**Myopathy**

Myopathy is a common manifestation of Mitochondrial Disease (MD). Here we will focus on primary mitochondrial myopathy (PMM), defined as genetic disorders of the mitochondrial respiratory chain affecting predominantly, but not exclusively, skeletal muscle. Secondary involvement of mitochondria is frequently observed in several neuromuscular diseases (i.e. inclusion body myositis, Ullrich and Bethlem myopathy, Kennedy disease, etc.) but is not presented nor discussed here.

PMM may present at any age, although typically the more severe phenotypes present earlier in life, and milder phenotypes present later in life. The commonest phenotype of PMM is progressive external ophthalmoplegia (PEO), characterized by bilateral eyelid ptosis accompanied by a slowly progressive usually symmetrical limitation of eye movement (ophthalmoplegia) in all direction of gaze; the patients sometimes report diplopia. PEO is often associated with other signs of skeletal muscle involvement, i.e. slow progressive axial and proximal limb weakness affecting predominantly the limb girdle muscles often with muscle wasting. Muscle weakness may also cause difficulty swallowing (dysphagia) and respiratory failure. Distal muscle weakness is rare. Other manifestation of PMM are exercise intolerance, myalgia, muscle wasting, fatigue, muscle cramps and recurrent rhabdomyolysis with myoglobinuria triggered by exercise. Hypotonia, floppy infant syndrome, respiratory insufficiency and reduced/absent deep tendon reflexes are common in early onset forms of PMM. Myopathy can be both the only clinical features of a MD but also a component of other mitochondrial syndromes.

The prevalence of PMM among MD is still unknown. Most of the published studies have examined single cases or families, or have been conducted by recruiting a limited number of patients. In the Italian MD registry, exercise intolerance, ptosis/ophthalmoparesis and muscle weakness were three of the four clinical manifestations in term of frequency (with hearing loss being the 4th) (Mancuso et al, 2011).

From a genetic point of view, PMM may be autosomal dominant or recessive (due to nDNA mutations), sporadic (due to single large-scale deletion of mtDNA), or maternally inherited (due to mtDNA mutation). PMM is very rare in LHON, OPA1, and some infantile forms of mitochondrial depletion syndrome (i.e. in DGUOK); exercise intolerance is much more common in patients with m.3243A>G or cytochrome *b* mutations compared to m.8344A>G.

The importance of excluding other causes of myopathy in a MD patient should not be overlooked, unless if myopathy is detected in MD that do not typically have such findings (for example in OPA1 or Leber patients). Nevertheless, a minimum set of blood exams is always recommended when myopathy is detected, including at least CK, a full blood count and TSH.

If a syndrome/disease possibly leading to myopathy as a clinical sign is suspected, the patient should be referred to the appropriate neuromuscular specialist. If CK levels are severely increased (above 1000 UI/l) a secondary mitochondrial myopathy should also be suspected, and additional diagnostic testing is warranted. An exception includes the myopathic form of mtDNA depletion linked to TK2 gene mutations, where CK levels may be above 1000. A detailed analysis for drugs potentially causing myopathy (i.e. corticosteroids, statins) should be also performed.

Although cardiac dysfunction can occur in patients with myopathies, these concerns are summarized separately.

Monitoring lactate AND CK is indicated once *every 12 months* in stable myopathic patients, earlier in case of worsening of symptomatology. In case of suspected myoglobinuria (triggered by exercise, fever or other events), renal function tests, acylcarnitine analysis (to rule out fatty acid oxidation defects), CK and urine analysis (including organic acids to investigate fatty acid oxidation defects) must be performed as soon as possible.

Several agents (mostly nutritional supplements) have been investigated with double-blind, placebo-controlled studies (Glover et al 2010; Parikh et al. 2013; Pfeffer et al, 2012 and 2013; Rodriguez et al, 2007, Viscomi et al, 2015). These include riboﬂavin, thiamine, L-carnitine, creatine, coenzyme Q10 (CoQ10), dimethylglycine, and the combination of creatine, CoQ10 and alpha lipoic acid. None has demonstrated a striking efficacy in clinical trials, although numerous non-blinded studies and small series have suggested modest efficacy. Therefore, a mitochondrial cocktail may be used depending on individual cases. The only exception is the PMM caused by CoQ10 deficiency that may respond to high dose of CoQ10 supplementation. Finally, exercise protocols of training are encouraged, because of the benefits of exercise in PMM due to reversal of deconditioning, a common feature of many muscle diseases. Indeed, in PMM exercise seems to alter the underlying pathology by promoting mitochondrial biogenesis. There are multiple clinical studies indicating that aerobic and resistance exercise programs are safe and beneficial for many aspects of PMM, including strength, fatigue, and quality of life (Cejudo et al, 2005; Jeppesen et al, 2006; Taivassalo et al 1998 and 2003; Vissing et al, 2001; Tarnopolsky 2004).

In case of myoglobinuria, i.v. hydratation must be started and the patient should be immediately evaluated in the emergency room. It is also important to avoid agents that may worsen the patient’s condition. Statins often cause toxic effects on skeletal muscle, although the precise mechanism(s) remain unclear. Statins should therefore be used cautiously in mitochondrial myopathy, with careful monitoring of symptoms and the serum creatine kinase, and supplementation with CoQ10 and possibly L-carnitine (if the total carnitine levels are low) should be considered. Antiretroviral agents are known to cause reversible and dose-dependent mitochondrial toxicity. Chronic use of corticosteroids, as well as metformin, can worsen myopathy and lead to muscle atrophy.

***Reader Comments***

Contrary to beta oxidation defect treated with dextrose infusion, often with a D10NS, patient’s response to glucose IV infusion should be monitored carefully with glycemia and lactate levels as well, as a lower level of dextrose infusion should be given (D5 or solely NS if there is no risk of low blood sugar in these patients. Close monitoring of CK, electrolytes, urea, creatinine, lactate, glycemia is thus recommended during a rhabdomyolysis episode).

**Recommendations**

* Myopathy and muscle dysfunction can be common findings in patients with mitochondrial disease. An evaluation of muscle function is routinely needed in these patients including assessment of strength, muscle CK and consideration of an EMG Score 4.65
* Secondary causes of a myopathy should always be assessed for and include at least a full blood count, TSH level and toxicology screen when appropriate Score 4.79
* CK levels in primary mitochondrial disease are typically not elevated above 1000, outside of *TK2*-related disease; persistently elevated CK levels should prompt an evaluation for another underlying myopathy. Score 4.50
* Annual CK levels are recommended in mitochondrial patients with underlying myopathy Score 3.8; 4 on repeat
* Some patients with mitochondrial disease are at risk for recurrent rhabdomyolysis and myoglobinuria, at times triggered by exercise or illness. Management should follow general recommendations for the treatment of rhabdomyolysis and include IV hydration and routine monitoring of renal function and CK. Score 4.76
  + Acylcarnitine and urine organic acid analysis may be needed to rule out fatty acid oxidation defects. Score 4.47
* Exercise may benefit patients with mitochondrial myopathies (see prior exercise recommendations) Score 4.82
* Agents such as statins, corticosteroids, metformin and antiretrovirals should be used with caution in patients with mitochondrial disease as they may exacerbate the underlying myopathy. Score 4.82
* Riboflavin should be considered for myopathy associated with ACAD9 deficiency Score 4.41
* A combination of CoQ10 and riboflavin should be considered for ETFDH myopathy Score 4.41

**References PMM**

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