Karolinska Institutet

Från Institutionen för Kvinnor och Barns Hälsa

Energy Metabolism and Clinical Symptoms in Beta-oxidation Defects, Especially Long-Chain 3-Hydroxyacyl-Coenzyme A Dehydrogenase Deficiency

AKADEMISK AVHANDLING
som för avläggande av medicine doktorsexamen vid Karolinska Institutet offentligen försvaras i Hörsalen Novum, plan 4, KI Campus Huddinge, Karolinska Universitetssjukhuset

Fredagen den 20 maj 2016, kl 09.00

av

Charlotte Bieneck Haglind
MD, Pediatrik

Huvudhandledare:
Docent Anna Nordenström
Karolinska Institutet
Institutionen för Kvinnor och Barns Hälsa

Bihandledare:
Maria Halldin Stenlid, MD, PhD
Uppsala Universitet
Institutionen för Kvinnor och Barns Hälsa

Docent Ulrika von Döbeln
Karolinska Institutet
Institutionen för medicinsk biokemi och biofysik

Fakultetsopponent:
Professor Cary Harding
Oregon Health & Science University, Portland
Department of Molecular and Medical Genetics

Betygsnämnd:
Allan Meldgaard Lund, MD DMSc
Rigshospitalet, Copenhagen
Department of Clinical Genetics

Professor Olov Ekwall
Göteborgs Universitet
Institutionen för Pediatrik

Docent Lars Hagenäs
Karolinska Institutet
Institutionen för Kvinnor och Barns Hälsa

ABSTRACT

Long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency (LCHAD) is a severe inborn error in the beta-oxidation of long-chain fatty acids. The disease presents during the first years of life. Hypoglycemia, hepatic manifestations, muscle hypotonia and episodes of rhabdomyolysis, cardiomyopathy and even sudden death are common symptoms. Despite life-long complicated treatment with a low fat diet and fasting avoidance, episodes of rhabdomyolysis and liver abnormalities may still occur. Patients with LCHAD develop a specific chorioretinopathy, not seen in any other beta-oxidation deficiencies.

The aim of this thesis was to describe the clinical outcome for patients with LCHAD, and investigate the energy metabolism with particular emphasis on the dynamics of fasting. Ten patients were included in the studies.

The patients had rapid weight gain after diagnosis and initiation of dietary treatment. The nutritional surplus caused overweight and accelerated linear growth in the majority of the children, however not affecting final height.

Patients with LCHAD had a decreased fasting tolerance with increased lipolysis. Fat and carbohydrate metabolism during fasting was investigated by stable isotope technique, microdialysis, and biochemical measurements. Despite normal blood glucose and normal glucose production rate (19.6 ± 3.4 umol/kg/min), lipolysis was induced after 3–4 hours, shown by increased glycerol production rate (7.7 ± 1.6 umol/kg/min), as well as by increased levels of fatty acid intermediates, and plasma and microdialysate glycerol. Indirect calorimetry showed increased respiratory quotient, indicating mainly glucose oxidation. Our results imply that frequent meals are essential in order to avoid lipolysis and diminish accumulation of the incompletely degraded toxic fatty acid metabolites.

All patients developed ocular changes with retinal pigmentations and chorioretinopathy. Early diagnosis and treatment may delay but not prevent the ocular outcome.

Neuropsychological deficits were more common than expected, and demonstrated a specific cognitive pattern. The patients either had normal IQ scores with a particular weakness in auditive verbal memory and executive functions, or developmental delay and autistic behaviors.

In conclusion, this thesis shows that patients with LCHAD have an increased lipolysis with considerably impaired fasting tolerance. Shorter fasting intervals than has been advocated are thus crucial in order to reduce the accumulation of fatty acid metabolites and improve the metabolic control. The shorter fasting tolerance should be weighed against the risk for overweight. All patients develop retinal and cognitive symptoms; however, these symptoms may be improved with good adherence to the complicated diet. Neuropsychological screening is important for the identification of special needs early on.