

MITO 101 – Movement Disorders and Abnormal Tone

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Key points

- Abnormal movements and tone are common in mitochondrial diseases¹.
- Ataxia is especially frequent and can be caused by cerebellar dysfunction, proprioception loss, or both.
- Myoclonus is also a common feature of mitochondrial diseases and can be part of a myoclonus epilepsy syndrome².
- Parkinsonism has been noted in patients, particularly in association with *POLG* mutations^{3,4}.
- Tremors are not uncommon and often overlooked in mitochondrial disorders.
- Dystonia and chorea are occasionally seen.
- Abnormalities of tone include: spasticity due to corticospinal tract dysfunction; hypotonia associated with cerebellar ataxia or neuromuscular weakness; and rigidity due to parkinsonism.
- Management includes pharmacological therapy for myoclonus, Parkinsonism, and spasticity, while physical therapy and supportive devices may be helpful for ataxia.

Clinical investigation of movement disorders and tone

- **Neurological examination** is important to assess tone and to characterize the abnormal movements.
- **Electroencephalograms** (EEGs) should be performed in patients with overt or suspected seizures (see Epilepsy section). In patients with myoclonus epilepsy, EEGs may reveal epileptiform activity.
- **Brain magnetic resonance imaging (MRI)** typically reveals non-specific atrophy, but more mitochondrial-specific abnormalities include basal ganglia lesions (in Leigh syndrome) or calcification, and atypical strokes (MELAS). In patients with cerebellar ataxia, brain **MRI** may show cerebellar atrophy.
- **Somatosensory evoked potential (SSEP)** may show giant cortical responses in patients with myoclonus epilepsy⁵.
- Functional magnetic resonance imaging, positron emission tomography (PET) scans, and transcranial magnetic stimulation are currently used in research but may develop into clinical diagnostic tests to assess movement disorders and corticospinal tract functions.
- In patients with one of the well-defined mitochondrial disease phenotypes and maternal inheritance (e.g. MELAS, MERRF, or NARP), **mtDNA mutation screening** in blood often reveals the causative mutation. In patients with autosomal dominant or recessive parkinsonism associated with PEO or early menopause, screening blood DNA for *POLG* mutations may reveal pathogenic mutations^{3,4}.
- For patients with movement disorders suspected to be due to mitochondrial disease, but not conforming to a well-characterized syndrome, **muscle biopsy** for histological, 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 movement disorders and altered tone in mitochondrial diseases

- Movement disorders and abnormal tone are often part of multisystem mitochondrial disorders.
- **Ataxia**, due to cerebellar dysfunction, proprioception loss, or both, is one of the defining clinical features of several mitochondrial disorders including: myoclonus epilepsy with ragged-red fibers (MERRF); neuropathy, ataxia, and retinitis pigmentosa (NARP), sensory ataxic neuropathy, dysarthria, ophthalmoplegia (SANDO), and mitochondrial autosomal recessive ataxia syndrome (MIRAS)⁶⁻¹⁰. Cerebellar ataxia with prominent cerebellar atrophy on brain MRI is the most common clinical presentation of coenzyme Q₁₀ (CoQ₁₀) deficiency¹¹. In addition, ataxia is common in Kearns-Sayre syndrome (KSS).
- **Myoclonus** is a defining feature of MERRF, but is also common in MELAS and other mitochondrial disorders^{1,12}. The myoclonus frequently affects limbs and can interfere with normal physical activities.
- **Parkinsonism** is often, but not invariably, associated with progressive external ophthalmoplegia (PEO) in patients with *POLG* mutations^{3,4}.
- **Tremors** are probably under-recognized in mitochondrial disorders and include: intention tremors due to cerebellar ataxia and resting tremor as a manifestation of parkinsonism^{3,4}.
- **Dystonia** and **chorea** are not very common in mitochondrial disorders but are sometimes present in patients with Leigh syndrome or MELAS¹³.
- **Increased tone** due to **spasticity** is often the result of stroke-like episodes in MELAS or corticospinal tract lesions in other mitochondrial diseases. **Rigidity** in patients with parkinsonism can be severe.

Management of movement disorders and abnormal tone in mitochondrial diseases

- **Symptomatic treatment** of movement disorders is important in mitochondrial diseases.
- **Myoclonus** typically improves with benzodiazepines such as clonazepam. Myoclonic epilepsy usually responds 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 hepatopathy. If prescribed, L-carnitine supplementation is recommended to minimize the risk of secondary carnitine deficiency.
- Patients with **ataxia** sometimes benefit from physical therapy and use of assistive devices (such as canes and walkers). Canes with four-prong bases provide greater stability to patients with ataxia than standard canes.
- In patients with cerebellar ataxia associated with **CoQ₁₀ deficiency**, high-dose **CoQ₁₀ supplementation** often leads to stabilization or mild improvement of the ataxia. CoQ₁₀ doses up to 30mg/kg/day in children and up to 3000 mg/day in adults are commonly used.
- Severe **spasticity** may be treated with baclofen or tizanidine.
- For mitochondrial patients with **parkinsonism**, L-dopa with carbidopa is usually effective^{3,4}.

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