Metabolic Myopathies and the Respiratory System

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KEYWORDS

• Metabolic myopathies • Glycogen storage disease • Mitochondrial disease • Lipid • Purine • Metabolism • Myopathy

KEY POINTS

- Primary care providers and pulmonologists are inexperienced in diagnosing and treating metabolic myopathies, and there is a paucity of literature to guide management decisions.
- A defect in lipid metabolism can cause exercise intolerance usually later in exercise when glycogen stores are exhausted and the energy source is switched to fatty acid oxidation.
- Mitochondrial dysfunction can present in adulthood and may constitute a substantial proportion of patients seen in a tertiary care dyspnea clinic.
- Cardiopulmonary exercise testing is useful in differentiating among glycogen storage disease, disease of lipid metabolism, and mitochondrial disease being the cause of myopathy.
- Management of metabolic myopathies using nonpharmacologic therapy, such as noninvasive ventilation, pulmonary toileting, special diets, and judicious exercise prescription, has been the mainstay of treatment.

INTRODUCTION: NATURE OF THE PROBLEM

Most of the inherited metabolic myopathic diseases are caused by a deficiency of an enzyme responsible for glycogen, lipid, or purine metabolism or by a defective transporter or mitochondrial electron transport chain protein. Although several metabolic diseases have been associated with respiratory disorders, they are uncommon, usually present in the younger population, have variable symptoms, and mimic other neuromuscular disorders. For the most part, respiratory physicians are inexperienced in diagnosing and treating these diseases, and there is a paucity of literature to guide management decisions.

With the inherited metabolic diseases, multiple organs are usually affected. Although several anatomic components of the respiratory system such as the airways, pulmonary interstitium and the pulmonary arterial tree may be affected by metabolic disorders, this review focuses on myopathies affecting the respiratory system and causing dyspnea, impaired exercise tolerance, or respiratory failure. The mechanism of exercise intolerance for each of the diseases is discussed in detail elsewhere in this article.

OVERVIEW OF THE METABOLIC MYOPATHIES

Contracting muscles use multiple substrates to supply energy for contraction. For high-intensity, short-duration contractions, the substrate of choice is glucose, which is derived from the breakdown of muscle glycogen. Thus, disorders of glycolysis or glycogenolysis present with muscle cramps, weakness, and rhabdomyoglobinuria during high-intensity muscle contraction. Glycogen

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accumulates in the muscle cell in these glycogen storage diseases (GSD).

For sustained, endurance-type muscle activity or during fasting, free fatty acids in the fatty acid acetyl-coenzyme A form are used for energy. The fatty acid acetyl-coenzyme A substrates are bound to carnitine by carnitine palmitoyl transferase I, translocated across the mitochondrial membrane by carnitine translocases and released into the mitochondrial matrix by carnitine palmitoyl transferase II, for oxidation. Defects in this pathway cause myopathy during sustained activity and in fasting states.

The purine nucleotide cycle in muscle allows the synthesis of adenosine triphosphate (ATP) from the high energy bond of adenosine diphosphate or adenosine diphosphate during anaerobic exercise when oxygen supplies are limited. The resulting adenosine monophosphate (AMP) is converted to inosine monophosphate and ammonia by adenylate deaminase. Adenylsuccinate diffuses out of the cell preventing accumulation of AMP and allowing anaerobic synthesis of ATP to continue. Deficiency of myoadenylate deaminase ultimately interferes with the synthesis of ATP during anaerobic conditions causing a myopathy.

Impairment of oxidative phosphorylation localized to the mitochondria is due to defects in either maternally inherited mitochondrial DNA (*mt*DNA) or defects in the autosomally inherited nuclear genome that also encode mitochondrial proteins. The various protein subunits of the components of the oxidative phosphorylation cascade are encoded by genes from both genomes and each mitochondrion may have 2 to 10 copies of *mt*DNA, some normal and some mutant. This is the basis for the phenomenon of genetic heteroplasmy, with varying relative proportions of wild-type and mutant DNA in each affected individual and cell and tissue. In some cases, complementation may allow defects of *mt*DNA to be compensated for by other copies of normal *mt*DNA in the same mitochondrion. Further, even in normal cells, *mt*DNA mutations accumulate with aging, rendering the cell more susceptible to impairments of ATP synthesis. This genetic complexity underpins the variable age of presentation, severity of illness, and distribution of tissue involvement in patients with these disorders and prevents ready genotype–phenotype correlations. Clinical disease is expressed primarily in tissues with the highest oxygen requirements and, hence, myopathy is a constant feature, but multiple organ systems are affected, especially the central nervous system, retina and optic nerve, and cardiac and endocrine systems. A characteristic feature of all mitochondrial myopathies is the abnormal proliferation and accumulation of mitochondria in a subsarcolemmal location. With the Gomori trichrome stain, muscles fibers have a characteristic ragged red fiber appearance.[1,2]

METABOLIC MYOPATHIES AFFECTING THE RESPIRATORY SYSTEM

Glycogen Storage Diseases

Deficiency in glycogen metabolism is the mechanism for GSD. It is inherited genetically as an autosomal-recessive disorder. The incidence of GSD is approximately 1 case per 20,000 to 43,000 live births.[3] In GSD, the absence of a particular enzyme blocks glycogen processing to produce ATP. As a result of impaired metabolism, glycogen accumulates in skeletal and cardiac muscle. There are 12 types of GSD.[4] Types II and V GSD are known to affect the respiratory system.

Type II GSD is caused by a deficiency in α-glucosidase deficiency, which impairs the degradation of glycogen to glucose. This disease is also known as acid maltase deficiency or Pompe disease.[5] There are 3 known subtypes of Pompe disease: classical (complete enzyme deficiency), a nonclassical infantile form, and a late-onset form. The classical form is associated with early mortality in the first year of life.[6] The late-onset subtype occurs later in life starting during childhood or even during adulthood. It is a milder form that affects the skeletal muscles and not the cardiac muscle.[7,8] It may cause severe diaphragm weakness, which eventually could lead to alveolar hypoventilation and chronic hypercapnic respiratory failure. Additionally, the reduced inspiratory pressure generated by a weakened diaphragm may result in an ineffective cough owing to reduced inspired volumes, leading to recurrent pneumonias and atelectasis.[6]

Type V GSD, also known as McArdle disease, affects only the skeletal muscles. It is caused by a deficiency of myophosphorylase, which is an isoform of glycogen phosphorylase.[9,10] The deficiency of this enzyme prevents breakdown of glycogen into glucose-1-phosphate. Interestingly, patients with this disease complain of exercise intolerance, but they do not produce lactic acid during anaerobic exercise owing to the glycolysis pathway being proximally blocked and preventing pyruvate synthesis, which is required for lactate production. Additionally, owing to the pathway being hindered proximally, the amount of substrate for oxidative phosphorylation is also limited leading to exercise intolerance.[11] The lack of lactate production during initial exercise is pathognomonic for McArdle disease, and the disease is