Lipid Storage Myopathies

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The Lipid myopathies represent a heterogeneous group of disorders of cellular metabolism characterized by insufficient energy production as a result of specific defects of lipid metabolism. Some defects in lipid metabolism present with exercise intolerance and episodes of rhabdomyolysis. The prototypes of this group are Carnitine palmitoyl transferase II (CPT-II) deficiency and Very long-chain acyl-coenzyme A (CoA) dehydrogenase (VLCAD) deficiency.

Another group of lipid metabolism disorder, called Lipid Storage Myopathies (LSM), manifest mainly with fixed muscle weakness and is pathologically characterized by prominent lipid accumulation in muscle fibers. The most common types of genetically distinguishable lipid storage myopathies are Multiple Acyl-coenzyme A Dehydrogenase Deficiency (MADD), Primary Carnitine Deficiency (PCD), Neutral Lipid Storage Disease with Ichthyosis (NLSDI), and Neutral Lipid Storage Disease with Myopathy (NLSDM).

Clinical phenotypes of MADD patients are relatively heterogeneous. The mild late-onset form presents with episodic metabolic decompensation, muscle weakness, and respiratory failure. Mutations in the ETFA, ETFB, and ETFDH genes are responsible for MADD; they encode the alpha and beta subunits of electron transfer flavoprotein (ETF) and ETF-coenzyme Q oxidoreductase. MADD caused by ETFDH often responds favorably to riboflavin treatment.

Neutral lipid storage disease with myopathy (NLSDM) is a rare genetic disorder caused by mutations in the Patatin-like phospholipase domain-containing-2 (PNPLA2) gene encoding adipose triglyceride lipase (ATGL). ATGL enzymes are involved in triglycerides hydrolysis in adipose tissue, and when PNPLA2 mutations impair their activity, lipid accumulates in most organs. While NLSDM primarily affects skeletal and cardiac muscles, it can also affect other organs. NLSDM typically manifests in young adults with asymptomatic hyperCKemia, symmetric or asymmetric limb-girdle/distal weakness, and/or cardiomyopathy. The appearance of lipid deposition and rimmed vacuoles in muscle pathology and neutral lipid droplets in granulocytes (Jordan's anomaly) may be diagnostic for NLSDM, which could be confirmed by genetic testing.

In Neutral Lipid Storage Disease with Ichthyosis (NLSDI), which is also known as Chanarin- Dorfman syndrome, patients typically have rather extensive nonbullous congenital ichthyosiform erythroderma, and although myopathy can be seen but the weakness is usually mild. NLSDI is caused by mutations in ABHD5.

Primary Carnitine Deficiency (PCD) is an autosomal-recessive disorder, caused by the mutations in SLC22A5, which encodes a carnitine/organic cation transporter OCTN2. Infantile patients principally present with hypotonia, Reye-like syndrome, and cardiomyopathy. However, cardiomyopathy may develop in isolation or with a milder metabolic presentation in childhood or older age. Muscle weakness can also be seen. Conversely, some individuals can be asymptomatic for the whole life. PCD patients usually respond very well to high-dose L- carnitine supplementation.