine should consider either frequent dosing or a slow release formulation.

Patient van 2 maanden met Wolman: effecten van Sebelipase en dieet.

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Introductie: Lyosomal Acid Lipase deficiëntie (LAL-D) is een uiterst zeldzame en ernstige SWZ die behandeld kan worden met enzym Sebelipase. Veel is echter nog onduidelijk over de behandeling.

Casus: Op leeftijd van 2 maanden presenteerde een jongen zich met koorts, hepatosplenomegalie. X-thorax liet calcificaties van de bijnieren zien. De verdenking LAL-D werd bevestigd door enzym studies (LAL 3%, homozygotie c.894+1G>A *LIPA*). Sebelipase startte op 1 mg/kg/wk maar werd opgeklommen naar 5 mg SA/kg/5 dagen bij klinische verslechtering (ascites niet op eerste echo maar later fors).

Resultaten: Na ongeveer 2 maanden was de 'turning point', begon de lever en miltomvang af te nemen, zag je na nog wat pieken de laboratoriumwaarden normaliseren. Gewichtstoename en enterale voeding (diarree) waren de laatste zaken die verbeterden, waarbij ook sprake was van een microcephalie die later weer werd ingehaald. De patient is nu bijna anderhalf jaar, loopt los, praat nog weinig, is sociaal vaardig en heeft een goed fijne motoriek.

Discussie: Hoewel de eerste 2 weken winst werd geboekt leek daarna de situatie alleen maar weer slechter te worden, waarbij het mogelijk zou kunnen zijn dat de verhoging van de dosering van Sebelipase maar ook de special TPN de 'turning point' mogelijk maakten. Biochemische follow-up met niet alleen ferritine, TG, leverwaarden maar ook chitotriosidase en organische zuren kan behulpzaam zijn om te begrijpen waar patient 'staat'. Teameffort met een team dat niet alleen metabole specialisten maar ook 'OLT en darmtransplantatie kennis' heeft is nodig om deze kinderen in expertise centrum te behandelen.

Identification of a human D-lactate dehydrogenase.

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Introduction: Human knockouts may provide direct insight into gene function. We identified two patients homozygous for loss-of-function variants in LDHD, lactate dehydrogenase D. Lactate dehydrogenases catalyze the interconversion of pyruvate and lactate during anaerobic glycolysis, with L-lactate the form utilized in eukaryotic metabolism. D-lactate, the stereoisomer, is normally present physiologically at much lower levels. D-lactate in the human body has received recent attention due to D-lactic acidosis incidence, a complication of short bowel syndrome.

Materials and Methods: Mass spectrometry performed on two patients identified increased urine excretion and elevated plasma concentration of D-lactate, D-2-hydroxyisovaleric acid and D-2-hydroxyisocaproic acid. Sanger sequencing was performed on LDHD, a candidate gene in a region of homozygosity identified by SNParray. Functional studies were performed in the zebrafish model organism using a LDHD knockout line and patient variant expression. Metabolic levels of D-lactate were evaluated by mass spectrometry.

Results: Sanger sequencing identified two novel, homozygous LDHD missense variants. LDHD loss-of-function in zebrafish resulted in increased D-lactate concentration. Expression of human wildtype LDHD rescued D-lactate metabolism resulting in D-lactate concentration decrease. In contrast, patient variant LDHD expression was unable to restore LDHD function and resulted in elevated D-lactate levels. Together our results confirmed a role of LDHD in D-lactate metabolism and the loss-of-function effect of our patient's variant.

Conclusion: LDHD has been identified as a putative metabolizer of D-lactate but its function had not been shown in vivo. Our work provides the first evidence that LDHD is essential for D-lactate metabolism in humans.

Phenotype, disease severity and pain are major determinants of quality of life in Fabry disease: results from a large multicenter cohort study.

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Background: Quality of life (QoL) is decreased in patients with Fabry disease (FD). To improve QoL, it is important to understand the influence of FD related characteristics, symptoms and complications. In this retrospective cohort study we explored the effect of *pain, phenotype, treatment and FD-related complications on QoL.*

Methods: QoL data of Fabry patients as assessed by the EuroQol five dimension questionnaire (EQ- 5D) from two international centers of excellence were retrospectively collected. Health profiles and utilities were calculated per sex and phenotype, and the effect of age, pain and ERT was studied. In addition, we evaluated whether different states of disease severity impacted on QoL.

Results: For 286 adult FD patients (mean age 42.5 years, 40% men, 60% classical phenotype) 2240 EQ-5Ds were available. QoL is decreased in men as well as women with FD, especially in older men with a classical phenotype. At age 50, utility was lower in men with classical FD compared to those with non-classical disease ($\beta = -0.12$, 95% CI: -0.23 – 0.01, $p=0.037$) with further difference in the years thereafter. Cardiovascular disease, stroke or transient ischemic attacks, multiple FD-related complications and pain were also associated with decreased utilities. Overall, no change in utility was seen in patients on ERT over a mean follow-up of 6.1 years.

Conclusion: FD leads to a decreased QoL compared to the general population. Disease complications and pain both negatively influence QoL. Adequate assessment and treatment of pain as well as improved strategies to prevent disease complications are needed to improve QoL in the FD population.

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