Opinion

The Multifaceted Cause of Lipid Storage Myopathies, Genetics, and Treatment

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Abstract

Several inherited metabolic fatty acid disorders present with myopathies. Skeletal muscle accounts for 40% of the body and is important for metabolism, exercise, and movement. Muscle energy failure is manifested by metabolic crises with muscle weakness, sometimes associated with muscle fatigue and failure resulting in acute necrosis or rhabdomyolysis/myoglobinuria episodes. Lack of energy leads to muscle necrosis. Other presentations are weakness and myalgias with lipid storage myopathies in the biopsy. The biomarkers of such disorders are acyl-carnitine with various profiles and need to be carefully evaluated to plan supplementary therapy and specific diets. If red flags are not distinctly followed and diagnosed in time they might lead to a metabolic or cardiac failure.

Keywords: carnitine; fatty acid oxidation; CPT II

1. Introduction

Fatty acid oxidation and carnitine cycle disorders are essential topics, this opinion paper aimed at detecting such metabolic disorders in newborn infants and adults [1–3]. These metabolic diseases affect the body’s ability to metabolize fatty acids and utilize carnitine, a molecule transporting fatty acids into the mitochondria for energy production. In newborns and adults, diagnosis is important and can be done either on biopsy or dried blood spot. This blood sample is then tested for specific metabolites that indicate the presence of these disorders. The most commonly tested markers are acylcarnitines, abnormal byproducts of fatty acid metabolism.

Lipid Storage Myopathies (LSM) is a group of clinically, biochemically, and genetically heterogeneous disorders characterized by the accumulation of lipid droplets (LDs) in muscle close to mitochondria, with clinically prevalent limb muscle weakness [4], associated with multisystem dysfunction, characteristic biomarkers symptoms and laboratory findings (Table 1). This opinion paper aims to underline present and future diagnostic and therapeutic approaches to such entities.

2. Diagnosis and Discussion

An early diagnosis is crucial, as some LSMs can be managed for instance [3], high-dosage l-carnitine is an effective intervention for patients with Primary Carnitine Deficiency (PCD).

Multiple acyl-CoA dehydrogenase deficiencies (MADD, MIM#231680) are related to ETF-dehydrogenase, a mitochondrial enzyme, its pathogenic variants are often associated with riboflavin-responsive MADD [4] which phenotype in late-onset patients consists of proximal myopathy, high creatine kinase (CK), lethargy, vomiting, hypoglycemia, metabolic acidosis, hepateomalgy, glutaric aciduria, and LSM. Most late-onset patients can be dramatically improved by riboflavin and carnitine supplementation. Riboflavin, also known as vitamin B2, is a coenzyme of mitochondrial oxidoreductases and participates in the energy metabolism process. Riboflavin supplementation can restore lipid mitochondrial metabolism and thus Riboflavin Responsive-Multiple AcylCoA Deficiency (RR-MADD) early recognition is crucial to improve a patient’s prognosis.

Neutral Lipid Storage Disease (NLSD) is a group of rare genetic disorders characterized by the abnormal storage of neutral lipids within various tissues and Jordan’s anomaly in leukocytes. NLSD can be caused by pathogenic variants in two genes that regulate lipid metabolism. There are two subtypes of NLSD: NLSD with Myopathy (NLSD-M) and NLSD with Ichthyosis (NLSD-I). The latter was described as a multisystem disorder in a child [5] found then affected by CGI-58 (ABDH5) defect like others [6].

Pathogenic variants in the PNPLA2 gene, which encodes adipose triglyceride lipase (ATGL), a crucial enzyme for lipid catabolism cause NLSD-M, a disorder characterized by progressive skeletal and cardiac muscle damage and LD accumulation in tissues.

Genetic variants in the PNPLA2 gene might affect the patatin-like domain, while others mediate ATGL-LC3 interaction. This bond plays a key role in targeting ATGL to LDs, enhancing their degradation through a combined mechanism of lipolysis and lipophagy. Pathogenic variants are inherited as an autosomal recessive trait. The patient inherits two copies of the mutated gene, one from each
The anti-aging gene Sirtuin 1 is critical for the regulation of ATGL and skeletal muscle mass [10–12]. miRNA-34 are involved in the regulation of Sirtuin 1 with relevance to neutral lipid storage disease with myopathy. Sirtuin 1 is important to mitochondrial biogenesis and function and acts as a PGC1 alfa stimulator. Sirtuin 1 activators versus inhibitors are critical to lipid metabolism in NLSD-M. Exercise, diet, and lifestyle determine Sirtuin 1 expression with relevance to the treatment of LSM. The role of Sirtuin 1 for the diagnosis and treatment of NLSD-M should be in the future be assessed.

There is a PCD clinically characterized by cardiopathy, limb muscle weakness due to OCTN2 gene defect [13–16], and numerous secondary carnitine deficiency (SCD) states [14] including RR-MADD. They lead to low carnitine in plasma and tissues. The severity of SCD is generally less noticeable when compared to PCD, the plasma carnitine levels are relatively higher and hence easier to treat using calculated carnitine supplementation from inferred loss. Patients with PCD, in general, might present cardiac involvement; they have various degrees of skeletal muscular dysfunction, that is reversed by carnitine therapy.

Similarly to PCD, hypoketotic hypoglycemia is found in mitochondrial fatty acid oxidation disorders, such as defects of very long-chain acyl-CoA dehydrogenase, medium-chain acyl-CoA dehydrogenase, or disorders of carnitine shuttle and fatty acid transfer across the mitochondrial membrane, due to defects in inner Carnitine Palmitoyl Transferase (CPT-II). Genetic studies [17] have identified a common p.Ser113Leu mutation in the muscle form along with around 100 different variants. Several inborn errors of fatty acid metabolism including CPT-II deficiency lead to an increase of serum palmitoyl carnitine (C16:0) and oleoylcarnitine (C18:1), with a characteristic profile of blood acylcarnitines, and patients undergo myoglobinuric attacks. The plasma and urinary acylcarnitine profile has a high value as a fast and non-invasive method for the detection of inborn errors of fatty acid oxidation in newborn screening, which can be done by the analysis of dried blood spots, followed by GC-MS analysis [18].

### 3. Conclusions

Drawing a balance between subjecting a patient to extensive investigations, which are likely to be expensive, disagreeable, and potentially unrewarding, and making an accurate diagnosis is a demanding challenge. Yet, diagnostic nihilism should be avoided in the LSMs field, as there are rare, but critically important, treatable conditions, an early, accurate diagnosis is critical and a demanding challenge as some LSMs can be managed by nutraceutical supplementation [3] and diagnosed by GC-MS analysis in a dried blood spot.

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