Teaching Course 10

Current treatments in neurology - Level 1

Current treatment of muscle disorders

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Metabolic myopathies are a group of inborn errors of muscle metabolism of growing interest for two main reasons: 1) because the characterization of the pathophysiological mechanisms underlying these rare diseases is highly relevant for the improvement of knowledge in the field of muscle physiology, and 2) because of the increasing number of therapeutic approaches which are now available for several of these disorders.

The metabolic myopathies are a group of inherited muscle disorders caused by enzymatic defects of the biochemical pathways that produce ATP. They can result either from defects in substrate utilization (disorders of glycogen and lipid metabolism) or mitochondrial respiratory chain (mitochondrial myopathies).

Two main clinical presentations may be observed: 1) Exercise intolerance with myalgias and cramps, sometimes complicated with recurrent rhabdomyolysis episodes due to acute muscle breakdown, and 2) Static symptoms with progressive muscle weakness, mimicking muscular dystrophies.

Muscle manifestations typically occur in older children and adults, whereas newborns and infants often exhibit severe multisystemic disorders. The severe phenotypes generally observed in children are explained by the presence of more deleterious gene mutations.
Although this division based on clinical presentation is very helpful, it should be known that patients with dynamic symptoms may also present with some degree of muscle wasting occurring during the course of the disease, and conversely patients with permanent muscle weakness may also have exercise-related symptoms of fatigue and pain.

The field of metabolic myopathies has changed rapidly in recent years, and new diagnostic tools are now available for the identification of the metabolic defects, in particular assessment of acylcarnitine profile with tandem mass spectrometry allowing more accurate diagnostic of FAO disorders. In addition genetic analysis are now available for almost all the disorders of glycogen and lipid metabolism, thus permitting direct molecular diagnosis and genetic counseling.

This teaching course we will focused on metabolic myopathies related to glycogen and lipid metabolism, caused by defects in substrate utilization.

1. **Muscle glycogenosis**

Deficiencies of virtually all enzymes which intervene in the synthesis or degradation of glycogen may cause glycogen storage disease (GSD) due to aberrant storage or utilization of glycogen. The different GSDs are each denoted by a roman numeral that reflects the historical sequence of their discovery and often also by the name of the author of the first description. These disorders are inherited as autosomal recessive traits, with the exception of phosphoglycerate kinase and phosphorylase b kinase deficiencies, which are X-linked recessive.
Patients with glycogenosis and exercise intolerance all develop symptoms early in exercise, but exercise intensity at which symptoms occur varies according to the residual activity of the affected enzyme.

The two most frequent glycogenosis are McArdle disease (GSDV) and Pompe disease (GSDII)

1.1. Myophosphorylase Deficiency (Glycogen Storage Disease Type V or McArdle disease)

Clinical presentation and diagnosis

GSD V, was first described in 1951 by Brian McArdle (McArdle, 1951), and is characterised by exercise intolerance with myalgia and stiffness of exercising muscles, which are relieved by rest. Onset of the disease occurs during childhood, but diagnosis is frequently missed at an early age because affected children are often considered to be lazy. Two types of effort are more likely to cause symptoms: brief intense isometric exercise, such as lifting heavy weights, or less intense but sustained dynamic exercise, such as running or climbing a hill. All the patients experience a constant phenomenon, named the “second wind”: when they rest briefly after the appearance of exercise-induced myalgias, they can continue to exercise with a lower level of pain and fatigue. This phenomenon is considered to be related to the ability to metabolize free glucose that is mobilized in the bloodstream. Myoglobinuria is the major complication, and occurs in about half of the patients. Creatine kinase level can increase to more than 100 000 to 1 000 000 UI/l during rhabdomyolysis episodes, inducing risk of acute renal failure. Neurological evaluation is usually normal between crises, but proximal muscle weakness and wasting occur in approximately 35% of the patients over 40 years of age. Muscle
biopsy shows vacuoles and subsarcolemmal accumulation of glycogen that is normally digested by diastase. Negative staining using a specific myophosphorylase histochemical reaction confirms the diagnosis.

GSD V is caused by deficient myophosphorylase activity, and the gene for the muscle isoform (PYGM) has been mapped to chromosome 11q13. The most common mutation in Caucasians is the p.R50X mutation, which accounts for 81% of the alleles in British patients, and 63% of alleles in U.S. patients. Nearly all mutations result in a totally dysfunctional enzyme, and therefore muscle glycogen breakdown is completely blocked in this disease.

**Treatment**

There is no pharmacological treatment, but exercise intolerance may be alleviated by aerobic conditioning programs, or ingestion of oral sucrose (37 g) which may have a prophylactic effect when taken 5 to 30 minutes before planned activity. This effect is explained by the fact that sucrose is rapidly split into glucose and fructose; both bypass the metabolic block in GSD V and hence contribute to glycolysis. A recent study indicates that work capacity and exercise tolerance is improved after a carbohydrate-rich diet, and suggest exploring this effect in larger controlled trials. Patients should also avoid strenuous efforts, and leisure activities that place them at risk such as swimming far from the shore, or mountaineering.

1.2. **Glycogen Storage Disease Type II (Pompe disease)**

GSDII, also named Pompe disease, α-glucosidase deficiency or acid maltase deficiency, is the only lysosomal storage disease among the
different glycogenosis, and is caused by deficiency of the lysosomal enzyme acid α-glucosidase. It is the second most common cause of muscle glycogenosis after McArdle disease.

**Clinical presentation**

Pompe disease presents as a spectrum, with infantile, juvenile and adult forms named according to the age at onset, rate of progression, and extent of organ involvement. The classical infantile form usually presents within the first months of life with hypotonia and hypertrophic cardiomyopathy. Major motor milestones are not achieved and patients most often die before one year of age from cardiopulmonary failure or aspiration pneumonia.

The juvenile forms are characterized by predominant skeletal muscle dysfunction, with motor and respiratory problems, but rarely cardiac involvement. Calf hypertrophy can be present, mimicking Duchenne muscular dystrophy in boys. Myopathy and respiratory insufficiency deteriorates gradually and patients often become dependant on ventilator or wheelchair.

The adult form develops in the third or fourth decade, and affects the trunk and proximal limb muscles, mimicking inherited limb-girdle muscle dystrophies. Involvement of the diaphragm is frequent, and acute respiratory failure may be the initial symptoms in some patients. By contrast with the infantile form, the heart is generally not affected. The major cause of death in adults is respiratory insufficiency. Rarer causes of death are strokes related to intracranial aneurysm or arteriopathy due to accumulation of glycogen in vascular smooth-muscle cells.
The diagnosis always relies on determination of acid α-glucosidase deficiency, knowing that infants with the classic infantile form have less than 1% residual activity, whereas children and adults have residual activity no more than 30% of normal values. New screening methods of acid α-glucosidase deficiency using assays in dried blood spots have been recently developed.

Muscle biopsy shows a vacuolar myopathy with PAS-positive material in approximately 2/3 of adults, but in 1/3 of cases the muscle biopsy may be normal or shows non specific changes, potentially misleading the diagnosis.

Over 200 mutations have been reported in the gene encoding acid α-glucosidase, about 75% of these being pathogenic mutations (www.pompecenter.nl). Some degree of genotype-phenotype correlation exists, with severe mutations (such as del exon18) associated with the infantile form, and leaky mutations associated with the adult variant. The most common mutation in adults and children with a slowly progressive course is c.-32-13T>G (approximately 80% of patients).

**Treatment**

Palliative therapy relies on prevention of cardio-respiratory failure, with the possibility of long lasting survival in adults with ventilatory support. Pulmonary function tests should be undertaken annually and respiratory support started when necessary as in some patients this can prolong life for decades. A major step towards treatment of Pompe disease has been achieved with the large-scale production of recombinant acid α-glucosidase (rhGAA), initially in milk of transgenic rabbit and further in
CHO cells (alglicosidase alfa). Alglicosidase alfa (Myozyme®) has been commercially approved since 2006 and two large studies in infants showed major beneficial effects on cardiomyopathy and muscle weakness, with increased survival. Doses of 20 mg/kg by infusion every other week are recommended. However less than half of the children on enzyme replacement therapy (ERT) gain normal motor function status and are ventilator free. Several factors may limit the efficacy of ERT in children, such as severe condition of the patient, extensive muscle damage at start of treatment, or appearance of high levels of IgG antibodies to rhGAA. A double-blind placebo-controlled trial in adults showed an improvement of the walking distance and a stabilization of vital capacity after 18 months of treatment. Long-term follow-up data are currently collected across all the spectrum of Pompe disease in order to better understand the effects of ERT, and to formulate guidelines for treatment.

Several other therapeutic approaches are currently developed for Pompe disease including next generation recombinant enzymes, combination of chaperone protein and recombinant enzyme, and gene therapy.

2. Disorders of muscle lipid metabolism

Disorders of lipid metabolism affecting muscle may involve endocellular triglyceride degradation, carnitine uptake, long-chain fatty acids mitochondrial transport, or β-oxidation. The pathological hallmark of some of these diseases is an increased neutral lipid content, which may be observed on muscle biopsies specimen with the specific stainings of Sudan black or oil red O techniques by optic microscopy. The term of lipid storage myopathies is often used when the accumulation of lipid droplets in muscle fibers is uppermost, and associated with a vacuolated
appearance on routine histological stains such as hematoxylin and eosin or Gomori Trichrome. Conversely, lipid metabolism disorders are inconstantly leading to a muscle lipidosis, and therefore awareness of their clinical features and main biological anomalies are essential for establishing accurate diagnosis. The diagnostic approach has been considerably improved in the last ten years with the possibility to analyse the acylcarnitine profiles with tandem mass spectrometry.

We describe below the main muscle lipid metabolism disorders which can be classified into two main categories according to the main clinical symptoms and the pathological findings: 1) recurrent rhabdomyolysis episodes and mild muscle lipidosis, and 2) permanent muscle weakness, cardiomyopathy and important muscle lipidosis on muscle biopsy.

2.1. Disorders of lipid metabolism with rhabdomyolysis episodes and inconstant muscle lipidosis

Main causes are Carnitine palmitoyl transferase II (CPT II), Very-long-chain acyl-CoA dehydrogenase (VLCAD), Mitochondrial trifunctional protein (MTP) deficiency, and Multiple acyl-CoA dehydrogenase (MAD) deficiencies.

These disorders are present different clinical phenotypes according to the age of onset, but muscular symptoms (recurrent myoglobinuria, muscle aching and stiffness on long-term exercise) occur mainly in the juvenile-adult onset form. Episodes of myalgias and rhabdomyolysis are triggered by prolonged exercise, infections, fasting, cold or emotional stress. Permanent muscle weakness is very uncommon, and heart is not affected. CK levels are normal outside episodes of muscle injury. A mild increase in
lipid content in muscle biopsy is observed in some cases. Patients with MTP deficiency may also present cardiomyopathy, pigmentary retinopathy and progressive sensorimotor axonal peripheral neuropathy, in association with rhabdomyolysis episodes. The sensorimotor neuropathy is a distinguishing feature which has not been reported in patients with other FAO defects, in combination with episodic rhabdomyolysis.

Acylcarnitine profile assessed by tandem mass spectrometry (MS/MS) may show characteristic increased long-chain acylcarnitines helping to diagnosis of these rare disorders: increase of (C_{16}, C_{18:1}, C_{18}) in CPT II deficiency, tetradecenoylcarnitine (C_{14:1}) in VLCAD deficiency, all chain lengths acylcarnitines (C_{4} to C_{16}) in MADD, and long-chain hydroxyacyl-carnitines in MTP deficiency.

Diagnostic finally relies on molecular analysis, either with targeted gene search, or with dedicated gene panels.

2.2. Disorders of lipid metabolism with muscle weakness and important muscle lipidosis

Primary Carnitine deficiency (PCD)

PCD (also called carnitine uptake defect or systemic carnitine deficiency) is the most classical cause of lipid storage myopathy but remains exceptional. This disease is caused by a defect in the high-affinity plasma membrane sodium-dependent carnitine transporter (OCTN2) in several tissues, including muscle, heart, and kidney, but not liver. This induces increased loss of carnitine in urine and decreased concentration in plasma, heart and skeletal muscle. The most common phenotype is characterized by generalized muscle weakness, and progressive hyper-
trophic or dilated cardiomyopathy leading to cardiac failure, occurring before the age of 10 years. Severe fasting hypoglycaemia leading to coma is sometimes observed in infants.

Massive lipid storage may be observed in skeletal muscle, heart and liver. Lipid vacuoles in skeletal muscle are predominantly observed in type 1 fibres, with often type 2 fibre atrophy. Biochemical investigations show a generalized reduction of carnitine content in all tissues (heart, muscle, liver) and in plasma. Plasma total and free carnitine are less than 10% of control, but carnitine esters are not increased (no acylcarnitines), and total carnitine is reduced to less than 5% of control in muscle. Diagnosis may be confirmed by demonstrating reduced carnitine uptake in lymphocytes or skin fibroblasts, and mutations have been found in SLC22A5, the gene coding for OCTN2.

Neutral lipid storage diseases (NLSD)

NLSD, initially named multisystem triglyceride storage disorder, are disorders of endogenous triglyceride catabolism due to deficiencies of hormone-sensitive lipases. Mutations in the gene coding for CGI-58 (ABHD5) are responsible for neutral lipid storage disease with ichthyosis (NLSDI) also called Chanarin-Dorfman syndrome. NLSDI is a multisystem triglyceride storage disease occurring in childhood, characterized by the presence of non-bullous congenital ichthyosiform erythroderma, mild proximal myopathy (around 60% of cases), and hepatomegaly. The most salient laboratory abnormality is the occurrence of intracytoplasmic lipid droplets in leukocytes, visible on peripheral blood smear (Jordan’s anomaly). A massive accumulation of lipid droplets is also present in type
1 and 2 muscle fibres, even in patients without clinical myopathy, and lipid vacuoles are also observed in keratinocytes.

Neutral lipid storage disease with myopathy (NLSDM) is caused by mutations of the gene coding for ATGL also named *PNPLA2*. Patients may present initially walking delay and sport activities impairment during childhood, but clinical investigations are generally undertaken because of a slowly progressive muscle weakness occurring between the second or third decade. Proximal and distal limb muscles may be involved, with a predominant distal weakness in some patients. Dilated cardiomyopathy, leading to heart failure and severe arrhythmia, has also been reported. In peripheral blood smears, neutral lipid vacuoles are always observed in leukocytes. Muscle biopsy shows a massive lipidosis. Biochemical analyses do not detect any defect in cholesterol, triglycerides, blood carnitine, mitochondrial FAO or respiratory chain activity. Most *PNPLA2* reported mutations are nonsense, duplication or insertion mutations responsible for the creation of a premature stop codon and an absence of protein production.

### 2.3. Treatment of muscle lipid metabolism disorders

Proposed treatment strategies for lipid metabolism disorders include:
1) avoidance of exacerbating factors, 2) carnitine supplementation,
3) riboflavin treatment and 4) dietary modifications (medium-chain triglycerides and triheptanoin).

Avoidance of exacerbation factors still plays a large part in the management of these diseases. In children with FAO defects, fasting and infections are the major causes of metabolic decompensation and
rhabdomyolysis. Patients need to avoid fasting and maintain a regular carbohydrate intake during infections to minimise lipolysis. Similar strategies are necessary in adults, with avoidance of intense or prolonged exercise, fast and alcohol ingestion.

PCD is one of the rare treatable aetiologies of metabolic cardiomyopathies. Literature data recommend intravenous therapy of 100-400 mg/kg per day of carnitine during life-threatening events, and 100-300 mg/kg per day of oral carnitine for chronic treatment. This treatment should be continued during all life with high risk of sudden death in case of interruption. This supplementation restores plasma and liver carnitine levels to normal, whereas muscle carnitine levels remain low.

Riboflavin treatment (100-400 mg/day) may induce within a few days, a dramatic improvement of muscle symptoms and encephalopathy in some patients with riboflavin-responsive MAD deficiency. A significant improvement of muscle weakness has also been observed after a few months of CoQ10 supplementation in patients with secondary coenzyme Q10 deficiency, but some of them improved even more with combined CoQ10 and riboflavin therapy.

Children with long-chain FAO defects are generally treated with a low long-chain fat diet and supplements of MCT, because medium-chain acyl-CoA esters bypass the carnitine shuttle and are converted to ketone bodies which may be protective by suppressing the production of long-chain esters. Benefit is less pronounced in patients whose problems are recurrent rhabdomyolysis. A remarkable improvement of cardiac and muscular symptoms also occurred in three children with VLCAD deficiency.
and in seven patients with CPT II deficiency after dietary supplementation with triheptanoin, a seven-carbon medium-chain fatty acid, which supposed mechanisms are the production of C5 ketone bodies and propionyl-CoA, allowing to replenish the pool of catalytic intermediates of the citric acid cycle. Further clinical trials and prolonged clinical follow-up are needed to confirm the benefit of these treatments.