REVIEW ARTICLE

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Mitochondrial and Metabolic Myopathies

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ABSTRACT

PURPOSE OF REVIEW: This article provides an overview of mitochondrial and metabolic biology, the genetic mechanisms causing mitochondrial diseases, the clinical features of mitochondrial diseases, lipid myopathies, and glycogen storage diseases, all with a focus on those syndromes and diseases associated with myopathy. Over the past decade, advances in genetic testing have revolutionized patient evaluation. The main goal of this review is to give the clinician the basic understanding to recognize patients at risk of these diseases using the standard history and physical examination.

RECENT FINDINGS: *Primary mitochondrial disease* is the current designation for the illnesses resulting from genetic mutations in genes whose protein products are necessary for mitochondrial structure or function. In most circumstances, more than one organ system is involved in mitochondrial disease, and the value of the classic clinical features as originally described early in the history of mitochondrial diseases has reemerged as being important to identifying patients who may have a primary mitochondrial disease. The use of the genetic laboratory has become the most powerful tool for confirming a diagnosis, and nuances of using genetic results will be discussed in this article. Treatment for mitochondrial disease is symptomatic, with less emphasis on vitamin and supplement therapy than in the past. Clinical trials using pharmacologic agents are in progress, with the field attempting to define proper goals of treatment. Several standard accepted therapies exist for many of the metabolic myopathies.

SUMMARY: Mitochondrial, lipid, and glycogen diseases are not uncommon causes of multisystem organ dysfunction, with the neurologic features, especially myopathy, occurring as a predominant feature. Early recognition requires basic knowledge of the varied clinical phenotypes before moving forward with a screening evaluation and possibly a genetic evaluation. Aside from a few specific diseases for which there are recommended interventions, treatment for the majority of these disorders remains symptomatic, with clinical trials currently in progress that will hopefully result in standard treatments.

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INTRODUCTION

Metabolic myopathies is a term applied to the individually rare genetic disorders involving energy metabolism that cause muscle disease. The process of energy metabolism involves the hundreds of metabolic reactions that convert the food we consume in the forms of carbohydrates, fats, and proteins

into the molecules such as ATP that drive nearly all the energy-requiring biochemical reactions in the body. The metabolic processes that commonly result in muscle disease involve disorders of respiratory chain mitochondrial function, some of the steps of lipid metabolism, and disorders of glycogen storage or use. The muscle phenotypes generally involve weakness and exercise intolerance, but the specific symptoms and severity vary greatly. Some of these disorders result in muscle breakdown, which can be mild or severe. Rhabdomyolysis represents a specific characteristic of a few disorders, which is the result of intermittent severe muscle destruction. Patients with rhabdomyolysis may have normal neurologic examinations between events. Disorders of mitochondrial metabolism may result in a wide phenotype of disorders involving both neurologic syndromes as well as diseases involving extraneurologic systems, but muscle involvement is common and is the most common feature of this group of disorders as a whole. The other metabolic myopathies tend to be the result of disorders of glycolysis (the breakdown of glucose) or glycogenolysis (the formation and breakdown of glycogen), which are characterized as the glycogen storage diseases or the result of lipid dysmetabolism. Although all disorders in this article are technically metabolic disorders, the use of the term *mitochondrial diseases* refers to the genetic disorders affecting respiratory chain function, mitochondrial DNA and mitochondrial DNA maintenance, and mitochondrial morphology. The biochemical pathways involving lipid and other intermediary metabolism are discussed in the other sections.

KEY POINTS

- ***Primary mitochondrial disease*** **is the current designation for the illnesses resulting from genetic mutations in genes whose protein products are necessary for mitochondrial structure or function.**
- **Most primary mitochondrial diseases, as defined by the illnesses caused by mutations in mitochondrial-targeted genes, are a result of deficient energy production or excessive free radical production.**

MITOCHONDRIAL MYOPATHIES

Mitochondrial diseases are an increasingly recognized cause of human illness. Mitochondrial diseases encompass hundreds of disorders caused by mutations in the more than 1200 known genes dedicated to mitochondrial function.[1] The estimated incidence of primary mitochondrial disease is about 1 in 4300 people.[1,2] Most primary mitochondrial diseases, as defined by the illnesses caused by mutations in mitochondrial-targeted genes, are a result of deficient energy production or excessive free radical production.[3,4] As mitochondria are found in all human cells aside from the mature erythrocyte, patients who have primary mitochondrial diseases generally have multisystem involvement, although in some cases single organs can be affected. The nervous system is typically involved in most mitochondrial diseases, and combinations of specific organ system involvement widely vary with the vast array of different mitochondrial diseases.[3] Metabolic myopathies encompass a vast array of different genetic illnesses that result in muscle disorders that typically involve the utilization of glycogen or fatty acids and present with myopathy, exercise intolerance, or rhabdomyolysis. Mitochondrial diseases can present with or without muscle disease but when presenting with muscle disease can be considered a subset of the metabolic myopathies.

Mitochondrial Genetics

The mitochondria and proteins required for mitochondrial maintenance require more than 1200 genes,[1] most of which are dispersed over the 23 pairs of chromosomes found in the nuclear DNA. In addition to the mitochondrial genes found in nuclear DNA, the mitochondrion itself has retained a small piece of critical DNA, referred to as *mitochondrial DNA* (mtDNA). Unlike nuclear DNA, the mtDNA molecule is small, 16,569 base pairs in length, circular, and located in

the mitochondria. The rules that govern mtDNA inheritance are very different from those of mendelian disorders. During fertilization, only the nucleus of the spermatozoa enters the ova; thus, all the mitochondria and mtDNA are maternal in origin. Any mtDNA mutation in the mother would be passed on to all her children, and any mtDNA mutation in the father would not be passed on. However, most of the mitochondrial genes are located in the nucleus, and therefore, autosomal dominant and autosomal recessive genetics are a cause of some primary mitochondrial diseases (TABLE 11-1).[1–5] In total, human primary mitochondrial disease has been linked to essentially all 37 mtDNA genes and 350 nuclear DNA genes to date.[4]

Mitochondrial Biochemistry

Carbohydrate energy metabolism begins in the cytoplasm with the process of glycolysis, where a six-carbon sugar, glucose, is spilt into 2 three-carbon molecules of pyruvate. Pyruvate is moved into the mitochondria and

TABLE 11-1 **Types of Genetic Mutations Causing Mitochondrial Disease**

Mutation Type	Inheritance Pattern	Comment	Example
Mitochondrial (mtDNA) point mutation	Maternal	Disease severity affected by the percentage of mutant heteroplasmy	Mitochondrial encephalopathy, lactic acidosis, and strokelike syndrome (MELAS) due to m.3243A>G, which can result in progressive external ophthalmoplegia, myopathy, gastroparesis, and epilepsy
mtDNA deletion	Usually sporadic, rarely maternal	Disease severity affected by location and size of deletion and percentage of mutant heteroplasmy; muscle is the best tissue to find mtDNA deletion	Kearns-Sayre syndrome, most often as a result of the mtDNA common 5-kilobase deletion
Nuclear DNA point mutation(s)	Mendelian and others (including autosomal recessive, autosomal dominant, X-linked, trinucleotide repeat, etc)	As a group, the most common cause of mitochondrial disease, but individually, the involved genes are quite rare	Myopathy, progressive external ophthalmoplegia plus, *POLG* p.G484S, p.W849S
Nuclear DNA copy number variant (typically microdeletion) with or without single nuclear DNA point mutation on other allele	Mendelian and others	Rarely reported but worthy of evaluation if a phenotype fits either the discovered copy number variant or heterozygote point mutation	Spastic paraparesis type 11; heterozygote point mutation and a copy number variant deletion in *SPG11* E582X (paternal) and del 15:44.902,877–44,905,979 (~3000 base pairs) exons 17–18 (maternal)
mtDNA depletion (a subset of nuclear DNA point mutation involving ~13 genes) that results in depletion of mtDNA	Generally autosomal recessive	Results in depletion of wild-type mtDNA over time with diseases presenting from infancy through the seventh decade of life	Infantile myopathy, *TK2* c.760C>T, p.Arg254Ter, homozygote

decarboxylated into a two-carbon acetyl moiety and activated with coenzyme A (CoA) to form acetyl CoA. Through a complex series of chemical reactions, the mitochondria oxidize the acetyl component of acetyl CoA, which is also formed by the β-oxidation of fats, into molecular oxygen and carbon dioxide and, in that process, create usable energy stored in the final phosphate bond in ATP. Oxidative phosphorylation is the final phase of energy metabolism, which occurs inside a complex series of proteins buried in the inner mitochondrial membrane. In this process of oxidative phosphorylation, the electrochemical energy results in the mechanical fusion of molecular phosphate (PO_4^-) and adenosine diphosphate (ADP) to form ATP. ATP can exit the mitochondria in exchange for ADP and PO_4^- to be used in a hydrolytic reaction to perform cellular work, which in turn regenerates ADP and PO_4^-. As part of normal oxidative phosphorylation, not all electrons are conserved; some escape the milieu as free radicals. This standard mitochondrial physiology of free radical generation is responsible, in part, for damaging lipid membranes and DNA, especially the mtDNA that is in close proximity to the source of free radical generation. The mtDNA, localized within the mitochondrial matrix, is the template for future generations of mtDNA, and the cumulative burden of oxidative damage eventually results in additional mitochondrial dysfunction. In primary mitochondrial disease, mutations in the genes responsible for the oxidative phosphorylation process cause protein dysfunction and loss of normal ATP production or excessive free radical production with secondary consequences or both. It is not clear how much of the organ system damage is caused by either mechanism. Extreme examples of secondary mitochondrial failure with a lack of energy production where oxidative phosphorylation ceases include stroke and myocardial infarction. Mitochondrial dysfunction has been demonstrated in many neurodegenerative disorders, including Alzheimer disease, Parkinson disease, amyotrophic lateral sclerosis, some cancers, and the aging process itself. It is of note that several well-characterized inheritable forms of Parkinson disease and Charcot-Marie-Tooth disease are, in fact, primary mitochondrial diseases because the illness is a result of a mutation in mitochondrial-localized genes.[1–6]

Mitochondrial Structure

In the living cell, the mitochondrion is a dynamic structure and undergoes constant change in its structure. The appearance of the mitochondria in vivo is not a static form but is a large syncytial structure, forming a network within the cell. The specific structure of this network is both tissue and state dependent, and many mitochondrial proteins control the harmony of the mitochondrial dynamics of fission and fusion.[4]

An understanding of two components of the mitochondrial structure, the inner mitochondrial membrane components and the mtDNA, is necessary to better comprehend the pathophysiology of mitochondrial diseases. Embedded within the inner mitochondrial membrane are the five multicomplex proteins referred to as the electron transport chain, also known as the respiratory chain. The purpose of the respiratory chain is to generate ATP, which is the main source of energy used by the cell. ATP is formed as a condensation of ADP and PO_4^- within complex V. ATP is hydrolyzed back into ADP and PO_4^- with the release of energy that is used by the cell to create the necessary work. The ADP and PO_4^- then translocate back into the mitochondria to be condensed again into ATP.[6–8]

The total ATP content in the adult human is about 250 grams. Each complex V protein can generate about six ATP molecules per second, and the total ATP utilization in a resting adult is about 5.8×10^{20} molecules per second. Depending on activity level, the author calculates that this process results in the gross production of about the body's weight of ATP recycled per day in an adult human.

The tricarboxylic acid cycle functions to further metabolize carbohydrates and proteins, and the β-oxidation cycle to metabolize fatty acids, which results in the production of nicotinamide adenine dinucleotide (NADH) and flavin adenine dinucleotide hydrogenated ($FADH_2$). The NADH donates electrons into complex I, and $FADH_2$ donates electrons into complex II of the respiratory chain. As these electrons are passed through the chain via mobile electron carriers (coenzyme Q10 and cytochrome c), protons in the mitochondrial matrix are pumped into the intramembrane space that exists between the inner and outer mitochondrial membranes. The electrons that pass down the chain tetravalently reduce molecular oxygen into water within cytochrome c oxidase (COX), often referred to as *complex IV*. The electrochemical force driving the translocation of the protons comes from the reduction-oxidation reactions of electron transfer. The resulting electrochemical charge across the inner mitochondrial membrane, specifically the accumulation of protons in this inner membrane space, is the driving force that results in ATP formation. The physical and electrochemical integrity of the inner mitochondrial membrane is a critical property of the lipid bilayer because it must not allow small molecules or electrolytes to penetrate or the proton motive force will be lost.[5–8] The bilayer itself is composed of the two-tailed phospholipids that include phosphatidylcholine, phosphatidylethanolamine, and phosphatidylinositol and the four-tailed phospholipid cardiolipin. The shape of cardiolipin allows the crista to take on its highly curved structure and provides the chemical milieu to hold the electron transport chain supercomplexes in place.[9] The process of condensing a phosphate onto ADP to form ATP is known as oxidative phosphorylation. As mentioned earlier, the process of oxidative phosphorylation is not 100% efficient, and unpaired electrons do escape the respiratory chain to form free radicals. These free radicals are a normal part of healthy respiration but are produced excessively in mitochondrial dysfunction. Mutations in the mitochondrial-targeted genes result in an absence of proteins that are involved in the assembly or structure of the mitochondria or in the critical enzymatic components and result in human disease.[2–4,6–8,10]

The organs associated with primary mitochondrial disease are those with high energy needs. These tissues also tend to be relatively nonreplicative after birth. These include cell types found in the brain, retina, and cochlea; muscle fibers (skeletal, cardiac, and smooth); nerves (including the cardiac conduction system); hepatocytes; both the exocrine and endocrine cells of the pancreas; and renal tubular and glomerular cells. Most patients with primary mitochondrial disease have at least one nervous system or special sensory system tissue involved. Other organs can be affected, with patterns of involvement recognized by any clinician.[7,8] Mitochondrial injury can be the result of genetic disorders not primarily involving the mitochondria, such as some disorders of iron or copper metabolism, as well as the result of some prescription medications or industrial toxins. These disorders may result in clinical scenarios similar to the genetic mitochondrial disorders and are not a subject of this discussion.[8,11]

History of Mitochondrial Disease

KEY POINT

- Most patients with primary mitochondrial disease have at least one nervous system or special sensory system tissue involved.

The history of mitochondrial discovery explains the varied nomenclature used to describe these illnesses.[12] As of now, no single nomenclature is used to categorize mitochondrial diseases. Historically, the first mitochondrial diseases described were assigned names eponymously or based on a clinical-pathologic correlation.[9] For example, the findings of chronic progressive external ophthalmoplegia (CPEO, sometimes referred to as *PEO*) were named as such. When CPEO was accompanied by myopathy or other findings, the designation was *CPEO plus*. Leigh syndrome was first reported by Archibald Denis Leigh in 1951 and was defined by the pathologic findings in brain regions along with the clinical picture of stepwise neurologic deterioration. In many but not all patients with Leigh syndrome, the blood lactic acid level was elevated. By the mid-1980s, many well-defined syndromes were recognized, and many of the clinical symptoms were clinically and pathologically defined. More recently, mutations in hundreds of nuclear DNA genes affecting the mitochondrial proteins have been discovered. Mutations in genes affecting mtDNA structure and maintenance of wild-type mtDNA are referred to as mitochondrial depletion disorders. In general, the mtDNA depletion disorders result in reduced amounts of wild-type mtDNA or infidelity of the mtDNA daughter copy or both.[1–8,12–17]

In the past 5 years, numerous mitochondrial-localized genes and even new mechanisms of mitochondrial diseases have been uncovered as part of gene and protein discovery. The next decade will likely lead to discovery of more genes that contribute to human mitochondrial diseases.[1,2,4] Although the historical names of diseases will likely remain, the trend is to address patients' illnesses with both a genetic (genotype) and clinical (phenotype) descriptor. The list of clinical features defined by early reports of mitochondrial diseases has held true over the years, and these classic clinical features were fundamentally correct (**TABLE 11-2**).

What was apparent early in the descriptions of these diseases was a lack of typical age of onset and the possible involvement of multiple organ systems, both of which challenged specialty medical care, which is organized by age or organ system involvement. **CASE 11-1** demonstrates the broad range of age of onset and of symptoms and signs of a mitochondrial illness, the need to toggle between history and examination, and an illness that spans the fields of pediatrics, adult internal medicine, orthopedics, neurology, ophthalmology, and hepatology.

There have been three eras of diagnostic testing for mitochondrial diseases. Before 2000, most patients diagnosed with mitochondrial disease had combinations of analyte (eg, elevations of serum or CSF lactic acid, abnormal organic acid patterns), pathologic (eg, ragged red fibers, paracrystalline structures), or enzymatic testing of the respiratory chain complexes (eg, complex I+III or complex IV deficiency) to confirm the diagnosis. However, analyte testing alone is not sufficiently specific or sensitive to make any absolute decision regarding the firm diagnosis and should be used with clinical acumen for determining further evaluation. It is important to understand no biomarkers of mitochondrial disease are sufficiently sensitive or specific to be viewed as near reliable, but obtaining these screening laboratory tests will often guide the clinician or consulting expert to the next steps in the evaluation that may help in diagnosis of illnesses that can appear mitochondrial in nature (**TABLE 11-3**).[8,9,18–21] The process and evolution of respiratory chain enzymatic

testing performed in Clinical Laboratory Improvement Amendments (CLIA)-certified laboratories require special comment. This formerly standard evaluation is no longer performed for most patients like it was only 10 years ago. Although each reference laboratory used its own methodology to measure enzyme activity, the variability in internal standards (ie, the system each laboratory used to establish control ranges and report standards for the data) was high, and this was inherently problematic for clinicians. Without questioning the accuracy of the data, the reporting of "normal" or "abnormal" enzyme activity was based on the individual laboratory's control values (sometimes set as high as 50% of the control value) and did not use the clinically relevant values established by the published research diagnostic criteria, where

TABLE 11-2

Organ System Involvement in Mitochondrial Diseases and Modified Classic Features[a]

Organ System	Clinical Feature
Muscle	Skeletal myopathy,[b] smooth muscle myopathy, ptosis, ophthalmoplegia; patients with true myopathy may have pain, exertional intolerance, and easy fatiguability; low muscle tone is seen in children and can be mistaken for tendon laxity
Brain	Seizures, dementia, strokes, and strokelike episodes, atypical migraine, ataxia, dystonia, other movement disorders, developmental regression, neuropsychiatric symptoms, and mood disorder; MRI changes[c]
Nerve	Demyelinating and axonal neuropathies,[b] neuropathic pain, dysautonomia that includes gastrointestinal problems (gastroesophageal reflux, constipation, bowel pseudo-obstruction)
Bladder	Dysfunction from long tract, nerve, or smooth muscle involvement
Gastrointestinal	Dysmotility from nerve or smooth muscle involvement with pseudo-obstruction as a result; exocrine pancreatic failure
Kidney	Proximal renal tubular dysfunction, may result in loss of amino acids, electrolytes
Heart	Cardiac conduction defects, cardiomyopathy (hypertrophic, dilated, noncompaction)
Liver	Nonalcoholic steatohepatitis, hepatocellular dysfunction
Eyes	Optic atrophy, retinopathy, cataract, corneal clouding
Ears	High-frequency hearing loss
Endocrine	Diabetes mellitus, including insulin resistance in patients who are not obese; other endocrine disorders may be more prevalent than the general frequency found in the population
Systemic	Short stature, lipomatosis (primarily neck or paraspinal)

[a] Modified with permission from Cohen BH, Neurotherapeutics.[8] © 2013 The American Society for Experimental NeuroTherapeutics, Inc.
[b] This can be confirmed with EMG, nerve conduction studies, and muscle histology.
[c] MRI changes tend to be syndrome specific when present but include bilateral deep gray matter injury, periaqueductal gray injury, and occipital parietal stroke in a nonvascular distribution.

the requisite enzyme level necessary for diagnosis was typically 20% of control.[13–17] This discrepancy led to confusion among clinicians and their patients and often frustration in wondering if the data from this testing were clinically relevant. Broad genetic sequencing became increasingly available as an alternative, less expensive, and more specific test, and clinicians moved away from respiratory chain enzyme testing. Regardless, respiratory chain enzymatic testing has inherent value when performed and reported under tightly controlled standards. A recent report demonstrated a reasonable correlation of rigidly performed enzyme testing with genetic results.[17] One unintended consequence of not performing respiratory chain enzyme testing is also no longer having muscle tissue for histologic examination, which is potentially helpful or necessary to differentiate mitochondrial disease from other disease processes. Furthermore, muscle is the preferred tissue for interrogating mtDNA. Although blood or saliva serves well for sequencing for point mutations in the mtDNA, muscle is a better tissue for heteroplasmy determinations and a much better source for long-range polymerase chain reaction or Southern blot analysis, which is required when testing for an mtDNA deletion or duplication.

The second era of testing began in the mid-1990s with the availability of genetic testing for known mutations in mtDNA that cause human disease. Over

CASE 11-1

A now 71-year-old woman was healthy until she was 35 when she developed muscle fatigue, myalgia, and headache. She was diagnosed with a myopathy at that time. Over the next 20 years, the symptoms worsened, and at age 56, she was diagnosed with chronic progressive external ophthalmoplegia (CPEO) by a neuro-ophthalmologist. Over the following 10 years, she had successive medical issues including lipomas, mood disorder, fatty liver disease, parkinsonism, and congestive heart failure. Her family history was significant for CPEO in her mother (diagnosed at age 40 years) and in two brothers, now in their seventies. Evaluation at age 61 demonstrated complete external ophthalmoplegia, mild parkinsonism, myopathy, and lipomas.

Genetic testing at age 71 discovered a heterozygote mutation in *RRM2B* c.979C>T, p.Arg327Ter, a mutation with autosomal dominant expression causing mitochondrial (mtDNA) depletion and the CPEO plus syndrome.

COMMENT

This patient's first symptoms of muscle fatigue and myalgia led to the initial diagnosis of myopathy, although no evaluation was performed at that time. For adult patients, it is not uncommon for core features of the illness to be dismissed by the patient or physicians because they do not appear to be urgent issues. In this case, the patient's symptoms and signs of a mitochondrial illness developed in the 1980s and 1990s, when the clinical aspects of mitochondrial disease were being described in the literature. Mutations in *RRM2B* cause a depletion of mtDNA, and in children the autosomal recessive mutations lead to a devastating myopathy or encephalomyopathy. This patient's particular autosomal dominant mutation causes CPEO plus disease.

TABLE 11-3

Screening Laboratory Tests for Mitochondrial and Metabolic Myopathies[a]

Blood

- Lactic acid: elevated values in resting subjects, best performed without a tourniquet
- Amino acids: elevated alanine in fasting sample or alanine-to-lysine ratio greater than 4:1; elevated proline or sarcosine, low arginine, taurine, or citrulline in some mitochondrial myopathies
- Carnitine: low free carnitine (may be low in infants and vegetarians), as well as abnormal acylcarnitine intermediates in some primary mitochondrial diseases and lipid myopathies
- Creatine kinase: nonspecific but elevated in some mitochondrial and metabolic myopathies
- Growth differentiating factor-15: elevated in mitochondrial myopathy, false elevation in diabetes mellitus, not elevated in nonmitochondrial myopathies
- 3-Methylglutaconic acid: elevated in some mitochondrial disease

CSF

- Lactic acid: elevated; folate: decreased (not specific)

Urine

- Organic acids: elevated lactic acid, pyruvic acid, tricarboxylic acid cycle intermediates, dicarboxylic acids, 3-methylglutaconic acid in some primary mitochondrial diseases and disorders of lipid metabolism

Systemic Evaluation (As Deemed Necessary Based On Clinical Presentation)

- Brain: MRI, EEG
- Muscle: EMG, polysomnography
- Nerve: nerve conduction study
- Eyes: ophthalmologic evaluation, electroretinogram
- Ears: audiogram
- Gastroenterology: consultation, swallowing study, gastric emptying test, stool fat
- Heart: ECG, echocardiogram
- Lung: pulmonary function test, cardiopulmonary exercise testing

Other Laboratory Tests to Consider for Disease Mimicry

- Hemogram, iron, and ferritin
- Complete metabolic panel
- Vitamin B_{12} level and methylmalonic acid
- Thyroid-stimulating hormone (TSH), free T4
- Hemoglobin A_{1c}
- Paraneoplastic/autoimmune panel
- Selective vitamin levels, vitamin deficiencies, including micronutrient disorders seen in patients who have undergone bariatric surgery, on chronic total parenteral nutrition, self-induced restrictive diets, inflammatory bowel disease, or short bowel syndrome

[a] Modified with permission from Cohen BH, Neurotherapeutics.[8] © 2013 The American Society for Experimental NeuroTherapeutics, Inc.

the next decade, the ability to sequence the entire mtDNA molecule became accessible. In 2006, the first clinically available gene test for a nuclear DNA mitochondrial disease became available with the development of about 100 individual gene tests over the next several years. During this era, the choice of gene test needed to be hypothesis-driven and phenotype-driven; specifically, the clinician needed to suspect not only a mitochondrial disease but also the particular gene that was causing the disease. Also, during this time period the use of the chromosomal microarray became commonplace for children with developmental disabilities. During this second era, the genetic laboratory was used in addition to all the testing that had been developed in the first era.

The third era began in 2010 with the clinical application of next-generation sequencing, also known as massively parallel sequencing. Initially, this testing included both mtDNA whole-chromosome sequencing as well as sequencing of both known nuclear genes that caused mitochondrial disease and genes that were suspected to cause mitochondrial disease. By late 2013, the first whole-exome testing became clinically available. It is during this era that clinicians began using the genetic laboratory, often resulting in both a rapid diagnosis and one that did not require many invasive tests, as well as a process that was less expensive. Furthermore, the exome sequencing included all the genes associated with human disease, and not infrequently the diagnosis of nonmitochondrial disorders, often other metabolic myopathies, could be identified.

Currently, testing of blood and urine for the presence and concentrations of biochemical intermediates (eg, lactic acid amino acids, organic acids, and acylcarnitines) remains in use to assist in the identification of patients who may have mitochondrial dysfunction, but the reliance on CSF analytes and on muscle biopsy for pathologic and enzymatic evaluation has waned as the use of large panels or whole-exome genetic testing has flourished. As more patients with suspected mitochondrial disease underwent exome testing, accurate diagnoses of mitochondrial and nonmitochondrial disorders occurred. It remains common for exome testing to reveal a nonmitochondrial disease if the working diagnosis is a primary mitochondrial disease. Each era of diagnostic testing improved the accuracy of diagnosis and, in a reiterative process, an improved understanding of the specific clinical criteria that patients will present with that ultimately will have a correct diagnosis of a mitochondrial disease.[20,21]

Nomenclature and the Pathologic–Biochemical–Genetic Correlates to Disease

Mitochondrial diseases have been cataloged with different nomenclatures over the years, which have included eponyms, such as Alpers-Huttenlocher syndrome, Leigh syndrome, and Kearns-Sayre syndrome, as well by the phenotypic presentation, such as CPEO plus or neuropathy, ataxia, and retinitis pigmentosa (NARP) or mitochondrial encephalopathy, lactic acidosis, and strokelike syndrome (MELAS); and histologic presentation, such as ragged red fiber disease. Enzymatic abnormality categorical descriptions began to include complex I disease, COX, and sometimes the genetic finding, such as mtDNA A3243G mutation. None of these naming mechanisms alone was entirely accurate because rarely does a phenotypic presentation have a direct correlation with any given enzymatic, biochemical, histopathologic, or genetic finding.[5] The discovery of the widely different phenotypes associated with mutations in genes such as *POLG,*[22,23] responsible for mtDNA replication, and *BCS1L,*[24] responsible

for complex III assembly, showed that mutations in one gene could result in vastly divergent clinical findings (CASE 11-2). For patient care, it is most logical to classify the patient's illness by both genotype and phenotype, if available. It is recognized that no well-structured nomenclature for classifying all the mitochondrial diseases exists.

A definitive diagnosis for a primary mitochondrial disease requires the combination of accepted pathogenic genetic findings that correlate with the corresponding phenotype associated with that genetic finding. As discoveries are made, it is imperative that adequate proof is present that the phenotype is driven by the genetic findings. In clinical practice, it is common for the patient's phenotype to not correspond with what genetic testing reveals, and in these situations, the diagnosis of primary mitochondrial disease should not be made. Although pathologic muscle findings and enzymatic or other biochemical findings are often available as part of the patient evaluation, these findings alone are not accepted as definitive evidence of a primary mitochondrial disease. The classic symptoms alone are not specific (TABLE 11-2), and features within the primary common phenotype, which have held true over the years, are also seen in nonmitochondrial disease.[25]

CASE 11-2

A 15-year-old girl with normal cognitive function presented because of a 2-year history of slowly progressive ataxia and dysarthria. She had been a dancer and participated in track and field events but was now finding these activities difficult to perform. Her family history was significant for an older sister who had early normal development but then developmental language decline. This sister had chronic fatty diarrhea and repeated episodes of severe emesis; she went into status epilepticus and, despite maximum efforts, died 3 days into the event at age 3 years.

Examination demonstrated mild ataxia involving the patient's limbs and trunk, absent muscle stretch reflexes, poor position sensation, poor vibratory sensation, and dysarthria. Brain MRI and EEG were normal. Further evaluation included normal serum and CSF lactate, with an elevated CSF protein (150 mg/dL). Sequencing of *POLG* found compound heterozygote mutations in trans (ie, one inherited from each parent): p. G484S and p.W849S.

Over the subsequent 3 years, the patient developed myopathy, progressive external ophthalmoplegia, myoclonus, neuropathy, and worsening ataxia. She began attending college.

COMMENT

Although the older sister did not undergo genetic testing, her illness fit perfectly with how children with Alpers-Huttenlocher syndrome present. The younger sister presented with ataxia neuropathy syndrome, also known in the literature as sensory ataxic neuropathy, dysarthria, ophthalmoplegia (SANDO) syndrome. Six main syndromes are caused by mutations in *POLG*, and the sisters in this case illustrate the variability and diversity in clinical presentation.[22,23]

Clinical Presentation of Mitochondrial Diseases

KEY POINT

● For patient care, it is most logical to classify the patient's mitochondrial illness by both genotype and phenotype, if available. It is recognized that no well-structured nomenclature for classifying all the mitochondrial diseases exists.

The clinical features of mitochondrial disease are highly variable, even in patients (and sometimes related patients) with identical genetic findings or genetically untested family members, often deceased, with a phenotypic fit for the disease (CASE 11-2). This variability applies to the age of onset and severity of specific organ involvement, as well as the spectrum and pattern of different organ system involvement in any one patient. In patients with mutations affecting mtDNA, the disease variability, specifically the age of onset and severity, has been attributed to the percentage of mutant heteroplasmy and the tissue-to-tissue variation caused by the random segregation of mutation burden between tissues that occurs early in embryonic development. A higher percentage of mutant heteroplasmy correlates, in general, with a younger age of onset and increased severity of the disease. Heteroplasmy describes the phenomenon that mtDNA mutations occur in a variable percentage of mtDNA molecules within a cell, tissue, or a whole organism. A person can have anywhere from 0% mutant heteroplasmy, which corresponds to the healthy state, to 100% mutant heteroplasmy, which would cause early-onset and severe disease. In general, mutant heteroplasmy of less than 50% is not thought to result in illness. The percentage of mutant heteroplasmy determination resulting in variable severity and age of presentation is a real feature of the illnesses but hard to translate reliably to the human condition because it is technically difficult to measure and can vary from tissue to tissue. The percentage of mutant heteroplasmy in the white blood cells in a blood specimen may be quite different from that in neurons in an epileptic zone, which may be different from what would be found in the same patient's skeletal muscle. These differences in mutant heteroplasmy also vary significantly within families. However, some animal studies suggest this effect of successive segregation of mutant mtDNA may not be as variable a process as once thought, and therefore, other causes that could explain variable patterns of disease function likely exist.[26] Additional variability that could occur within families, and certainly between families, may be accounted for by confounding mutations that serve to modify the severity of the primary mutation. New data suggest that background mtDNA (non–disease-causing variants) may be responsible for the disease variability in patients with primary mitochondrial disease caused by pathogenic mtDNA mutations.[27] Although generalizations have exceptions, in babies, toddlers, and children, a central nervous system presentation is more common than a myopathic presentation, but the opposite is true in adults. However, it is not uncommon for two members of a family, for example, a child with myopathy and an adult with status epilepticus as his or her first onset of illness, to both have a diagnosis of MELAS due to m.A3243G. The major clinical phenotypes that are important for a deeper understanding of mitochondrial presentations are summarized in TABLE 11-4.[28–48] Reference to this table will often clarify further evaluation and management strategy.

Any patient will have a point in time with only one recognized sign or symptom; however, when that patient presents to medical attention, generally more signs or symptoms are uncovered by the history or examination. The two most notable exceptions include aminoglycoside-induced deafness associated with the m.1555G mutation and subacute central visual loss associated with the mtDNA mutations causing Leber hereditary optic neuropathy (LHON). In addition, the clinician should not overextend the classic features (TABLE 11-2

TABLE 11-4 **Common Classic Mitochondrial Phenotypes Due to Mitochondrial DNA Mutations and Deletions, and Nuclear DNA Mutations[a,b]**

Mitochondrial Phenotypes	Key Features	Other Features	Key Genetics
Leber hereditary optic neuropathy (LHON)[28,29]	Subacute (over weeks to months) painless central visual loss: typically starts unilaterally but then bilaterally; onset in late adolescence or young adulthood; males more frequently affected than females; 25% may recover some vision (specific mutation dependent); discontinuation of ethanol or tobacco smoking may help in recovery; visual recovery after one year is rare	Wolff-Parkinson-White syndrome, white matter lesions	Most mutations causing LHON found in the mtDNA-encoded complex I genes, and unique to LHON is that these mutations are found as mutant homoplasmy (all mtDNA carries the mutation): m.G11778A (69% of LHON with 4% recovery), m.G3460A (13% of LHON with 22% recovery), m.T14484C (14% of LHON with 65% recovery); other rare LHON mutations m.G3635A, m.G3700A, m.G3733A, m.C4171A, m.T10663C, m.G13359A, m.C13382A, m.C13382G, m.A14495G, mT14502C, m.C14568T
Mitochondrial encephalomyopathy, lactic acidosis, and strokelike syndrome (MELAS)[30–32]	Onset from infancy into late adulthood; elevated lactate in blood and CSF; stroke and strokelike events in nonvascular territories (typically parietal-occipital); varying degrees of cognitive impairment and dementia; short stature; epilepsy and subclinical epilepsy; myopathy	High-frequency hearing loss; diabetes mellitus; Wolff-Parkinson-White syndrome; varying degrees of gastrointestinal dysmotility including gastroparesis; weight loss; atypical migraine; vomiting spells	Most MELAS is caused by a few select mutations in the mtDNA *t RNA^{Leu}* gene with the m.A3243G representing 80% of affected patients, m.T3271C (7%), m.A3260G (about 5%), m.A3252G (<5%) and mutations in other mtDNA genes, such as *ND5* m.G13513A
Myoclonic epilepsy with ragged red fibers (MERRF)[33–35]	Progressive epilepsy in older children (variable age of onset) (100%); myoclonus (independent of the epilepsy) (100%); clumps of diseased mitochondria accumulate in the subsarcolemmal region of the muscle fiber, which appear as ragged red fibers when muscle is stained with modified Gomori trichrome stain (92%); adults may present with ataxia and cervical lipomas (3%)	Short stature (57%); dementia (75%); neuropathy (63%); sensorineural hearing loss (90%); cardiomyopathy (33%); Wolff-Parkinson-White syndrome (22%); retinopathy (15%); myopathy (80%); optic atrophy (40%)	Mutations in the mtDNA *tRNA^{Lys}* m.A8344G (80%), m.T8256C, m.G8363A, m.G8361A, and others

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Mitochondrial Phenotypes	Key Features	Other Features	Key Genetics
Leigh syndrome and neuropathy, ataxia, and retinitis pigmentosa (NARP)[36,37]	Following normal development, acute or subacute onset generally in the first or second year of life but may be later (Leigh syndrome), with NARP generally in adulthood. There tends to be a stepwise decline in neurologic function that primarily results from central gray matter involvement and includes long tract signs, ataxia, ophthalmoplegia, bulbar dysfunction, dystonia, dementia, and ventilatory failure. Peripheral neuropathy is common. NARP is found in adults with a lower level of mutant heteroplasmy involving only mtDNA genes; slowly progressive, often identified in the thirties or forties, often in mothers or other maternal relatives of the child with Leigh syndrome; clinical features include neuropathy, ataxia, retinitis pigmentosa, and ophthalmoplegia, but can include other features seen in Leigh syndrome.	Certain specific nuclear DNA mutations can result in early cardiac, hepatic, or renal involvement. Lactic acidosis may be present. MRI findings generally demonstrate involvement of central gray matter, cerebellar nuclei, the periaqueductal gray, and brainstem. MRI findings such as leukodystrophy can be seen in some cases.	More than 75 genes associated with Leigh syndrome involving mtDNA and nuclear DNA genes, most often involving complex I and IV subunits and assembly genes. The m.T8993G and m.T8993C mutations in the *ATP6* gene (subunit of complex V) are the most common mutations but make up probably less than 20% of all cases. Other major genes include *PC* (pyruvate carboxylase deficiency), *PDHC* (pyruvate dehydrogenase deficiency), and *SURF1*, *SCO1*, *SCO2*, *COX10*, *COX15*, *SERAC1* mutations. If a pattern of maternal inheritance is seen, testing the m.8993 allele is reasonable; otherwise using a large Leigh-syndrome genetic test panel or clinical exome sequencing is advised. The nuclear DNA mutations are overwhelmingly autosomal recessive, with some genes on the X-chromosome.

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Mitochondrial Phenotypes	Key Features	Other Features	Key Genetics
mtDNA deletion and depletion syndromes[38–45]	Major forms include hepatocerebral (epileptic encephalopathy, global developmental delay and/or regression, liver dysfunction and failure); encephalomyopathic (epileptic encephalopathy, developmental delay and/or regression), PEO, myopathy; neurogastrointestinal (gastrointestinal dysmotility, neuropathy, PEO, myopathy); myopathic (PEO, myopathy)	N/A	All phenotypes occur because of loss of wild-type mtDNA content over time, either due to an mtDNA deletion or nuclear DNA mutations affecting mtDNA replicase function. In some disorders the mtDNA nucleotide sequence may be normal or near normal, but the copy number is greatly reduced; in some disorders, the copy number may be normal or not, but the nucleotide sequence is markedly different from the wild-type sequence, and in others there may be one large or many (hundreds of) small deletions. In all cases, deletion and depletion result in an inadequate amount of wild mtDNA to support production of normal levels of mtDNA-encoded proteins, tRNAs, or rRNAs. The three well-described deletion disorders include chronic progressive external ophthalmoplegia (CPEO) plus, Kearns-Sayre syndrome (KSS), and Pearson syndrome. The depletion syndromes are typically caused by a mutation in one of the components of the mtDNA replisome, defined as the set of more than a dozen genes, whose gene products are responsible for the duplication with fidelity, and maintenance of mtDNA. The first discovered and most commonly affected gene is *POLG*. *DGIOK*, *POLG*, *MPV7*, *TWNK*, *SUGLG1*, *RRM2B*, *TFAM*, *SUCLA2*, *FBXL4*, *OPA1*, *ABAT*, *TYMP*, *TK2*, *AGK*, *MGM1*, *SLC25A4*

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Mitochondrial Phenotypes	Key Features	Other Features	Key Genetics
CPEO and CPEO plus syndrome	Adult-onset progressive external ophthalmoplegia, sometimes with an associated skeletal myopathy.	In the CPEO plus variants, features that are seen in KSS and *POLG*-spectrum disease may be present, but usually later in life and less severe than in those illnesses.	Most CPEO is caused by large single deletions in mtDNA, but with lower levels of mutant heteroplasmy than seen with KSS; point mutations in the mtDNA, such as m.A3243G, can cause (isolated) CPEO and CPEO plus.
Kearns-Sayre syndrome (KSS)[41]	Onset before the age of 20 years, external ophthalmoplegia, retinitis pigmentosa, and sensorineural hearing loss	Myopathy; cardiac conduction defects; renal impairment (tubular and glomerular); dementia, seizures; exocrine and endocrine pancreatic failure; bulbar dysfunction with hypernasal speech; short stature; cardiomyopathy; parkinsonism; neuropathy	Large-scale deletion of a 4977 base pair segment of mtDNA, rarely by mtDNA duplication; most mutations are sporadic
Pearson syndrome[42]	Failure to thrive due to exocrine pancreatic failure and sideroblastic anemia (transfusion-dependent) in the first year of life; lactic acidosis; multiple endocrinopathies (growth hormone failure, adrenal insufficiency, diabetes, hypoparathyroidism, hypothyroidism); and renal tubular acidosis. Death is common in the first few years of life.	Surviving children typically develop the clinical features of KSS with myopathy and progressive external ophthalmoplegia; the sideroblastic anemia can resolve.	Large-scale deletion (or duplication) in mtDNA, typically not the common 4977-base pair deletion seen in KSS; sporadic mutations.

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Mitochondrial Phenotypes	Key Features	Other Features	Key Genetics
***POLG*-spectrum disorders and other disorders of the mtDNA replisome**[23,38,43,c]	Myocerebrohepatopathy syndrome has its onset generally in infancy with failure to thrive, lactic acidosis, liver dysfunction, and early death, with variable muscle and brain involvement. Alpers-Huttenlocher syndrome (AHS) was the first described in the 1930s, and it was not until 2004 that it was associated with autosomal recessive mutations in *POLG*. AHS results in an explosive childhood onset of epileptic encephalopathy, cortical visual loss, long-tract findings in a child with normal development or cognitive delays, liver failure, and extreme valproate sensitivity resulting in liver failure. The other variants have clinical features characterized clinically by their syndromic name, with onset between late adolescence and mid-adult age. Many of these disorders vastly overlap. Fatal hepatic sensitivity to valproate is a feature of disease caused by mutations in *POLG*, and extreme caution should be used in other mtDNA depletion disorders. Ataxia neuropathy spectrum (ANS), sensory ataxia, neuropathy, dysarthria, ophthalmoplegia (SANDO), mitochondrial recessive ataxia syndrome (MIRAS), myoclonic epilepsy myopathy sensory ataxia (MEMSA) have adolescent or young-adult onset. The onset of autosomal dominant progressive external ophthalmoplegia (adPEO) and autosomal recessive progressive external ophthalmoplegia (arPEO) are adult to late-adult onset and can also have CPEO plus features.	Headache and mood disturbance are common in the adult disorders.	Mutations in *POLG* but also described in *DGUOK*, *MPV17*, *POLG2*, *C10orf2*, *TFAM*, *SUCLA2*, *FBXL4*, *SUCLG1*, *RRM2B*, *OPA1*, *ABAT*, *TYMP*, *TK2*, *AGK*, *MGME1*, and *SLC25A4*. Aside from autosomal dominant progressive external ophthalmoplegia, most but not all mutations are autosomal recessive.
Mitochondrial neurogastrointestinal encephalopathy (MNGIE)[46]	Gastrointestinal dysmotility with subsequent cachexia, neuropathy, hearing loss, ptosis, with high plasma thymidine	Leukodystrophy	Mutations in *TYMP* encoding thymidine phosphorylase; autosomal recessive

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Mitochondrial Phenotypes	Key Features	Other Features	Key Genetics
Mitochondrial myopathy due to thymidine kinase 2 deficiency[47]	Myopathy with a broad range of severity, elevated creatine kinase level	Infants may have an associated encephalopathy, epilepsy along with a profound myopathy	Mutations in *TK2*, autosomal recessive
***OPA1* disorders**[48]	Painless visual loss in childhood	Adult-onset peripheral neuropathy, hearing loss, ataxia syndromes, CPEO plus syndromes	Mutations in *OPA1*; protein product controls mitochondrial fusion, autosomal dominant
***BCS1L* syndromes**[24]	Growth restriction, aminoaciduria, cholestasis, iron overload, lactic acidosis, and early death (GRACILE) syndrome causing death in the first years of life and/or Björnstad syndrome (congenital profound hearing loss and pili torti/kinky hair). Diverse phenotype determined by specific allelic mutation in *BCS1L*.		Mutations in *BCS1L*, protein product controls assembly of complex III

[a] Modified with permission from Cohen BH, Neurotherapeutics.[8] © 2013 The American Society for Experimental NeuroTherapeutics, Inc.

[b] Nomenclature in specifying mutations:

1. Genes are always indicated in italics whereas the proteins they encode are in standard font. For example, the gene *POLG* encodes for the protein polymerase γ or pol γ or polγ.
2. If the mutation is in the mtDNA, the mutation is identified with "m." followed by the normal wild-type nucleotide (A, T, C, or G), followed by the numeric designation of the nucleotide in the mtDNA molecule (eg, 3243, 8993), followed by the mutant nucleotide. Other accepted systems place the nucleotide designations at the end, separated by the ">" symbol or simply do not indicate the wild-type nucleotide. For example, m.A3243G, m.3243A>G, and m.3243G all are accepted nomenclature.
3. If the mutation is in the nuclear gene, the mutation may be specified by two methods. A common mutation causing *POLG*-spectrum disease is designated *POLG* c.1399G>A or *POLG* p.Ala467Thr. The first designation implies the gene affected is *POLG*, with the nucleotide position 1399 having a mutation A as the substitute for the wild-type G, whereas the second designation is the resultant amino acid change that occurs with this nucleotide change, with a threonine amino acid substituting the normal alanine amino acid in the 467th position in the polymerase protein. The amino acids have two different naming structures, one with three and one with only one alphabetical symbol. As with the mtDNA nomenclature, c.1399G>A can be represented as c.G1399A or c.1399A. At times the nucleotide change may result in a stop codon, also known as a nonsense mutation, which would be designated by an X or Ter (terminate). More complicated mutations do exist but will not be discussed here.

[c] The six well-described and sometimes overlapping major phenotypes include infant-onset MCHS; AHS; ANS, which also includes SANDO, with or without epilepsy, and MIRAS; MEMSA; adPEO; and arPEO.

and TABLE 11-4) to include other organ system findings. This includes not only symptoms but also laboratory values. As one example, patients with myopathy often have exercise intolerance. However, exercise intolerance cannot be assumed to be caused by myopathy without further evaluation. Therefore, it is not acceptable to substitute myopathy for exercise intolerance when referring to the classic descriptions in TABLE 11-2 and TABLE 11-4. As another example, consider a patient with myopathy and several measures of alanine transaminase (ALT) that are found to be between 55 U/L and 60 U/L (reference range less than 45 U/L) over a year with several normal values interspersed. Although the ALT value is elevated, it does not warrant, without further exploration, a designation of hepatopathy or liver failure and should not be used as a second classic feature that could be used to justify a mitochondrial diagnosis. It is tempting for clinicians to objectify such symptoms or include that symptom or a slightly abnormal laboratory value as a mitochondrial finding, but because the ramifications can lead to an unnecessary evaluation or misdiagnosis, remaining objective and avoiding overinterpretation of results are critical. Finally, if it is not certain that mitochondrial disease is the cause of the patient's illness, it is highly recommended to avoid using the terms *possible* or *probable* as adjectives or descriptors of the term *mitochondrial disease*. Risks of mislabeling include failing to make the correct diagnosis, creating unnecessary worry, initiating unnecessary therapies, and providing incorrect genetic counseling.[21,25]

Specific Organ System Involvement

Extensive variability exists in specific organ system involvement within the different mitochondrial diseases, and it is rare to have only one organ system involved. The following discussion of objective findings should be considered during the evaluation and ongoing management of patients.

MUSCLE. Weakness, early fatigability, and exercise intolerance caused by myopathy are common symptoms of muscle involvement, but aside from external ophthalmoplegia, which is prevalent in primary mitochondrial disease, the pattern of skeletal muscle weakness does not differentiate a mitochondrial myopathy from other causes of myopathy. In general, most mitochondrial myopathic processes are symmetric and tend to initially affect the more proximal than distal skeletal muscles. Progressive external ophthalmoplegia is a very important sign when present but may be a feature in myasthenia gravis, myotonic dystrophy, oculopharyngeal muscular dystrophy, and other disease processes. Atrophy of facial muscles and the intrinsic muscles of the hands or feet or symmetric atrophy in other muscle groups can occur. All skeletal muscles are at risk of involvement, and smooth muscle and cardiac muscle can be involved, as well. Myopathy may begin at any age but tends to be a more common feature in adults than children.

When a patient presents with isolated symptoms of weakness and exercise intolerance with or without obvious features of myopathy, the evaluation becomes more complicated. An elevation in creatine kinase (CK) or myopathic findings on EMG are supportive findings if present although not specific.[8,20] A new clinically available test, growth differentiating factor-15 is elevated in mitochondrial but not other myopathies, but it can also be elevated in diabetes mellitus, cancer, heart disease, and pregnancy. Although helpful when elevated, growth differentiating factor-15 is not yet considered a definitive biomarker for

mitochondrial myopathy.[49] The muscle biopsy can also yield findings that point away from a mitochondrial etiology. Muscle histology and enzymology are also helpful tools, but they are not specific, except under some well-known circumstances. Even the presence of ragged red fibers, ragged blue fibers, COX-negative fibers, and subsarcolemma accumulation as seen on electron microscopy, which are pathologic if excessive, can be seen in other myopathic processes.[5,20]

BRAIN. The central nervous system manifestations of mitochondrial disease are quite diverse and may include migraine, dementia, seizures, ataxia, movement disorders, mood disturbances, strokes, and strokelike episodes. The onset of brain involvement may be abrupt and devastating. Patients may present with an encephalitic picture of alteration in mentation with or without seizures. The use of continuous EEG can help identify subclinical seizures, but at times it is difficult to differentiate clinically among an atypical migraine, stroke, a strokelike episode, and the effects of subclinical epilepsy. In children, the acute or subacute loss of ventilatory drive, ataxia, dystonia, or long tract findings should suggest Leigh syndrome. The MRI findings generally correlate with the examination in these circumstances. The classic MRI findings in MELAS include restricted diffusion and fluid-attenuated inversion recovery (FLAIR)/T2 changes consistent with stroke, most commonly in the parietal or occipital lobes, but outside of a vascular distribution. It is not clear if some strokes and strokelike episodes are a result of untreated or untreatable subclinical (or clinical) status epilepticus. Although strokes are common features in some patients with MELAS, they can be seen in other mitochondrial disorders, mainly those caused by mtDNA mutations. In Leigh syndrome, the typical findings are hyperintense symmetric changes affecting central gray matter, cerebellum, and periaqueductal gray on FLAIR and T2-weighted images.[5,20,50]

Epilepsia partialis continua in any age group warrants consideration of a mitochondrial disease and is a common presentation in both MELAS and *POLG*-related disorders.[34,39,51] It is rare for dementia or mood disturbance to be the initial presentation in mitochondrial diseases, but either can be an accompanying feature. Dementia with or without psychiatric manifestations is associated with many mtDNA mutations, such as myoclonic epilepsy with ragged red fibers (MERRF) and MELAS, as well as those illnesses caused by mutations in *POLG*. Mood disorders occur in at least one-half of patients with some mitochondrial phenotypes. Migraine, complex migraine, and abdominal migraine (ie, cyclic vomiting variant) are features in some patients with mitochondrial disorders.[5,9,12,18,22]

PERIPHERAL NERVE. The clinical features, as expected in a neuropathic process, most commonly include symmetric distal weakness and loss of muscle stretch reflexes with loss of vibratory and position sensation. Neuropathic pain may be present.[5] A demyelinating pattern has been observed in few patients, with some having an IV immunoglobulin (IVIg)-responsive course for unclear reasons. Varieties of the Charcot-Marie-Tooth syndromes are in fact caused by mutations in nuclear mitochondrial genes, including mutations in *POLG*, *MPV17*, *MFN2*, *OPA1*, *GDAP1*, and others.[5,38,52] Autonomic nerve dysfunction may occur and can result in gastrointestinal and bladder dysfunction, cardiac conduction issues, and orthostatic hypotension. When dysautonomia without an objective large

KEY POINT

- **If it is not certain that mitochondrial disease is the cause of the patient's illness, it is highly recommended to avoid using the terms *possible* or *probable* as adjectives or descriptors of the term *mitochondrial disease*. Risks of mislabeling include failing to make the correct diagnosis, creating unnecessary worry, initiating unnecessary therapies, and providing incorrect genetic counseling.**

fiber neuropathy is the lone symptom and without other classic features of mitochondrial disease, identifying a mitochondrial etiology has been elusive. Efforts to biochemically or genetically characterize primary dysautonomia as a mitochondrial disorder have not yielded firm evidence.

More common disorders, such as postural tachycardia syndrome or atypical demyelinating polyneuropathy syndromes, may mimic mitochondrial disease (TABLE 11-5).[5,8] A number of severe neurologic and systemic disorders include dysautonomia as a prominent feature, but other more severe symptoms are present that distinguish these from isolated primary dysautonomia. Dysautonomia can be seen in diabetes mellitus, alcoholism, and the many hereditary neuropathies. Multiple system atrophy, which remains a clinical diagnosis, shares many features of (and can be confused with) a mitochondrial disorder and may present with profound dysautonomia and parkinsonism, hypophonia, dementia, and impotence. Familial transthyretin amyloidosis is a severe disorder caused by mutations in the transthyretin gene (*TTR*) with autosomal dominant inheritance, although most patients present with de novo mutations. Symptoms associated with familial transthyretin amyloidosis can mimic the mitochondrial phenotype and include severe dysautonomia, including bowel dysfunction, peripheral neuropathy, blindness, cardiomyopathy, and nephropathy.[53,54]

HEART. The high energy requirements of the heart are obvious, and although muscle and nerve have been discussed, the mitochondrial pathophysiology of tissues in the heart requires some additional discussion. The sinoatrial and atrioventricular nodes are the most metabolically active tissues in the body, and the heart remains in constant motion from its embryonic state until death. Given this constant demand for energy, it remains a mystery why cardiac conduction defects and cardiomyopathy are not more frequent complications of mitochondrial dysfunction. It is rare for a cardiac issue to be the isolated presenting feature of any mitochondrial disorder at any age; however, the cardiac event may be the first issue that brings the patient to medical attention. Progressive cardiac conduction defects culminating in complete heart block may develop quickly in Kearns-Sayre syndrome,[55] and although the common features of Kearns-Sayre syndrome (TABLE 11-4) may have been unrecognized, they are usually present at the time of the cardiac event. Wolff-Parkinson-White syndrome can develop in patients with LHON[56] and in MELAS associated with the m.A3243G mutation, but again, these are generally not the true sentinel event.[57] No feature of the cardiomyopathy differentiates a mitochondrial disorder from other etiologies of heart failure, although hypertrophic cardiomyopathy is the most common form seen in mitochondrial disorders, with noncompaction (arrested endomyocardial morphogenesis) cardiomyopathy being rare. Deletions in the mtDNA, specific mtDNA point mutations, and many nuclear genes are associated with the risk for cardiomyopathy.[58] The clinical presentation of heart failure or cardiac conduction defects is no different in mitochondrial diseases than in other populations of patients, and evaluation begins with a screening ECG and echocardiogram.

LIVER. Liver dysfunction can occur in mitochondrial diseases, but outside of infancy where the mtDNA depletion disorders can present with liver failure, it is unusual for liver dysfunction to be the initial or isolated presentation. Clinical

Common Medical Disorders That Mimic Some Features of Primary Mitochondrial Disease[a]

TABLE 11-5

Endocrine

- Hyperthyroidism or hypothyroidism
- Adrenal insufficiency
- Diabetes mellitus
- Hypoparathyroidism and related disorders

General medical illnesses

Obstructive sleep apnea

Metabolic syndrome

Deconditioned state

Fibromyalgia

Chronic fatigue syndrome

Inflammatory

- Systemic lupus erythematosus (SLE)
- Other collagen vascular disorders
- Inclusion body myositis

Paraneoplastic and autoantibodies

- Anti-Hu antibody
- Anti-Yo antibody
- Anti-*N*-methyl-D-aspartate receptor antibody
- Opsoclonus-myoclonus syndrome
- Voltage-gated potassium channel complex autoantibodies and associated disorders

Congenital muscular dystrophies

- Central core disease
- Multiminicore disease
- Ullrich and Bethlem myopathies (*COL6A* disorders)

Muscular dystrophies

- Oculopharyngeal muscular dystrophy
- Other dystrophies (Note: ragged red fibers are common in the muscular dystrophies)

Channelopathies (eg, *RYR1* mutations)

Chronic renal failure with acidosis or loss of amino acids (note: systemic carnitine deficiency occurs in patients on dialysis)

Vitamin deficiencies: vitamin B_{12} deficiency, other cobalamin disorders, vitamin E deficiency, micronutrient disorders seen in patients who have undergone bariatric surgery, on chronic total parenteral nutrition, self-induced restrictive diets, inflammatory bowel disease, or short bowel syndrome

[a] Modified with permission from Cohen BH, Neurotherapeutics.[8] © 2013 The American Society for Experimental NeuroTherapeutics, Inc.

findings generally include elevation in liver enzyme levels, evidence of synthetic liver dysfunction, or fibrosis or cirrhosis as identified on imaging studies. The most common genetic causes include the group of mtDNA depletion disorders, especially in *POLG, MPV17*, and *DGUOK* (in both children and adults), and mutations in a complex IV assembly gene, *SCO1*, which is more common in children.[21,38,39,43,45,59,60] However, adult-onset hepatic disease can be a feature of pathogenic mutations in *POLG* presenting with the syndrome of fatty liver and hepatic fibrosis, culminating in nonalcoholic steatohepatitis. Nonalcoholic steatohepatitis can also be a feature of fatty acid oxidation disorders, as well.[61,62] For patients at risk, screening with the liver enzyme ALT is generally adequate, but for those with identified liver involvement, liver function tests that are a measure of hepatic synthetic function include fasting glucose, ammonia, amino acids, bilirubin, cholesterol, albumin, and coagulation studies (eg, prothrombin time/international normalized ratio [INR]).[23]

EYES. Eye involvement is a common manifestation of mitochondrial disorders.[63,64] Both retinitis pigmentosa[63–66] and optic atrophy[63–65] are features caused by many mitochondrial-targeted genes. Retinitis pigmentosa is not uncommon in mtDNA point mutations and mtDNA depletion disorders. Optic atrophy is most frequently associated with LHON,[67–69] which usually presents in late adolescence; its clinical presentation can overlap with multiple sclerosis. Optic atrophy can also be seen in the syndrome referred to as *autosomal dominant optic atrophy*, which is caused by mutations in *OPA1*, a gene encoding for a protein responsible for proper mitochondrial fusion.[67,70] Optic atrophy with severe subacute central visual loss is a hallmark of LHON and usually the only features. The optic atrophy that occurs with *OPA1* mutations presents in the first decade of life and is not as severe as in LHON.[67–70] The differential diagnosis of retinitis pigmentosa and optic atrophy is broad, and many genetic and acquired disorders are associated with these conditions, but ocular findings should be considered in the context of a suggestive history, family history, or physical examination as a sign of mitochondrial disease.

EARS. Sensorineural hearing loss occurs in some patients with mitochondrial diseases.[71,72] This often begins as a high-frequency hearing loss, and in some patients progresses to total deafness. The mtDNA mutation, m.A1555G, occurs in approximately 1 in 1200 people[73] and predisposes to an extreme ototoxic sensitivity to aminoglycosides, with hearing loss occurring after a single dose and, occasionally, even without exposure to aminoglycosides. A number of disorders caused by mtDNA point mutations are associated with hearing loss, and trying to avoid aminoglycosides in identified patients is reasonable. The role of specific nuclear gene mutations in worsening the hearing loss seen with m.A1555G mutation has been elucidated[74,75] and can serve as an another example of the effects of modifying mutations even outside of the primarily affected gene. High-frequency hearing loss is common in many genetic mitochondrial disorders but is probably most frequent in MELAS caused most commonly by m.A3243G.

KIDNEY. Renal dysfunction in mitochondrial disease typically involves an inability to reabsorb electrolytes and amino acids and is more common in infants. In adults, m.A3243G MELAS has been reported to result in both tubulopathy and focal segmental glomerulosclerosis.[76–78]

ENDOCRINE SYSTEM. Diabetes mellitus is a common feature of mitochondrial diseases[79–81] and is especially common in MELAS. Other endocrine disorders, including adrenal insufficiency, hypoparathyroidism, hypothyroidism, and hyperthyroidism, have been described in a number of disorders, but the absolute incidence is not known.[82,83]

Diagnostic Approach

The key to an early diagnosis of mitochondrial myopathy is recognizing that the myopathy or exercise intolerance has a pattern common in mitochondrial diseases, such as progressive external ophthalmoplegia, or that the myopathic symptoms are occurring along with signs or symptoms involving other organ systems. Knowledge of the key features of mitochondrial disease is essential (**TABLE 11-2** and **TABLE 11-4**). As noted earlier, patients with mitochondrial disease may present with a single symptom or clinical feature and may, over time, develop other symptoms and signs, but in most circumstances, more than one finding exists at the initial presentation. For example, a patient may come to clinical attention for what seems to be a single symptom (eg, subacute ataxia) but on examination may be found to have progressive external ophthalmoplegia and signs of a long-standing neuropathy, such as pes cavus and absent reflexes. Inquiring about other symptoms is important because many may be relatively mild or chronic in nature and overlooked by both the patient and other clinicians.

Once mitochondrial disease is suspected, it is reasonable to perform screening laboratory tests and selected testing of organ systems based on presentation to aid in diagnosis or to help with symptomatic treatment. The screening blood and urine testing may be helpful, but it is important to remember these tests are neither sensitive nor specific because they can be affected by secondary mitochondrial dysfunction, technical errors in obtaining the sample, overinterpretation, and nonstandardization between laboratories. For example, the plasma lactate will be falsely elevated after exercise, with prolonged tourniquet time, or if the patient struggles. Urine organic acid results can be misleading based on dietary intake of carbohydrates or special diets consumed in the several hours before sampling.

In clinical practice, it is often difficult to distinguish or categorize the different types of metabolic myopathies because the myopathic component appears the same in all types of myopathies, and findings entrenched in the mitochondrial literature, such as lactic acidosis and ragged red fibers, can be seen in nonmitochondrial metabolic myopathies. Some patients may present with a constellation of signs and symptoms that fit reliably within the well-described clinical features of mitochondrial syndromes. Each of these syndromes is known to be associated with well-described mutations within known genes, and therefore, focused genetic testing may yield a rapid definitive diagnosis. Common medical practice for ordering genetic testing requires a formal informed consent, and it is advised that only clinicians familiar with obtaining genetic informed consent order genetic tests. Referral to a genetic counselor or medical geneticist or a colleague with this skill set is recommended if the clinician is not comfortable with the process of informed consent for genetic testing. In recent years, some commercial genetic laboratories have hired genetic counselors to assist the clinician by obtaining the informed consent. Although having the testing laboratory pay for this genetic counseling requirement is an obvious potential conflict of interest, in practice the process has functioned responsibly.

Even if the results uncover a disease that has no specific therapy, reaching a firm diagnosis is almost always beneficial. The major reason for pursuing genetic testing is to best understand a patient's illness, resulting in ending further unnecessary diagnostic testing, changing therapy, stopping unnecessary therapies, and providing proper genetic counseling. Genetic counseling can offer a framework for addressing all the clinical needs of the patient as a result of the diagnosis, allow for reproductive risk counseling, and in some cases allow for rapid diagnosis of living relatives. The emotional benefits of simply knowing the name of their illness is comforting to most patients. Finally, although the illness may not have a specific treatment, knowledge gained from the literature can directly benefit management.

Aside from an occasional new discovery, as all of the mtDNA genome has been mapped, all known pathogenic mutations have been linked to specific mitochondrial phenotypes. With the mitochondrial-targeted nuclear DNA genes, the situation is quite different. New disease-associated genes are reported monthly, and new pathogenic alleles within known disease-causing genes are identified continuously. As these new genes are added to the list of known disease-causing genes and new mutations within those genes are reported, data are being stored within a project known as the Mitochondrial Disease Sequence Data Resource (MSeqDR) Consortium, which can be accessed and browsed without a fee at *MSeqDR.org*.[84]

Management

Currently, no US Food and Drug Administration (FDA)-approved medications or therapies used to treat mitochondrial disease exist. Phase 2 and phase 3 clinical trials with several pharmacologic agents are underway in mitochondrial diseases. For all metabolic myopathies, standard pharmacologic and nonpharmacologic therapy should be directed at symptomatic relief of specific symptoms and signs, and the goal of surveillance and management is to address and treat disabilities and prevent complications. For most mitochondrial myopathies, some disease manifestations can be detected before they are symptomatic, such as sensorineural hearing loss, cardiac conduction defects, nocturnal hypoventilation, and renal tubular acidosis; performing disease-specific surveillance studies is important.

For decades, experts have been treating primary mitochondrial diseases with vitamins and cofactors. However, despite years of study, evidence is lacking, based on analysis of controlled clinical trials, that these therapies are effective.[85] A full Cochrane review, as well as overview of all important trials, has left clinicians and their patients questioning the use of vitamins and cofactors.[86] In practice, individual patients have benefited from the use of particular supplements, but evidence to suggest that all of these supplements be used as universal treatment is lacking. Regardless, experts continue to offer and recommend a variety of supplements while recognizing the need for both identified outcome measures for each supplement and a better base of evidence.[20,87,88] Most clinicians prefer to start one supplement at a time and evaluate based on the clinical status. The most common supplement recommended for patients, at least as a trial supplement, is coenzyme Q10 in its reduced form (ubiquinol). A trial of α-lipoic acid and riboflavin has also been recommended for most patients. Levocarnitine is no longer recommended routinely unless the patient has a documented carnitine deficiency. Folinic acid

should be used for patients with a CSF folate deficiency or in disease states in which CSF folate deficiency is common, such as some of the mtDNA depletion disorders. IV levoarginine (or levocitrulline or both) has been recommended as acute therapy for strokes in patients with MELAS, as well as in the oral forms as a potential prophylactic therapy for strokes. True evidence-based guidelines are still lacking. In an attempt to address all management and surveillance evaluation issues facing mitochondrial patients, a large panel of experts participated in an iterative consensus process using the Delphi method aimed at reaching consensus (at least 80% agreement) for all potential management issues.[20,89]

Preemptive routine evaluation is reasonable, but no studies have made firm recommendations on the frequency or extent of laboratory testing or organ system monitoring, although suggested guidelines are available based on expert opinion.[89] One goal of frequent patient visits is to obtain an interval history that can target many of the disease complications. It is reasonable to evaluate fasting glucose, liver and kidney function, and blood cell counts 1 or 2 times a year. For patients with syndromes that are known to have cardiac conduction defects that may be life-threatening, obtaining biannual ECGs is reasonable.

For patients with epilepsy, evaluation and management are the same as with other epilepsies, with a few exceptions. Epilepsia partialis continua, subclinical seizures, or subclinical status epilepticus can be a feature of a primary mitochondrial disorder, and early evaluation with EEG should be considered in the proper clinical context. Valproate may be safe in many mitochondrial disease genotypes and phenotypes, but it is contraindicated in those with mutations in *POLG* and probably in other genes affecting mtDNA replication and mtDNA maintenance.[39] Vigabatrin interferes with the nucleotide salvage pathway, making this a potential toxic medication in mtDNA depletion syndromes. For patients with intractable epilepsy, the control of seizures must be balanced against the sedation caused by the anticonvulsants. The same argument applies to the use of benzodiazepines for the treatment of myoclonus. Although the drug class is effective at reducing myoclonus, the dosage required to bring symptoms into some control may be so sedating that the quality of life is worsened.

For patients with myopathy or with brainstem disease affecting ventilation, evaluating ventilation during wakefulness and sleep can be very important. It is not uncommon for patients to develop symptomatic hypercarbic states that can respond to varying types of noninvasive or invasive treatment. Both central and obstructive sleep apnea are common in mitochondrial disease, and the quality of life can be vastly improved with the use of nocturnal bilevel positive airway pressure. For patients with motor disabilities or central nervous system disease that affects motor tone or movements, the assistance of colleagues in physical medicine and rehabilitation can be helpful; these patients can benefit from therapies including orthotics and botulinum toxin injections.

As with other neurologic diseases affecting swallowing and ventilatory function, both gastric feeding and tracheostomy with respiratory support may improve quality of life and life span, even if they do not change the course of the illness. In practice, this discussion is very difficult to have with patients and their families before these options may be absolutely needed because it can suggest the clinician is giving up hope. However, it is reasonable to have discussions about using these technologies early in the disease course and then moving forward with the procedure if the patient choses so at a time before they are absolutely necessary.[89]

METABOLIC MYOPATHIES

The metabolic myopathies are individually rare genetic disorders of generally lipid and carbohydrate metabolism with the primary feature of the illness affecting muscle. As stated, the mitochondrial diseases are, in fact, metabolic myopathies, but most commonly they have other features, both within the central nervous system and disease involving organ systems outside of the nervous system, which is why they are discussed separately.

Lipid Myopathies

The lipid myopathies encompass the group of genetic disorders involving metabolism of fats that cause muscle weakness or exercise intolerance, often with an associated accumulation of lipids on histological examination. Much of lipid metabolism occurs within the mitochondria; however, these are discussed separately here because of their historical context, and the metabolism is distinct from the respiratory chain. Included in these illnesses are disorders of β-oxidation and those involving carnitine, which is responsible for shuttling the free fatty acids into the mitochondrial matrix. The onset of weakness, muscle fatigue, and exercise intolerance is variable and depends on the involved gene and the mutations' impact on the enzyme function. Although the predominant feature is exercise-induced weakness, patients can have a static myopathy, fasting hypoglycemia, and rhabdomyolysis. These disorders can start early in life or remain preclinical until later decades. Muscle atrophy or dystrophic changes are generally uncommon with the lipid myopathies. An elevation of the baseline CK level and the propensity for rhabdomyolysis and myoglobinuria are associated with some but not all the lipid disorders. These disorders are often grouped because, as a rule, most but not all cause an excessive accumulation of lipid in the cytoplasm, which can be identified by staining muscle fibers with Oil Red O or Sudan black. The myopathic clinical presentation is similar to that of a mitochondrial myopathy, and the approach to the laboratory evaluation would remain the same. An elevation in the CK level without an elevation in growth differentiating factor-15 and low plasma free carnitine values with abnormal acylcarnitine intermediates are features of some of the lipid myopathic disorders. It is important to note that laboratory findings and muscle biopsy can be normal with some of the disorders.

Free fatty acids are from either dietary intake or mobilized from fat stores. The free fatty acid is activated with CoA into its acyl-CoA form and then is able to enter the mitochondria through the carnitine transport system. This necessitates the exchange of the CoA with carnitine, requiring the enzyme carnitine palmitoyltransferase I, then the transport across the inner mitochondrial membrane by a translocase; then the carnitine is exchanged for CoA on the other side by the enzyme carnitine palmitoyltransferase II. Once inside the mitochondrial matrix, the process of β-oxidation begins, which cleaves off two carbon units, first by a series of very-long-chain, long-chain, medium-chain, and short-chain acyl-CoA dehydrogenases. The two carbon units, acetyl-CoA, that result in each "turn" of the β-oxidation pathway enter the tricarboxylic acid cycle as an alternative fuel to the acetyl-CoA generated from glycolysis.

The three most common lipid myopathies are carnitine palmitoyltransferase II deficiency (incidence of 1 in 250,000), very-long-chain acyl-CoA dehydrogenase deficiency (estimated incidence of 1 in 40,000 to 1 in 120,000), and trifunctional protein deficiency (extremely rare). The most common feature of these disorders is exercise-induced weakness or pain along with rhabdomyolysis.

Although dozens of lipid myopathies exist, a special mention of a newer disorder is necessary. Mutations in the *LPIN1* gene cause a deficiency in phosphatidic acid phosphatase and present as an autosomal recessive disorder that typically causes recurrent, severe rhabdomyolysis in children 2 to 6 years old, with some patients showing symptoms in their forties. Because the events of myoglobinuria may have been subclinical or ignored, this illness can present in adults with myopathy. Literature about associations with both insulin resistance and the metabolic syndrome in adults is evolving. The children are asymptomatic between events, but a crisis can be precipitated by physiologic stress, fasting, fever, exercise, and anesthesia. The events may decrease in frequency as the patient ages, with some adults having a residual myopathy.[90,91]

KEY POINT

- **Treatment for the lipid myopathies depends on the specific enzyme defect; some disorders have no specific therapy and others have treatments, which often involve dietary manipulation or the use of cofactors or vitamins.**

DIAGNOSTIC APPROACH. Blood testing for CK, lactate, carnitine, and acylcarnitine levels, along with urinary organic acids, is the standard evaluation for lipid myopathy. The CK, lactate, and carnitine levels and organic acids are generally normal between exacerbations, but the CK level does elevate, often dramatically during rhabdomyolysis. Acylcarnitine profiles and organic acid testing may be abnormal between exacerbations and demonstrate elevation in one or several acylcarnitines in specific patterns that identify the specific enzyme deficiencies, and organic acids may show dicarboxylic acids. During the episode, there can be an elevation in the CK level along with urinary pigmenturia, specific acylcarnitines, and nonketotic hypoglycemia. In the recent past, the evaluation for these disorders, once suspected clinically or on the basis of abnormal blood biomarkers, was to perform a skin biopsy and generate fibroblasts or perform a muscle biopsy for the purpose of specific enzymatic testing. Although these tests remain available to the clinician, a faster and less expensive path is to perform genetic testing, using either a large panel of genes or an exome platform. In some situations, the acylcarnitine pattern, along with the clinical features, may be highly suggestive of a specific enzyme deficiency, and performing gene sequencing on a single gene is appropriate. Because the clinical and laboratory features overlap, large-panel genetic sequencing is the best method of determining the diagnosis.[92]

THERAPEUTIC APPROACH. Treatment for the lipid myopathies depends on the specific enzyme defect; some disorders have no specific therapy and others have treatments, which often involve dietary manipulation or the use of cofactors or vitamins. In general, the therapy for these disorders is to avoid fasting; eat frequent, smaller meals rich in complex carbohydrates; and consume fluids and carbohydrates before and during physical activity. Levocarnitine supplementation should be used if there is a carnitine deficiency or if there is a mutation in *SLC22A5*, the gene encoding the carnitine transporter protein that is necessary for carnitine transport into the cell.

Therapy for rhabdomyolysis requires frequent monitoring of renal function and electrolytes with intravenous hydration with isotonic saline and bicarbonate. The CK level is a guide for monitoring improvement. For patients likely to have episodes, education of both the patient and the family is as critical as the education of the emergency department staff to ensure the safety of these patients when they do present with episodes.[91,93]

Glycogen Storage Disease Myopathy

Glycogen is a branching polymer composed of glucose molecules linked in a complex structure involving α(1–4) and α(1–6) bonds. Glycogen can be stored in many organs, but the vast majority is stored in the liver and muscle. The exact size and structure of each glycogen molecule differ. In the liver, glycogen is available for the purpose of maintaining steady glucose levels for all tissues, and it mainly functions in this role during normal fasting between meals. In muscle, glycogen provides a rapid source of glucose for several minutes after intense periods of muscle activity. Glycogen storage diseases result from deficiencies in the enzymes that build glycogen, as well as those that interfere with the degradation of glycogen and subsequent mobilization of glucose. In general, the glycogen storage diseases that affect the liver present with fasting hypoglycemia with or without liver enlargement. The glycogen storage diseases that affect muscle present either with exercise intolerance and rhabdomyolysis, as seen with McArdle disease (GSD5) or Tarui disease (GSD7), or with myopathy without rhabdomyolysis, as in Pompe disease (GSD2) or debrancher defect (GSD3a). Although many glycogen storage diseases can have muscle involvement, only those for which muscle involvement is the primary presentation are discussed in this article. In general, these disorders result in exercise intolerance that begins soon after exertion. Weakness may or may not be present, and the severity of the weakness is variable. Cramping and intermittent rhabdomyolysis are common features of these disorders. The baseline CK level can be normal in some disorders, and the EMG pattern may also be normal. The severity of the disease is a result of the specific effect of each individual mutation on enzyme function.[94]

Pompe disease, or GSD2, is an autosomal recessive disease caused by mutations in the gene *GAA*, leading to an enzymatic deficiency in acid maltase, and occurs in 1 in 9000 to 1 in 40,000 people, depending on heritage. The severity of illness can range from the infant presentation with a profound myopathy, ventilatory failure, and cardiomyopathy to a milder, adult-onset presentation with a mild myopathy. Phenotypes range between these two extremes. The CK level at baseline is usually elevated, and the diagnosis is confirmed by enzyme testing or genetic sequencing of the gene. Clinical acumen is critical because enzyme replacement with acid maltase can dramatically improve the muscle symptoms of this illness. GSD3, also known as Cori disease, affects 1 in 100,00 people. This rare autosomal recessive disease is due to mutations in the gene *AGL*, which encodes for the glycogen debrancher enzyme. The clinical phenotype is mutation dependent. When presenting in infancy, GSD3 causes fasting hypoglycemia, hepatomegaly, and failure to thrive. A cardiomyopathy can appear in childhood, and the onset of weakness may not occur until adolescence.

Affecting 1 in 100,000 to 1 in 167,000 people, McArdle disease, or GSD5, is an extremely rare autosomal recessive disease caused by mutations in *PYGM*, leading to myophosphorylase deficiency. Symptoms appear in childhood and include variable degrees of skeletal muscle weakness, cramping with exertion, and rhabdomyolysis. Patients with this can demonstrate a "second wind phenomenon" in which symptoms improve or disappear after a period of exercise.

Glycogen storage disease IX is caused by a deficiency in phosphorylase kinase. This enzyme has four different subunits encoded by four different genes, with muscle involvement occurring as a result of mutations in two different subunits.

Mutations in *PHKA1*, encoding subunit α, is a very rare X-linked disorder causing muscle phosphorylase kinase deficiency, and mutations in *PHKB* that encodes subunit β cause an autosomal recessive phosphorylase kinase deficiency that results in both muscle and liver disease. Patients with the muscle phenotype can present at any age with myopathic symptoms.

Glycogen storage disease VII, or Tarui disease, is caused by mutations in *PFKM* that encode for phosphofructokinase. As with the other glycogen storage diseases, the phenotype varies in age of onset and severity as functions of the specific mutations present. The infantile form is the most severe, with an encephalopathy, hepatopathy, and myopathy. The later-onset forms of the illness present with exercise intolerance, weakness, and at times rhabdomyolysis.

DIAGNOSTIC APPROACH. There are no specific blood or urine biomarkers for glycogen storage diseases. The CK level is variably elevated in the glycogen storage disorders involving muscle, but it can be normal. The CK level is usually chronically elevated in McArdle disease and Pompe disease. Urine oligosaccharides are nonspecifically elevated in these disorders as well but do not differentiate the specific diseases. Historically, the use of the ischemic forearm test, the nonischemic forearm test, EMG, muscle MRI, and muscle biopsy were common modalities used to lead clinicians toward the diagnosis of a glycogen storage disease. The specific diagnosis usually required enzymatic testing on liver obtained from an open liver biopsy. Current testing involves sequencing the suspected gene or genes. One approach to genetic testing is to order single-gene analysis, using clinical features to guide the choice of which gene to test. The other approach is to use a panel of genes that include some or all the known genes causing a myopathy. Enzymatic testing is now reserved for cases in which the genetic testing is not diagnostic or results are not clear.

THERAPEUTIC APPROACH. In general, dietary therapy is a mainstay of therapy. Patients with glycogen storage diseases should be managed in conjunction with a dietician, using disease-specific recommendations tailored to the patient's ability to follow those plans. Avoidance of fasting is critical, and patients should avoid meals high in simple carbohydrates, although patients with McArdle disease may feel better after a meal rich in simple carbohydrates. The use of high-protein diets with complex carbohydrates is recommended. Lifestyle modifications also include avoidance of strenuous exercise, although patients may benefit in terms of exercise tolerance from moderate amounts of physical activity. Many patients with these disorders do not have baseline weakness, but for those with chronic muscle weakness, standard approaches to screening and treating the manifestations of muscle weakness, nutrition, and respiratory insufficiency should be taken.

Pompe disease has a specific therapy referred to as enzyme replacement therapy, which involves IV infusion of alglucosidase alfa. Patients with Pompe disease should be monitored and treated for cardiomyopathy and cardiac conduction defects.

CONCLUSION

Although the individual disorders are rare, taken as a whole, the mitochondrial and other metabolic myopathies are not uncommon in neurologic practice, and

KEY POINTS

- Glycogen storage diseases result from deficiencies in the enzymes that build glycogen, as well as those that interfere with the degradation of glycogen and subsequent mobilization of glucose.
- The glycogen storage diseases that affect muscle present either with exercise intolerance and rhabdomyolysis, as seen with McArdle disease (GSD5) or Tarui disease (GSD7), or with myopathy without rhabdomyolysis, as in Pompe disease (GSD2) or debrancher defect (GSD3a).
- Enzyme replacement with acid maltase can dramatically improve the muscle symptoms of Pompe disease.
- Patients with McArdle disease can demonstrate a "second wind phenomenon" in which symptoms improve or disappear after a period of exercise.
- The creatine kinase level is usually chronically elevated in McArdle disease and Pompe disease.
- Dietary therapy is a mainstay of therapy for the glycogen storage diseases.
- Pompe disease has a specific therapy involving IV infusion of alglucosidase alfa.

with basic knowledge of the pathophysiology, organ system disease spectrum, and about a dozen well-described phenotypes (TABLE 11-4), the clinician can identify potential patients with mitochondrial myopathies and better decide which patients warrant an evaluation. Tremendous overlap exists in clinical features of all metabolic myopathies, including mitochondrial, lipid, and glycogen disorders, and by definition, these disorders involve muscle weakness, exercise intolerance, cramping, or intermittent rhabdomyolysis. Other organ systems may be involved, and the initial evaluation is directed to a specific organ system evaluation based on the presentation and biochemical laboratory testing of body fluids. With the advent of massive parallel-processing genetic testing and the bioinformatic data to support the application of this genetic technology, patients are now able to undergo testing that can result in a rapid and accurate diagnosis. Along the diagnostic journey, the clinician must be aware of other "look-alike" disorders that are not mitochondrial or metabolic in origin and avoid pitfalls that lead to overdiagnosis.[8,25]

As the field has advanced, several major changes in practice have occurred. For the mitochondrial disease, the importance of the well-described clinical features is critical to recognize, and the concept of the definition of a primary mitochondrial disease seems to be accepted. This has allowed clinicians to focus on this group of patients and will allow the field of secondary or environmental mitochondrial injury to evolve in parallel. A better understanding of the effects of secondary mitochondrial dysfunction is clearly needed because this knowledge will allow medicine to conquer diseases of aging, inflammation, injury, and environment.[6,10] Also, the reliance on muscle biopsy has waned for the evaluation of all of the metabolic myopathies. Although clinicians find muscle histology important as a diagnostic tool, and it certainly can be helpful in diagnosing some nonmetabolic disorders, genetic testing can often give a definitive answer without an invasive procedure and is less expense, although insurance coverage is sometimes difficult to obtain. Another practice evolution in the field of mitochondrial medicine has been the understanding that vitamins and supplements have limited evidence of efficacy, and although they are still recommended for patients, the number of supplements recommended has been curtailed in recent years. As pharmaceutical-sponsored clinical trials are underway in mitochondrial disorders, the importance of a better understanding of the goals of therapy has been highlighted, and the need for both clinically relevant patient-reported outcomes and clinically relevant objective end points of therapy has now become a focus of those conducting the trials. As with the mitochondrial myopathies, the use of the genetic laboratory for patients with lipid myopathies and glycogen storage diseases has streamlined the speed and accuracy of diagnosis. For all patients, lifestyle modification and dietary changes may provide great benefit to the patient.

USEFUL WEBSITES

GENE REVIEWS
This website contains updated and curated chapters authored by content-specific experts on more than 700 genetic disorders. Every chapter is written in a standardized format.
ncbi.nlm.nih.gov/books/NBK1116/

GENETICS HOME REFERENCE (NATIONAL INSTITUTES OF HEALTH, US LIBRARY OF CONGRESS)
This website provides updated and easy to understand diagnostic and treatment information for most identified genetic disorders.
ghr.nlm.nih.gov/

MITOACTION
MitoAction creates a community of support that fosters awareness and advocacy for patients affected by a mitochondrial disease.
mitoaction.org

MITOCHONDRIAL DISEASE SEQUENCE DATA RESOURCE CONSORTIUM
The Mitochondrial Disease Sequence Data Resource Consortium is a global effort of more than 100 mitochondrial disease experts who collect and share data for rare diseases and causative mutations. The website is free to use.
MSeqDR.org

MITOCHONDRIAL MEDICINE SOCIETY
The Mitochondrial Medicine Society represents an international group of physicians, researchers, and clinicians working toward advancing education, research, and global collaboration in clinical mitochondrial medicine.
mitosoc.org

UNITED MITOCHONDRIAL DISEASE FOUNDATION
The United Mitochondrial Disease Foundation promotes research and education for the diagnosis, treatment, and cure of mitochondrial disorders. The website provides information for patients, their families, and clinicians.
umdf.org

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