slightly elevated but may rise excessively after exercise. CSF protein is normal. The EMG is myopathic, and nerve conduction studies are usually normal. Ragged red fibers are prominently displayed in the muscle biopsy. Southern blots of muscle reveal a normal mtDNA band at 16.6 kb and several additional mtDNA deletion bands with genomes varying from 0.5 to 10 kb.

This autosomal dominant form of CPEO has been linked to loci on three chromosomes: 4q35, 10q24, and 15q22–26. In the chromosome 4q-related form of disease, mutations of the gene encoding the heart and skeletal muscle–specific isoform of the adenine nucleotide translocator 1 (*ANT1*) gene are found. This highly abundant mitochondrial protein forms a homodimeric inner mitochondrial channel through which adenosine diphosphate (ADP) enters and ATP leaves the mitochondrial matrix. In the chromosome 10q–related disorder, mutations of the gene *C10orf2* are found. Its gene product, *twinkle*, co-localizes with the mtDNA and is named for its punctate, starlike staining properties. The function of twinkle is presumed to be critical for lifetime maintenance of mitochondrial integrity. In the cases mapped to chromosome 15q, a mutation affects the gene encoding mtDNA polymerase (*POLG*), an enzyme important in mtDNA replication. Autosomal recessive PEO has also been described with mutations in the *POLG* gene. Point mutations have been identified within various mitochondrial tRNA (Leu, Ile, Asn, Trp) genes in families with maternal inheritance of PEO.

Exercise may improve function but will depend on the patient's ability to participate.

MITOCHONDRIAL DNA SKELETAL MUSCLE–CENTRAL NERVOUS SYSTEM SYNDROMES

Myoclonic Epilepsy with Ragged Red Fibers (MERRF) The onset of MERRF is variable, ranging from late childhood to middle adult life. Characteristic features include myoclonic epilepsy, cerebellar ataxia, and progressive muscle weakness. The seizure disorder is an integral part of the disease and may be the initial symptom. Cerebellar ataxia precedes or accompanies epilepsy. It is slowly progressive and generalized. The third major feature of the disease is muscle weakness in a limb-girdle distribution. Other more variable features include dementia, peripheral neuropathy, optic atrophy, hearing loss, and diabetes mellitus.

Serum CK levels are normal or slightly increased. The serum lactate may be elevated. EMG is myopathic, and in some patients nerve conduction studies show a neuropathy. The electroencephalogram is abnormal, corroborating clinical findings of epilepsy. Typical ragged red fibers are seen on muscle biopsy. MERRF is caused by maternally inherited point mutations of mitochondrial tRNA genes. The most common mutation found in 80% of MERRF patients is an A to G substitution at nucleotide 8344 of tRNA lysine (A8344G $tRNA^{lys}$). Other $tRNA^{lys}$ mutations include base-pair substitutions T8356C and G8363A. Only supportive treatment is possible, with special attention to epilepsy.

Mitochondrial Myopathy, Encephalopathy, Lactic Acidosis, and Strokelike Episodes (MELAS) MELAS is the most common mitochondrial encephalomyopathy. The term *strokelike* is appropriate because the cerebral lesions do not conform to a strictly vascular distribution. The onset in the majority of patients is before age 20. Seizures, usually partial motor or generalized, are common and may represent the first clearly recognizable sign of disease. The cerebral insults that resemble strokes cause hemiparesis, hemianopia, and cortical blindness. A presumptive stroke occurring before age 40 should place this mitochondrial encephalomyopathy high in the differential diagnosis. Associated conditions include hearing loss, diabetes mellitus, hypothalamic pituitary dysfunction causing growth hormone deficiency, hypothyroidism, and absence of secondary sexual characteristics. In its full expression, MELAS leads to dementia, a bedridden state, and a fatal outcome. Serum lactic acid is typically elevated. The CSF protein is also increased but is usually ≤1 g/L (100 mg/dL). Muscle biopsies show ragged red fibers. Neuroimaging demonstrates basal ganglia calcification in a high percentage of cases. Focal lesions that mimic infarction are present predominantly in the occipital and parietal lobes. Strict vascular territories are not respected, and cerebral angiography fails to demonstrate lesions of the major cerebral blood vessels.

MELAS is caused by maternally inherited point mutations of mitochondrial tRNA genes. Most of the tRNA mutations are lethal, accounting for the paucity of multigeneration families with this syndrome. The A3243G point mutation in $tRNA^{Leu(UUR)}$ is the most common, occurring in ~80% of MELAS cases. About 10% of MELAS patients have other mutations of the $tRNA^{Leu(UUR)}$ gene, including 3252G, 3256T, 3271C, and 3291C. Other tRNA gene mutations have also been reported in MELAS, including G583A $tRNA^{Phe}$, G1642A $tRNA^{Val}$, G4332A $tRNA^{Glu}$, and T8316C $tRNA^{Lys}$. Mutations have also been reported in mtDNA polypeptide-coding genes. Two mutations were found in the ND5 subunit of complex I of the respiratory chain. A missense mutation has been reported at mtDNA position 9957 in the gene for subunit III of cytochrome C oxidase. No specific treatment is available. Supportive treatment is essential for the strokelike episodes, seizures, and endocrinopathies.

PURE MYOPATHY SYNDROMES

Muscle weakness and fatigue can be the predominant manifestations of mtDNA mutations. When the condition affects exclusively muscle (pure myopathy), the disorder becomes difficult to recognize. Occasionally, mitochondrial myopathies can present with recurrent myoglobinuria without fixed weakness and thus resemble a glycogen storage disorder or CPT deficiency.

Mitochondrial DNA Depletion Syndromes Mitochondrial DNA depletion syndrome (MDS) is a heterogeneous group of disorders that are inherited in an autosomal recessive fashion and can present in infancy or adults. MDS can be caused by mutations in genes (*TK2*, *DGUOK*, *RRM2B*, *TYMP*, *SUCLA1*, and *SUCLA2*) that lead to depletion of pools of mitochondrial deoxyribonucleotide (dNTP) pools necessary for mtDNA replication The other major cause of MDS is a set of mutations in genes essential for mtDNA replication (e.g., *POLG1* and *C10orf2*). The clinical phenotypes associated with MDS vary. Patients may develop a severe encephalopathy (e.g., Leigh's syndrome), PEO, an isolated myopathy, myo-neuro-gastrointestinal-encephalopathy (MNGIE), and a sensory neuropathy with ataxia.

DISORDERS OF MUSCLE MEMBRANE EXCITABILITY

Muscle membrane excitability is affected in a group of disorders referred to as *channelopathies*. The heart may also be involved, resulting in life-threatening complications (Table 462e-10).

CALCIUM CHANNEL DISORDERS OF MUSCLE

Hypokalemic Periodic Paralysis (HypoKPP) Onset occurs at adolescence. Men are more often affected because of decreased penetrance in women. Episodic weakness with onset after age 25 is almost never due to periodic paralyses, with the exception of thyrotoxic periodic paralysis (see below). Attacks are often provoked by meals high in carbohydrates or sodium and may accompany rest following prolonged exercise. Weakness usually affects proximal limb muscles more than distal. Ocular and bulbar muscles are less likely to be affected. Respiratory muscles are usually spared, but when they are involved, the condition may prove fatal. Weakness may take as long as 24 h to resolve. Life-threatening cardiac arrhythmias related to hypokalemia may occur during attacks. As a late complication, patients commonly develop severe, disabling proximal lower extremity weakness.

Attacks of thyrotoxic periodic paralysis resemble those of primary HypoKPP. Despite a higher incidence of thyrotoxicosis in women, men, particularly those of Asian descent, are more likely to manifest this complication. Attacks abate with treatment of the underlying thyroid condition.

A low serum potassium level during an attack, excluding secondary causes, establishes the diagnosis. Interattack muscle biopsies show the presence of single or multiple centrally placed vacuoles or tubular aggregates. Provocative tests with glucose and insulin to establish a diagnosis are usually not necessary and are potentially hazardous.