



MITO 101 – General Neurology

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Key points

- Although most mitochondrial diseases are multisystemic, neurological dysfunction is often the most prominent clinical feature.
- Common neurological manifestations include: seizures, migraine-like headaches, dementia, movement disorders, loss of vision, sensorineural hearing loss, strokes in young people, peripheral neuropathy, and myopathy^{1,2}.
- Vision loss may be due to optic neuropathy, retinopathy, or cerebral lesions³.
- Among infants, Leigh syndrome is the most frequent mitochondrial disorder and is characterized by psychomotor regression and brain lesions affecting the basal ganglia and brainstem.
- Mitochondrial neurological syndromes that can be diagnosed clinically include: mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS); myoclonus epilepsy and ragged-red fibers (MERRF); neuropathy, ataxia, retinitis pigmentosa (NARP); Kearns-Sayre syndrome (KSS); Alpers syndrome; and mitochondrial neurogastrointestinal encephalomyopathy (MNGIE) (Table)^{4,5}.
- Although there are few treatments for mitochondrial diseases, symptomatic therapy (such as anti-convulsant drugs) is important^{6,7}.

Clinical investigation of the nervous system

- Patients with mitochondrial disease often report multiple neurological symptoms; therefore, clinical evaluation must be targeted to the affected anatomical structures.
- **Neurological examination** is essential to screen for cognitive dysfunction, ataxia and other movement disorders, cranial neuropathies, myopathy, and peripheral neuropathy.
- **Electroencephalograms** (EEGs) should be performed in patients with overt or suspected seizures (see Epilepsy section)⁸.
- **Brain magnetic resonance imaging (MRI)** typically reveals non-specific atrophy, but more mitochondrial disease-specific abnormalities include: subacute necrosis of the basal ganglia in Leigh syndrome; basal ganglia calcifications; atypical strokes in MELAS; and diffuse leukoencephalopathy in MNGIE or primary respiratory chain defects⁹⁻¹¹ (Figure). The stroke-like lesions of MELAS are typically detected as regions of increased T2 or FLAIR signal, which do not conform to large-vessel territories and can affect any region of the cerebral hemispheres (particularly the occipital cortex)¹². Acute stroke-like lesions have increased diffusion-weighted imaging (DWI) signal with *normal or increased* apparent diffusion coefficient (ADC), which contrasts with the increased DWI and *decreased* ADC signals typically observed in ischemic strokes¹³. In patients with cerebellar ataxia, brain **MRI** may show cerebellar atrophy¹⁴.
- **Brain magnetic resonance spectroscopy (MRS)** is useful to screen for abnormal elevations of lactic acid in the ventricular cerebrospinal fluid or brain parenchyma in patients with mitochondrial encephalopathies¹⁵. In some patients with mitochondrial diseases, lactate peaks may be normal (i.e. undetectable).
- **Ophthalmological examination** including visual acuity testing, and fundoscopy are important to screen for optic neuropathy and pigmentary retinopathy. **Visual field** testing can reveal field cuts due to cerebral lesions or central and centrocecal scotoma caused by optic neuropathy. (See Ophthalmology section).
- **Audiogram** and possibly other specialized hearing tests are important to assess sensorineural hearing loss (See Audiology).
- Dysphagia should be evaluated by **barium swallow studies** with video fluoroscopy.
- Limb myopathy can be assessed by **electromyography** (EMG), which reveals low amplitude short duration motor units and early recruitment.

- In patients with peripheral neuropathy, **nerve conduction studies and electromyography** (NCS/EMG) typically reveal signs of axonopathy, but, in patients with MNGIE, NCS typically shows demyelinating neuropathy.
- Blood tests should include: lactate and pyruvate levels (preferably arterial or venous sample drawn without a tourniquet) and serum creatine kinase (CK) when myopathy is suspected.
- In patients with one of the well-defined mitochondrial disease phenotypes and maternal inheritance (e.g. MELAS, MERRF, NARP, or LHON), **mtDNA mutation screening** in blood often reveals the causative mutation.
- For patients suspected of having a mitochondrial disease, but not conforming to a well-characterized syndrome, **muscle biopsy** for histology, respiratory chain enzyme biochemistry, and molecular genetic testing can be very informative. In addition, muscle biopsy is generally required to detect single deletions or multiple deletions of mtDNA or to diagnose the myopathic form of mtDNA depletion syndrome.

Clinical features of neurological dysfunction in mitochondrial diseases

- Common central nervous system manifestations include: seizures, dementia, strokes, movement disorders (particularly myoclonus), hearing or vision loss, and cerebellar ataxia.
- **Seizures** are frequent in mitochondrial diseases and are usually partial complex. Myoclonus epilepsy is a defining feature of MERRF, typically affecting limbs, and can interfere with normal voluntary activities.
- **Dementia** may be due to recurrent strokes in MELAS or progressive encephalopathy.
- **Movement disorders**, particularly myoclonus and ataxia, are common. **Myoclonus** typically affects limbs and occasionally interferes with normal voluntary movements. **Cerebellar ataxia** is a prominent feature of MERRF and coenzyme Q₁₀ deficiencies and is usually associated with prominent cerebellar atrophy on MRI. **Sensory ataxic neuropathy** occurs in patients with polymerase gamma mutations. (See Movement Disorders section)
- The clinical hallmark of MELAS, **stroke-like episodes** typically occur before age 40.
- **Vision loss** may be due to optic neuropathy, pigmentary retinopathy, or cerebral abnormalities (particularly stroke-like lesions in MELAS). Although impaired vision can be the only clinical manifestation in patients with Leber hereditary optic neuropathy (LHON) or autosomal dominant optic atrophy (DOA) due to *OPA1* mutations, it is commonly part of multisystemic mitochondrial disorders such as MELAS or Kearns Sayre syndrome. (See Ophthalmology section)
- **Sensorineural hearing loss** is common in mitochondrial disease and frequently part of a complex multisystemic disorder (syndromic deafness) or less commonly isolated (non-syndromic). (See Audiology section)
- **Myopathy** is common and can affect extraocular muscles causing ptosis and ophthalmoparesis, oropharyngeal muscle leading to dysarthria and dysphagia, respiratory muscle producing shortness of breath, or limb muscles manifesting as exercise intolerance or proximal limb weakness.

Management of neurological dysfunction in mitochondrial diseases

- **Symptomatic treatment** of neurological deficits is important in mitochondrial diseases.
- Seizures usually respond to conventional **anti-convulsant** therapies (See Epilepsy section). Valproic acid should be avoided particularly in patients with Alpers syndrome as the drug can precipitate fatal hepatopathy¹⁶. If prescribed, L-carnitine supplementation is recommended to minimize the risk of secondary carnitine deficiency.
- **Nutritional supplements** that are commonly recommended include: CoQ₁₀, L-carnitine, anti-oxidants (alpha lipoic acid, idebenone, vitamins C and E, and beta-carotene), and creatine

monohydrate⁶ (See Nutrition section). High-dose CoQ₁₀ is particularly important in patients with CoQ₁₀ deficiencies¹⁷.

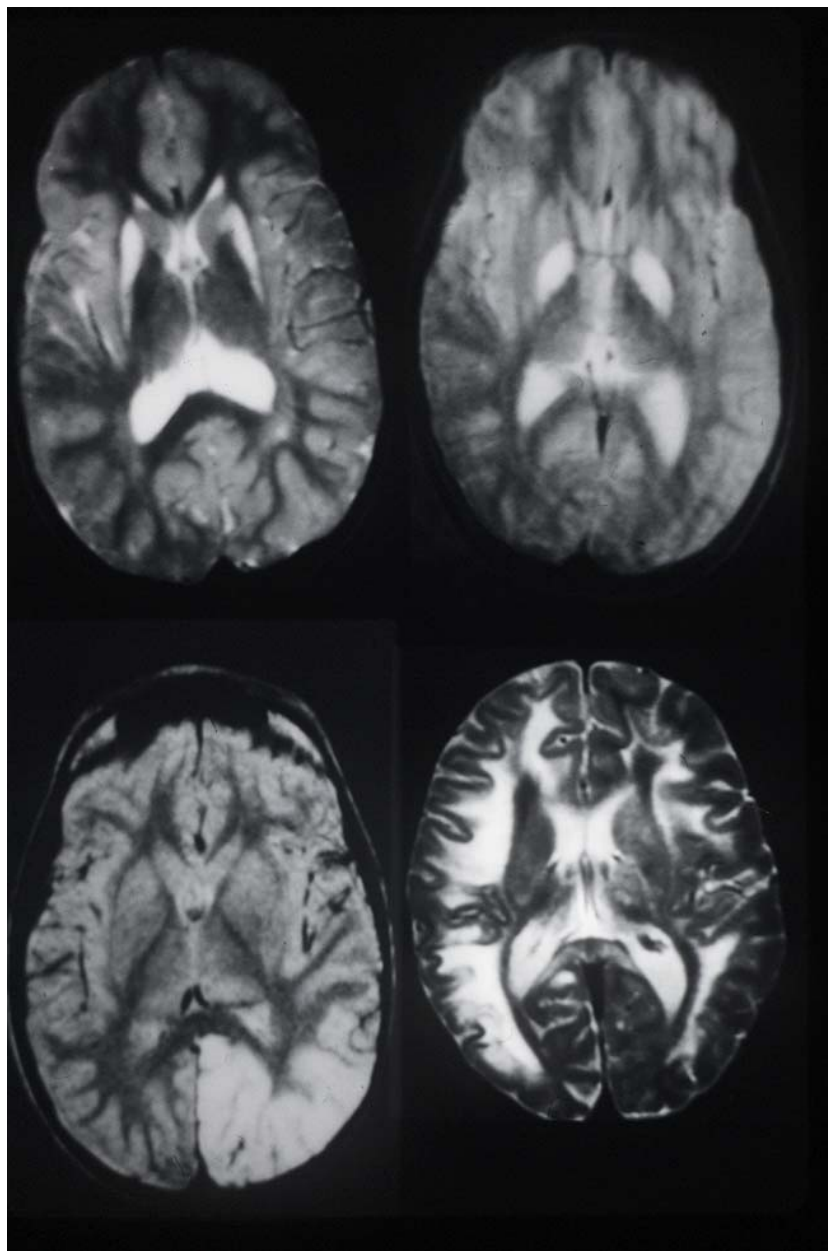
- **Aerobic exercise** reverses deconditioning in patients with mitochondrial myopathy and appears not to be harmful¹⁸.
- **Eyelid crutches or slings** are often helpful to patients with severe ptosis. (See Ophthalmology section)
- **Hearing aids** (binaural amplification or cochlear implants) can improve sensorineural hearing loss. (See Audiology section)

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Figure Legend:

Brain T2-weighted magnetic resonance imaging (MRI) scans of patients with LS (upper images), mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) (lower left image), and mitochondrial neurogastrointestinal encephalomyopathy (MNGIE) (lower right image). Brain MRIs of LS patients reveal increased T2-weighted signal in the putamen (upper left image) and in posterior lenticular nuclei (upper right image). MRI of a MELAS patient reveals an acute lesion in the left occipital lobe primarily affecting the cortex (lower left panel). MRI of a MNGIE patient demonstrates diffuse increased T2-signal in the white matter (lower right panel).



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Table 1. Neurological manifestations in mitochondrial disease.

Disorder	Principal clinical features	Molecular defect	Inheritance	Suggested Diagnostic tests
Leigh syndrome	Psychomotor regression +/-ptosis, ophthalmoparesis, retinopathy, seizures, ataxia, peripheral neuropathy, cardiomyopathy, hepatic failure	Nuclear or mtDNA	M or AR	Brain MRI; lactic acid in blood, CSF, or both; muscle biopsy; focused mutation screening based on respiratory chain enzyme defect(s)
Kearns Sayre syndrome (KSS)	Extraocular muscle weakness, pigmentary retinopathy, and onset before age 20, plus at least one of the following: cardiac conduction block, ataxia, CSF protein >100 mg/dl	mtDNA deletion	S	ECG; lactic acid in blood, CSF, or both; ophthalmological evaluation; audiogram; muscle biopsy
Chronic progressive external ophthalmoplegia (CPEO)	Extraocular muscle weakness (ptosis, ophthalmoparesis), +/- dysphagia, proximal limb weakness	mtDNA deletion or point mutation.	S or M	ECG; lactic acid in blood, CSF, or both; ophthalmological evaluation; audiogram; if sporadic, muscle biopsy; if maternally inherited, blood mtDNA mutation screen
Mitochondrial encephalomyopathy lactic acidosis and stroke-like episodes (MELAS)	Stroke-like episodes, seizures, dementia, +/- hearing loss, retinopathy, diabetes mellitus, cardiomyopathy, gastrointestinal dysmotility	mtDNA 3243A>G or other mtDNA mutation	M	Brain MRI; lactic acid in blood; audiogram; if maternally inherited, blood mtDNA mutation screen; cardiac evaluation
Myoclonus epilepsy, ragged-red fibers (MERRF)	Myoclonus, epilepsy, ataxia, myopathy, +/- encephalopathy, lipomas, peripheral neuropathy, optic atrophy, diabetes	mtDNA 8344A>G or other mtDNA mutation	M	Brain MRI; lactic acid in blood; audiometry; if maternally inherited, blood mtDNA mutation screen
Neuropathy, ataxia, retinitis pigmentosa (NARP)	Peripheral neuropathy, ataxia, retinitis pigmentosa	mtDNA 8993T>G or other mtDNA mutation	M	Brain MRI; lactic acid in blood; EMG/NCS; ophthalmological evaluation; blood mtDNA mutation screen
Leber hereditary optic neuropathy (LHON)	Subacute vision loss usually unilateral followed by loss of vision in the second eye weeks or months later. Peripapillary telangiectasia. Maternal inheritance, mainly affecting young men	mtDNA 11778G>A, 3460G>A, 14484T>C	M	Ophthalmological evaluation; ECG; blood mtDNA mutation screen
Aminoglycoside-associated deafness or non-syndromic hearing loss	Sensorineural hearing loss, maternal inheritance	mtDNA 1555A>G	M	Audiogram and other hearing tests; blood mtDNA mutation screen
Autosomal dominant PEO with multiple mtDNA deletions	Ptosis, ophthalmoparesis	<i>POLG1</i> , <i>PEO1</i> , <i>ANT1</i> , <i>POLG2</i>	AD	Ophthalmological evaluation; <i>POLG1</i> , <i>PEO1</i> , <i>ANT1</i> and <i>POLG2</i> gene sequencing
Autosomal recessive PEO with multiple mtDNA deletions	Ptosis, ophthalmoparesis	<i>POLG1</i>	AR	Ophthalmological evaluation; <i>POLG1</i> gene sequencing
Mitochondrial neurogastrointestinal encephalopathy (MNGIE)	Ptosis, ophthalmoparesis, peripheral neuropathy, gastrointestinal dysmotility, cachexia, leukoencephalopathy, +/- hearing loss	<i>TYMP</i>	AR	Ophthalmological and gastrointestinal evaluations; NCS/EMG; brain MRI; audiogram; plasma thymidine and deoxyuridine; buffy coat

				thymidine phosphorylase activity; <i>TYMP</i> gene sequencing
MtDNA depletion, myopathic form	Infantile or childhood-onset myopathy, lactic acidosis	<i>TK2</i>	AR	NCS/EMG; blood lactic acid; serum CK; muscle biopsy; EEG; <i>TK2</i> gene sequencing
MtDNA depletion, hepatic form or hepatocerebral form (including Alpers syndrome)	Infantile or childhood-onset hepatopathy and encephalopathy, lactic acidosis	<i>DGUOK, SUCLA2, MPV17, POLG1, SUCLG1</i>	AR	Blood lactic acid; hepatic enzyme panel; EEG; <i>DGUOK, SUCLA2, SULG1, POLG1</i> gene sequencing
Autosomal dominant optic atrophy or Autosomal dominant optic atrophy, hearing loss, and CPEO	Slowly progressive optic atrophy +/- sensorineural hearing loss, ptosis, and ophthalmoparesis	<i>OPA1</i>	AD	Ophthalmological evaluation; audiogram, <i>OPA1</i> gene sequencing
Mohr-Tranebjaerg syndrome	Dystonia, cortical blindness, paranoid delusions.	<i>TIMM8A</i>	XLR	Ophthalmological evaluation; audiogram; <i>TIMM8A</i> gene sequencing

Abbreviations: AD = autosomal dominant, AR = autosomal recessive, CPEO = chronic progressive external ophthalmoplegia, CSF = cerebrospinal fluid, ECG = electrocardiogram, EEG = electroencephalogram, M = maternal inheritance, XLR = X-linked recessive