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Mitochondrial disease clinical manifestations: An overview

Both pediatric and adult-onset mitochondrial disease can range from mild to severe and can involve more than one organ system.

ABSTRACT: Mitochondrial diseases are a heterogeneous group of disorders that can affect multiple organs with varying severity. Symptoms may be acute or chronic with intermittent decompensation. In childhood-onset disease, there is often a history of global developmental delay, while in adulthood the past history may be unremarkable prior to initial presentation. The unique character of mitochondrial genetics means family history patterns of inheritance may be both maternal and autosomal, making genetic counseling challenging. Tissue specificity and mitochondrial heteroplasmy may result in a spectrum of phenotypes even within a single family with the same molecular defect.

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Mitochondrial diseases are heterogeneous and multifaceted, and can present at any age. Clinical features may range from an acute life-threatening metabolic derangement to intermittent or episodic crises with partial recovery to a more gradual progressive neurodevelopmental decline or regression. Organ involvement may be isolated but often evolves into multisystem disease. Understanding the general characteristics of pediatric and adult-onset mitochondrial disease and some typical clinical manifestations can allow family physicians to better serve their patients.

General characteristics of pediatric and adult-onset disease

Childhood mitochondrial disease is typically more severe than adult-onset disease and includes progressive neurological, cardiac, and liver dysfunction. In pediatric mitochondrial disease, a broad spectrum of findings may be present, including lethargy, hypotonia, failure to thrive, seizures, cardiomyopathy, deafness, blindness, movement disorder, and lactic acidosis. The clinicians' index of suspicion must remain high when these symptoms are present. Referral to a tertiary

care centre for evaluation of a possible mitochondrial disease may originate from all levels of health care and include family practitioners, pediatricians, or subspecialists from medical genetics, neurology, cardiology, endocrinology, or infant and child development. A family history of illness may point toward maternally inherited mitochondrial disease, but the manifestation of the disease may vary tremendously among family members. Diagnosis is often challenging and several algorithms have been proposed specifically to characterize symptoms that may be more prominent in children.[1-5]

Adult-onset mitochondrial disease often presents in more subtle ways. The disease may manifest for the first time in adulthood or may be first recognized in adulthood after a history of symptoms dating back to childhood. Adult-onset mitochondrial disease is typically a progressive multisystem disorder. Even in patients presenting with symptoms mainly in one organ system (such as myopathy), there is often evidence of multisystem involvement upon physical examination and laboratory evaluation. Although adults with mitochondrial disease may present with findings that are characteristic of a typical syndrome, more commonly they do not. Mitochondrial disease should be considered when the characteristic clinical manifestations described below are present *and* these are accompanied by one or more of the following: (a) involvement of multiple organ systems and/or (b) unusual severity (i.e., early onset with progression over time) and/or (c) maternal inheritance pattern.

Table. Recognizable syndromes of mitochondrial dysfunction.

Syndrome and features	Genetics
Leigh syndrome Neonatal subacute encephalopathy with bilateral symmetric midbrain and basal ganglia necrosis on MRI	Autosomal recessive, mitochondrial DNA, X-linked
Pearson syndrome Sideroblastic anemia, pancytopenia, exocrine pancreatic insufficiency, and renal tubulopathy	Mitochondrial DNA
MERRF Myoclonic epilepsy with ragged-red fibres on muscle biopsy	Mitochondrial DNA
NARP Neurogenic weakness, ataxia, and retinitis pigmentosa	Mitochondrial DNA
MELAS Mitochondrial encephalopathy with lactic acidosis and stroke-like episodes	Mitochondrial DNA
Alpers syndrome Encephalopathy, seizures, and hepatic dysfunction	Autosomal recessive, autosomal dominant
MNGIE Mitochondrial neurogastronintestinal encephalopathy	Autosomal recessive
Kearns-Sayre syndrome External ophthalmoplegia, pigmentary retinopathy, elevated CSF protein, cerebellar ataxia, and cardiac conduction defects	Mitochondrial DNA; often sporadic
MIDD Maternally inherited diabetes and deafness	Mitochondrial DNA
SANDO Sensory ataxia, neuropathy, dysarthria, and ophthalmoplegia	Autosomal dominant

Clinical manifestations

Mitochondrial disease was first described in the context of patients presenting with recognizable constellations of clinical features that were subsequently shown to be related to genetic defects affecting mitochondrial function. A partial list of these syndromes appears in the accompanying **Table**.[6] It should be noted, however, that the majority of patients with mitochondrial disease do not present with these easily recognizable features and thus clinicians must have a high index of suspicion when considering the possibility of mitochondrial dysfunction in patients with nonsyndromic presentations, especially those that involve the following systems.

Central nervous system/ peripheral nervous system

Characteristic pediatric manifestations of mitochondrial disease include developmental delay or regression, seizures, and movement disorders.[7,8] Characteristic adult-onset manifestations include stroke or stroke-like episodes. Peripheral neuropathy, which may be symptomatic or only detected on physical examination or through nerve conduction studies, is also a frequent manifestation of mitochondrial diseases.

Visual system and auditory system

Sensorineural deafness (particularly when onset is early) is a common manifestation of mitochondrial disorders attributable to cochlear dysfunction in combination with dysfunction of cranial nerve VIII.[9,10] Because ocular muscles have the highest density of mitochondria per cell of any type of muscle and thus use a large amount of adenosine triphosphate (ATP), ophthalmological manifestations of mitochondrial disease are common. Common eye manifestations due to skeletal muscle involvement include

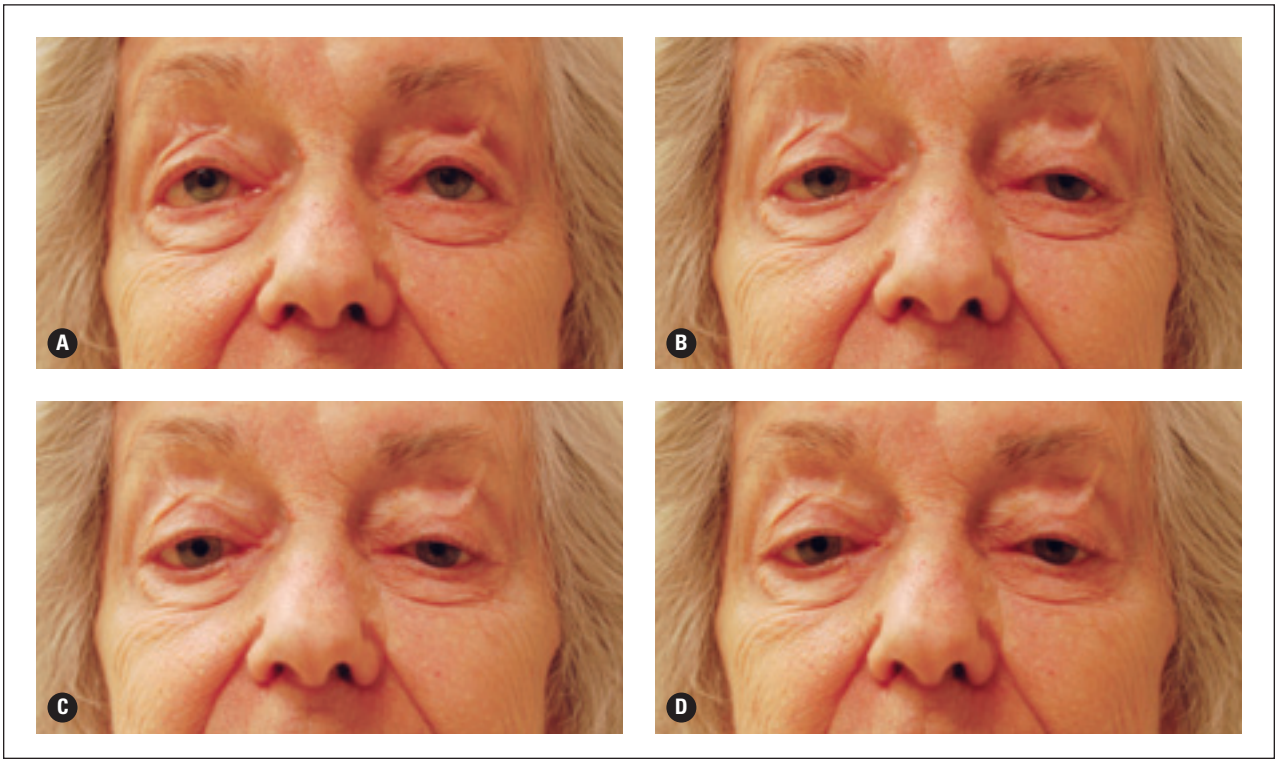

Figure. Chronic progressive external ophthalmoplegia (CPEO) and ptosis. The ptosis evident and the lack of eye movement demonstrated when the patient was asked to look up (A), to look left (B), to look right (C), and to look down (D) both indicate the presence of a mitochondrial disease.

progressive external ophthalmoplegia and ptosis as shown in the accompanying **Figure**. The retinal cells may be affected by pigmentary retinopathy. The nerve ganglion layer cells are specifically affected by certain mitochondrial diseases resulting in painless sequential loss of visual acuity followed by optic atrophy.

Neuromuscular system

Skeletal muscle manifestations are among the most common manifestations of mitochondrial disease.[11] Symptoms can range from relatively nonspecific exercise intolerance or exercise-induced myalgia to muscle wasting or weakness in a predominantly proximal distribution. All symptoms are exacerbated by inflammatory stress so patients may report prolonged recovery times after minor stresses such as illness or general anesthetic.

Cardiovascular system

Cardiac disease manifestations range from cardiac conduction block to predisposition to arrhythmia or development of Wolff-Parkinson-White syndrome.[12] More severe forms are associated with a metabolic cardiomyopathy, which can be hypertrophic or dilated.

Gastrointestinal system

Smooth muscle tissue, the autonomic nervous system, and the enteral neural plexus may all be affected, leading to gastrointestinal tract manifestations, namely those involving disorders of peristalsis.[13-16] Typical manifestations include delayed gastric emptying with nausea and vomiting, constipation, diarrhea, and intestinal pseudoobstruction. Fat malabsorption and poor growth due to exocrine pancreatic insufficiency can also occur.

Endocrine system

Endocrine disorders may present in childhood or may develop over time and present in adulthood.[17,18] Diabetes mellitus with a complex pathophysiology can occur. Even though mitochondrial dysfunction inhibits glucose-stimulated insulin secretion, most patients with diabetes related to mitochondrial disease present with a phenotype of type 2 diabetes.

Case examples

Cases from our pediatric and adult clinics demonstrate how some patients with mitochondrial disease present with nonspecific symptoms, while

others present with symptoms of recognizable syndromes.

Subacute necrotizing encephalopathy (Leigh syndrome)

Leigh syndrome is one of the most severe pediatric manifestations of mitochondrial disease.

Patient V-2 in Family A, the family described elsewhere in this theme issue (see pedigree in Figure 1 of "Primer on mitochondrial disease"), was born at term after an unremarkable pregnancy. The first concerns in patient V-2 were at 6 months of age, when she was seen to cross her eyes, especially when tired. She was hypotonic and had delayed developmental milestones. She sat at 8 months and didn't walk until 2 years. Her speech was delayed and dysarthric. Ptosis and ophthalmoplegia were observed at $2^1/_2$ years of age. Seizures began at $2^1/_2$ years with arm stiffness, then clusters of right-sided facial twitching and weakness, then staring spells, eye twitching, and myoclonic jerks. While ECG and echocardiogram results were normal, head MRI showed progressive areas of abnormal T2 hyperintensity in the caudate and lentiform nuclei, and the left frontal lobe. Magnetic resonance spectroscopy (MRS) showed intermittent abnormal lactate peaks in the midbrain. Eventually, the patient needed a gastrostomy tube for nutrition and had to use a wheelchair because of progressive weakness. Her condition continued to worsen until she died at 8 years of age.

Cardiomyopathy and conduction defects

Heart-related defects can be presenting features of mitochondrial disease in both adults and children.

A baby girl was born after an unremarkable prenatal history and birth. However, Apgar scores were low and she required ventilation at birth. She was found to have metabolic acidosis with an elevated lactate of 12 mmol/L (normal < 2.2), and was diagnosed as encephalopathic. Brain imaging showed delayed myelination but no cortical abnormalities. There was a persistent elevation of lactate peaks in the basal ganglia noted on MRS. Echocardiogram showed marked hypertrophy of all cardiac walls with reduced ejection fraction. On day 9 of life she remained encephalopathic with no spontaneous respiratory effort and died upon withdrawal of ventilator support. Heart biopsy showed marked complex IV (cytochrome *c* oxidase) deficiency inherited via an autosomal recessive genetic syndrome.[18]

Seizures

Seizures can be a presenting feature of mitochondrial disease in both adults and children. When present, seizures may be intractable and associated with a poor prognosis.

A 10-month-old child presented with focal status epilepticus in association with a viral infection and a normal brain MRI. His development had been previously normal but he subsequently displayed regression in both gross and fine motor skills with hypotonia. He had a subsequent episode of status epilepticus at 11 months of age in association with elevated liver enzymes. At 27 months of age he had failure to thrive and presented with abdominal distention, ascites, jaundice, low serum albumin, and elevated lactate. Brain MRI showed delayed myelination with normal MRS results. Liver biopsy revealed cirrhosis with no other findings specific for a distinct cause. Molecular testing identified an autosomal recessive disorder in a gene (POLG) associated with Alpers syndrome, a condition of progressive neurological deterioration, intractable seizures, and liver disease. This child continued to deteriorate with increasing seizure frequency despite anticonvulsants and died at 3 years of age.

Visual symptoms

Visual symptoms of mitochondrial disease can be related to problems with the optic nerve, retinal dysfunction, or eye movement.

A 34-year-old woman was investigated by an ophthamologist for mild ptosis and was found to have chronic progressive external ophthalmoplegia (CPEO). She reported a 20-year history of diplopia related to fatigue. She was referred to a neurologist who noted mild weakness in her deltoid, bicep, and neck flexor muscles. A muscle biopsy revealed a deletion in mitochondrial DNA, confirming the diagnosis of mitochondrial CPEO.

Stroke and stroke-like episodes

Stroke and stroke-like episodes (ischemic necrosis of brain tissue occuring in the absence of vascular occlusion) are a unique feature of mitochondrial disease.

A stable patient with longstanding sensorineural hearing loss and well-controlled type 2 diabetes presented acutely with bilateral strokes affecting the basal ganglia. There was a maternal inheritance pattern for the deafness and diabetes. The consulting geneticist recognized the association of maternally inherited diabetes, deafness, and stroke-like episodes as characteristic of the MELAS syndrome. Diagnostic tests confirmed the clinical impression. This gentleman had several typical features of stroke associated with mitochondrial disease:

- Relatively young age (mid-40s).
- Extraneurologic features of mitochondrial disease (diabetes, sensorineural hearing loss).
- No other cause of stroke identified (e.g., no source of cardiac emboli or

cerebral atherosclerosis).
- Presence of a stroke in a region of the brain that does not conform to regions of vascular distribution (bilateral basal ganglia infarction).

Exertional myalgia

Exertional myalgia is a common presenting symptom of mitochondrial disease, especially in adults.

A 40-year-old man presented with exertional myalgias dating back to the age of 14. He experienced fatigue with even minor activities such as walking up a flight of stairs, holding a clipboard, and filling a coffee pot with water. Clinical history revealed type 2 diabetes and progressive dysphagia. A muscle biopsy done at the time of a Heller esophagomyotomy for the dysphagia (caused by a hypertensive lower esophageal sphincter) revealed subsarcolemmal accumulation of mitochondria and cytochrome oxidase negative muscle fibres, confirming the diagnosis of mitochondrial myopathy.

Conclusions

Mitochondrial diseases can present at any age and with symptoms in any organ system, including the central nervous system, visual system, and neuromuscular system. Neurological manifestations include encephalopathy, cognitive regression, seizures, and peripheral neuropathy. Involvement of skeletal and cardiac muscle is frequent, while endocrine system manifestations commonly include diabetes mellitus.

Multisystem involvement is a clue to the diagnosis of possible mitochondrial disease in patients who present with nonspecific symptoms. Referral to a tertiary care centre should be considered when a family practitioner, pediatrician, or subspecialist suspects maternally inherited disease.

Competing interests

None declared.

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