P5.43

Fat and sugar metabolism during exercise, with and without L-Carnitine supplementation, in patients with medium chain acyl-CoA-d

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It is unclear to which extent skeletal muscle is affected in patients with Medium-chain acyl-CoA dehydrogenase deficiency (MCADD). L-carnitine is commonly used as a dietary supplement to MCADD-patients, though it has not been verified that they benefit from this. We investigated:

- fuel utilisation during prolonged low-intensity exercise in MCADD-patients using indirect calorimetry and stable isotope technique.
- if 4 weeks of L-carnitine supplementation has influence on fuel utilisation during exercise.

3 asymptomatic patients (18–33 years) with genetically verified MCADD and 12 untrained, healthy, age- and sex-matched controls (19–32 years) were included. Incremental cycling tests determined maximal oxidative capacities (VO2max) and maximal workload capacities. On a separate day, the subjects performed a 1 h cycling test at a constant workload equal to 55% of VO2max while given an infusion of the stable isotope [U-13C]-palmitate. Patients ingested L-carnitine (100 mg/kg/day) for 4 weeks, after which, the cycle tests were repeated. At rest, palmitate rates of appearance (Ra) did not differ significantly between patients (2.6 ± 0.5 μmol/kg/min) and controls (2.7 ± 0.3 μmol/kg/min). During exercise, palmitate Ra increased in healthy subjects with 3.9 ± 0.5 μmol/kg/min, whereas in patients palmitate Ra increased with 2.3 ± 0.5 μmol/kg/min, which is significantly lower ($p < 0.05$). L-carnitine supplementation did not induce changes in palmitate Ra in patients at rest (3.2 ± 0.3 μmol/kg/min) nor during exercise (4.8 ± 0.7 μmol/kg/min) Results indicate an impaired ability to increase fatty acid oxidation (FAO) in MCADD-patients during exercise. Increase is not absent, as in other FAO disorders, but is significantly lower than in controls. Thus patients may have a deranged skeletal muscle metabolism. We found no effect of L-carnitine in patients indicating that the possible benefit of it cannot be attributed to an increase in FAO in MCADD-patients.

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P5.44

Novel mutation in PNPLA2 presenting with distal myopathy and lipodystrophy

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Neutral lipid storage diseases are rare autosomal recessive disorders characterized by triglyceride accumulation in several tissues. Two distinct clinical entities have been described: neutral lipid storage myopathy with ichthyosis or Chanarin–Dorfman syndrome due to CGI-58 gene mutations, and neutral lipid storage disease with myopathy caused by mutations in PNPLA2 gene. To report on a novel mutation in PNPLA2 gene in a patient presenting with distal myopathy, abnormal adipose tissue distribution and mild skin involvement. A 46-year-old woman, born from healthy consanguineous parents, was referred for evaluation of distal asymmetrical weakness of upper extremities starting around the age of 32. Her younger sister and her two sons were healthy. On examination she had abnormal adipose tissue distribution and prominent asymmetrical weakness of distal muscles of upper extremities, and to a lesser extent in proximal muscles of upper limbs. In addition, she had a moderate skin xerosis and some plaques of eczema in periumbilical area and limbs. Deep tendon reflexes were present; sensation was intact. Cardiac evaluation revealed no abnormalities. CK levels were 5-fold increased. Muscle MRI revealed severe involvement of glutei, hip adductors, soleus, posterior tibialis and both grastocnemius. Peripheral blood smears showed Jordan's anomaly in leukocytes. A muscle biopsy showed abundant lipid droplets in type I fibers and rimmed vacuoles. Lipid droplets were also observed in the basal layer of the epidermis. Sequencing analysis of PNPLA 2 gene revealed a homozygous c896_897CCTA (p.LEU 03PorfsX4) mutation. We report a novel mutation in PNPLA2 gene causing distal asymmetrical myopathy, abnormal adipose tissue distribution and mild skin involvement. Our observations expand the clinical manifestations associated with PNPLA2 gene mutations.

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P5.45

Recurrent rhabdomyolysis caused by LPIN 1 gene mutation in a patient affected by Charcot–Marie–Tooth 1A

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Recently, LPIN1 gene mutation has being described as the main cause of recurrent episodes of rhabdomyolysis in early childhood. LPIN1 gene encodes the muscle-specific phosphatidic acid phosphatase, a key enzyme in triglyceride and membrane phospholipid biosynthesis. Herby we report a 9 year old boy affected by this condition. He was born from non consanguineous healthy Caucasian parents. From the age of 2 years, the patient presented tip-toe walking and pes cavus. At 5 years, he suddenly presented headache, vomiting, myalgia, generalized weakness, stupurous and breathing difficulties requiring mechanical ventilation. Deep tendon reflex were abolished and Achilles tendon retraction was observed. Patient recovered in tree weeks normalising the plasma CK values. Tree years later he presented another rhabdomyolisis episode. EMG showed a demyelinating polyneuropathy. EEG revealed slow background activity. Brain CT scan and echocardiogram were normal. CK levels were increased (peak level 270,000 IU/L) with overt myoglobinuria. Glycogenolysis, fatty acid beta-oxidation (FAO), and oxidative phosphorylation studies were normal. Muscle biopsy showed abundant basophilic regenerative muscle cells and inflammatory infiltrate. There were several necrotic fibres. Oxidative enzymes staining revealed myofibrillar disorganisation in some fibres. The size of the lipid droplets was increased but glycogen was normal observed. Homozygous intragenic deletion, c.2295-866 2410-30del, was detected in LPIN1gene. PMP22 duplication was also identified, confirming the associated diagnosis of CMT1a.

1. The screening for LPIN1 mutations should be included at early stage of the metabolic work up of myoglobinuria, after exclusion of FAO and glucogenoses.

2. It is important to perform genetic studies for PMP22 to explain the demyelinating neuropathy which in this case does not seem directly linked to the LPIN1 gene defect.

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P5.46

***LPIN1* gene mutations can cause familial rhabdomyolysis and unexpected death in infancy**

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Mutations in the *Lipin1* gene (LPIN1 MIM#605518) are associated with the second most frequent cause of early-onset rhabdomyolysis in children. Lipin-1 is predominantly expressed in muscle and exhibits a dual role as a phosphatidate phosphatase 1 and as a transcriptional co-activator. We report on two families in whom the previously healthy siblings of the indexpatients died unexpected in early infancy. Indexpatient P1 is the second child of healthy parents. At the age of eight years the girl developed a severe rhabdomyolysis following a mild upper airway respiratory infection and prolonged physical activity. Metabolic causes of acute rhabdomyolysis were excluded. Moleculargenetic analysis revealed a compound heterozygote mutation (c.2295-863_2410-27del/c.2401C > T) in the *LPIN1* gene. The elder brother of P1 had a mild episode of rhabdomyolysis following an orchidopexia at the age of three years and died acute with generalised muscle hypotonia, myalgia, vomiting and somnolence at age four years. Urine was reported to be "dark" and "liver enzymes" were elevated. Autopsy revealed signs of generalised lympho-plasmacellular infiltration of the analysed organs including the myocard. Indexpatient P2 is a four year old girl who had two episodes of rhabdomyolysis at the age of three and four years following prolonged physical activity and abrosia. Mutation analyses revealed a compound heterozygote *LPIN1* mutation (c.2253_2254del/c.57C > A). The younger brother of P2 died acutely at the age of 33 months following a viral myositis four weeks prior to his death. Autopsy showed left ventricular heart failure. He had the identical compound heterozygote *LPIN1* mutation as P2. Identification of *LPIN1* mutations should lead to extensive testing of all siblings and consecutively careful cardiorespiratory monitoring of all molecularly diagnosed individuals although asymptomatic. Impact of *LPIN1* mutations in (pediatric) patients with sudden death syndrome is unclear.

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P5.47

No second wind phenomenon, but glucose improves exercise capacity in Phosphoglucomutase deficiency

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Muscle specific Phosphoglucomutase (PGM) is a rare glycogenosis, which has been diagnosed in less than 5 persons. The function of the PGM enzyme is to facilitate the conversion of glucose-1-phosphate (released from muscle glycogen) to glucose-6-phosphate. We present a patient with symptoms of cramps and myoglobinuria after dynamic exercise. Due to the nature of the metabolic block, we hypothesised that the patient with PGM deficiency could improve exercise tolerance with IV glucose infusion, similar to what is seen in McArdle disease (Myophosphorylase deficiency). One male patient (37 years old), and five healthy male subjects were included (35 ± 14 years). Neurological examination of the patient showed mild pelvic weakness, but was otherwise normal. Peak oxidative capacity (VO2peak) was determined with an incremental cycle test. On separate days the subjects cycled at a constant load corresponding to 70% of their VO2peak for 32 min, after which workload was increased gradually every other minute until exhaustion. This was done with either a placebo infusion or an IV glucose infusion. There was no second wind and IV glucose infusion lowered heart rate and ratings of perceived exertion (RPE) (138 ± 4 vs. 151 ± 6 bpm and 12 ± 0 (easy) vs.15 ± 1 (hard)), and exercise was prolonged by 2 min by glucose. Workload and VO2peak (225 vs. 200 Watts and 43 vs. 29 mL min-1 kg-1) increased with IV glucose infusion. This was in contrast to findings in healthy controls, where no differences between the two trials were found. The patient with PGM deficiency improved exercise tolerance with IV glucose supplement during exercise, a finding that has so far only been found in patients with McArdle disease. This indicates that PGM is a key enzyme in the glycogenolytic pathway, and that the patients likely will benefit from oral sucrose before exercise. This might protect skeletal muscle from damage during high intensity exercise.

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P5.48

Infantile-onset permanent weakness in muscle phosphofructokinase deficiency

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Patients with muscle phosphofructokinase (PFK) deficiency typically present exercise intolerance, rhabdomyolysis episodes and haemolytic anemia. Two clinical variants have been described, one manifesting as late-onset muscle weakness in adult after a lifelong history of exercise intolerance, and the other occurring in young children with both generalised weakness and symptoms of multisystem involvement. We report the case of a patient with progressive muscle weakness without rhabdomyolysis episodes or anemia. A 41 years-old woman, originating from Morocco presented a progressive muscle weakness since the age of 7 years, with difficulties for climbing stairs and raising from the floor or a chair. She also mentioned muscle fatigability since childhood, but never noticed muscle pain or dark urines. Clinical examination revealed a limb weakness predominating on deltoids and psoas (3/5 on MRC scale). Echocardiography was normal. Muscle biopsy revealed vacuoles in the majority of muscle fibers with considerable glycogen storage (a massive increase in PAS staining) and polysaccharide deposits resistant