Metabolic Myopathies: Clinical Features and Diagnostic Approach

Edward C. Smith, MD[a], Areeg El-Gharbawy, MD[b], Dwight D. Koeberl, MD, PhD[b,*]

KEYWORDS

- Inherited disorders of metabolism • Metabolic myopathy
- Glycogen storage disease • Mitochondrial disorder
- Fatty acid oxidation

The metabolic myopathies are a heterogeneous group of disorders that share the common feature of inadequate production of cellular energy in the muscle (**Table 1**). These myopathies are often categorized as either hereditary (primary) disorders or acquired (secondary) disorders. A further clinical distinction can be made between those disorders associated with primarily dynamic features characterized by transient, exercise-induced fatigue, muscle cramping, and rhabdomyolysis and those disorders associated with primarily static features such as fixed weakness.

A detailed review of muscle energy metabolism is beyond the scope of this review, but a brief consideration of the pertinent metabolic pathways is useful to understand better this group of disorders. Under normal circumstances, energy for skeletal muscle function in the form adenosine triphosphate (ATP) is derived from muscle glycogen, blood glucose, and free fatty acids.[1] Each of these primary energy sources is metabolized through specific biochemical pathways into the final common product, ATP. The majority of fuel for muscle is provided by carbohydrates in the form of glycogen and by lipids in the form of free fatty acids. Through the process of anaerobic glycolysis, glycogen is metabolized to pyruvate inside the muscle cells (**Fig. 1**). Pyruvate is then decarboxylated into acetyl-coenzyme A (acetyl-CoA) inside the mitochondria. Similarly, β-oxidation of free fatty acids (fatty acid oxidation; FAO) inside mitochondria provides another source of acetyl-CoA (**Fig. 2**). Acetyl-CoA then enters

[a] Division of Pediatric Neurology, Department of Pediatrics, Duke University Medical Center, DUMC Box 3936, Durham, NC 27710, USA
[b] Division of Medical Genetics, Department of Pediatrics, Duke University Medical Center, DUMC Box 103856, Durham, NC 27710, USA
* Corresponding author.
E-mail address: dwight.koeberl@duke.edu

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Table 1
Classification of the metabolic myopathies

Disorder	Presentation	Provocation	Screening Laboratory Testing	Confirmatory Testing	Treatment	Differential Diagnosis	Inheritance	OMIM Number
Dynamic Myopathies								
McArdle disease (GSD V)	Acute rhabdomyolysis, second wind phenomenon	Vigorous exercise	Abnormal ischemic forearm test, ± elevated CK, elevated muscle glycogen content	Myophosphorylase gene mutation; phosphorylase activity	Oral sucrose before exercise	PK deficiency	Autosomal recessive	#232600
Carnitine palmitoyl transferase II (CPT II) deficiency	Delayed rhabdomyolysis	Fasting, prolonged exercise	Abnormal acylcarnitine profile when stressed, normal CK	CPT II gene mutation, CPT activity in fibroblasts or muscle	Carbohydrate ± MCT oil before exercise, avoidance of fasting	Disorders of β-oxidation of long-chain fatty acids	Autosomal recessive	#255110
Phosphofructokinase (PFK) deficiency (GSD VII/Tarui)	Exercise intolerance, muscle pain	Stressful illness, exercise	± Elevated CK, ± elevated muscle glycogen content	PFK gene mutation, PFK activity in muscle	High protein diet, aerobic conditioning	Mitochondrial disorders	Autosomal recessive	#232800
Phosphorylase *b* kinase (PK) deficiency (GSD IXd)[16]	Acute rhabdomyolysis	Vigorous exercise	± Elevated CK, elevated muscle glycogen content	PK gene mutation, PK activity in muscle	High protein diet	McArdle disease	Autosomal recessive or X-linked recessive	#300559
Static Myopathies								
Mitochondrial disorders (mitochondrial oxidative phosphorylation defects)	Exercise intolerance	Stressful illness, exercise	Abnormal urine organic acids, normal CK	Electron transport chain (ETC) testing in muscle, coenzyme Q_{10} in muscle	Coenzyme Q_{10}/ creatine monohydrate/α-lipoic acid supplementation	PFK deficiency	Autosomal recessive or maternal inheritance (mitochondrial DNA mutations)	MERRF #545000; Kearns-Sayre syndrome #530000; many others
Acid maltase deficiency (GSD II)/ Pompe disease	Proximal weakness	Not applicable	Elevated urinary glucose tetrasaccharide, baseline elevated CK, elevated muscle glycogen content	Acid α-glucosidase (GAA) gene mutations, GAA activity in blood, fibroblasts, muscle	Enzyme replacement with recombinant human GAA	Limb girdle muscular dystrophies	Autosomal recessive	#232300

Abbreviations: MCT, medium-chain triglyceride; MERRF, myoclonic epilepsy and ragged-red fibers; OMIM, Online Mendelian Inheritance in Man.