**Movement Disorders**

Volitional control of movement in humans remains incompletely understood. A complex series of neural processes are required to accomplish movement. Multiple brain regions are required for even the simplest movements, prefrontal cortex for motor planning; cerebellum for integration of movement; basal ganglia for fine control; visual system for localization; vestibular system for orientation; gross and fine motor regions for movement of body. Each of these regions requires proper network connections for continued “feedback” to ensure the efficacy of the movement.

Involuntary movements are by definition, movements that a healthy person cannot stop at the person’s own or an observer’s command. We usually think of involuntary movements are patterns of muscle contractions caused by lesions (structural or biochemical) in the circuitry of the basal motor nuclei, reticular formation, and cerebellum. These can be thought of in several broad categories: hyperkinetic/dyskinetic movements (chorea, athetosis, myoclonus, dystonia and ballism), benign movements (stereotypies, tics), cerebellar movements (tremor, dysmetria and ataxia) and hypokinetic movements (parkinsonian phenotypes) (Garcia-Cazorla and Duarte, 2014).

Insult to a variety of neuronal circuits can lead to any of these including the basal ganglia, cerebellum or cortex. Patients with primary mitochondrial disease are vulnerable to injury in any of these regions. Patients with Leigh syndrome with injury to the basal ganglia and cerebellar tracts, often have a mixed movement disorder that includes hyper- and hypo-kinetic and cerebellar types of movements. A recent review of a cohort of patients with mitochondrial disease identified extrapyramidal movements in 92% of patients, primarily in the context of Leigh syndrome. (Martikainen 2016) Ataxia, due to cerebellar dysfunction, proprioception loss, or both, and myoclonus are defining clinical features of many mitochondrial disorders including MERRF, NARP, SANDO, MIRAS, Kearns-Sayre syndrome and infantile onset spinocerebellar ataxia (IOSCA) (Fadic et al 1997, Tranchant 2016) Cerebellar ataxia with prominent cerebellar atrophy on brain MRI is the most common clinical presentation of Coenzyme Q10 deficiency. (Qunzi 2010). In a recent review, the movement disorders of myoclonus, ataxia and gait disturbance have been reported in 25 – 90% of MELAS patients (El-Hattab et al., 2015). In a large cohort of patients with cerebellar atrophy (n=300), mitochondrial diseases were routinely identified. The m.3243A>G mutation was sometimes found (n= 9) (Al-Maawall et al., 2012). Cerebellar atrophy was noted before the age of 1 year in 2 patients and 7 years in the other patients. All of the patients had their stroke-like events after the finding of cerebellar atrophy on MRI. In three other patients there was a large mtDNA deletion and clinical findings consistent with Kearns-Sayre syndrome. One patient had a mutation in m.8993T>C and findings of neuropathy, ataxia, and retinitis pigmentosa and 2 patients had homozygous mutations in the m. 11778G>A, giving rise to Leber hereditary optic neuropathy. Three other patients had mutation in the *POLG1* gene. Boddaert et al. found that out of 95 patients with cerebellar atrophy, 23 had defects in one or more aspects of the electron transport chain (Boddaert et al. 2010).

Parkinsonism in mitochondrial disease has also been described. mtDNA deletions have also been found in the substantia nigra pars compacta of *POLG* patients without Parkinsonism symptoms (Reeve et al., 2008). A recent review of a cohort of patients with mitochondrial disease showed the presence of Parkinsonism in 43% of whom 38% harbored mutations in *POLG*. (Martikainen,2016) In 2013, patients with *POLG* and *C10orf2* (Twinkle) mutations demonstrated a loss of dopaminergic neurons in the substantia nigra (Palin et al., 2013). In a study of other *POLG* patients, Tzoulis et al. demonstrated extensive nigrostriatal degeneration, but their patients had no Parkinsonian symptoms (Tzoulis, et al., 2013).

Acquired or secondary cause of movement disorders may also need to be considered in mitochondrial patients with a sudden onset of a new movement disorder. In this situation, movements are acquired from insults such as traumatic brain injury, hypoxic ischemic injury, infectious and autoimmune processes. A good history may help with identification of these processes. In the proper context, these conditions should be evaluated for as treatment will vary and the movement disorder may be reversible.

Treatment

The treatment of movement disorders in mitochondrial patients is similar to those with movement disorders from other causes. Symptomatic treatment of movement disorders is not complete and the goal is to only improve/decrease the symptoms. Decreasing the severity of the movement can improve quality of life. Therapy may assist in maintaining function and balance.

Recommendations

1. Patients with mitochondrial disease are at-risk for a variety of types of movement disorders Score 4.82

2. Sudden onset of a new movement disorder in mitochondrial patients should lead to an evaluation of disease worsening and potential treatable secondary causes of the symptoms Score 4.79

3. Patients with POLG mutations or mtDNA depletion syndromes are at-risk for Parkinsonism Score 4.21

4. Treatment of the movement disorder can improve quality of life Score 4.62

5. Management of movement disorders in mitochondrial disease is similar to that in patients with movement disorders of other causes though valproic acid should be avoided as a treatment Score 4.56

6. Physical therapy for balance, mobility and safety assessments should be considered. Score 4.71

7. One could consider assaying CSF NT and 5MTHF levels with worsening or new onset dystonia, hypertonia or dyskinesias Score 4.03

8. Deep brain stimulation should be considered when appropriate for treatment of mitochondrial movement disorders and dystonia – taking into account long term prognosis and level of morbidity. Score 4.15

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**Tone in Mitochondrial Diseases**

Tone in the neurological sense refers to the freedom of movement of a patient’s limb when flexed and extended by an examiner. Tone can be normal, increased or decreased. A reduction in tone is termed hypotonia and reflects a reduction in passive resistance of a limb or body part sometimes referred to in children as “floppiness”. Hypotonia is generally seen in children with mitochondrial cytopathies that affect peripheral nerve or muscle but can also be seen as a manifestation of a central nervous system disorder referred to sometimes as central hypotonia. A child with central hypotonia can progress to an increase in tone over time as cortico-spinal tract involvement develops. Assuming no joint restrictions, an increase in tone is reflective of a central neurologic issue.

Increased tone is divided into spasticity, rigidity and paratonia. Spasticity is a velocity dependent increase in tone, whilst rigidity is a velocity independent increase in tone. Paratonia is divided into Mitgehen and Gegenhalten with Mitgehen referring to the fact that the patient is assisting or following the examiner during the passive movement of the arm in the same direction whereas Gegenhalten is the opposite; namely, the patient is resisting the passive movement of the limb by the examiner. It is sometimes stated that if the examiner tells the patient to relax more than three times paratonia is likely present. Spasticity occurs with damage to the corticospinal tracts, rigidity occurs with basal ganglia lesions and paratonia is observed in bihemispheric disease, often in frontal white matter disorders.

Paratonia can be seen in patients with multiple strokes affecting both hemispheres and is most commonly seen in MELAS syndrome following multiple strokes. This may rarely be seen in other bihemispheric disorders such as progressive leukodystrophic change seen in Leigh’s disease. Unfortunately, there are no therapies that work for the treatment of paratonia and this will not be further considered in the monograph.

Spasticity is a final common pathway in diseases affecting the corticospinal tract and as a result there are a large number of mitochondrial diseases that can have spasticity as a defining clinical component of the neurological phenotype including common disorders such as Leigh disease (Laugel *et al.*, 2007; Cameron *et al.*, 2015), MELAS and MERRF syndrome (Finsterer, 2009), and other less common disorders (Binder *et al.*, 2003; Bienfait *et al.*, 2007; Scheper *et al.*, 2007; Pierson *et al.*, 2011; Dallabona *et al.*, 2014; Wortmann *et al.*, 2015; Koch *et al.*, 2016). In addition, spasticity can be the defining characteristic of the disease as is the case with the hereditary spastic paraparesis type 7 (HSP/SPG7) due to mutations in the mitochondrial gene paraplegin (van Gassen *et al.*, 2012; Pfeffer *et al.*, 2014). Other mitochondrial genes resulting in HSP include; *HSPD1* (SPG13/hsp60) (Fink, 2013), *c12orf65* (SPG55) (Antonicka *et al.*, 2010), and *DDHD2* (Gonzalez *et al.*, 2013).

ASSESSMENT OF SPASTICITY:

Spasticity is assessed with the muscle stretch reflexes and passive movement of the arm by the investigator. Increased muscle stretch reflexes are a characteristic of spasticity (3 = reflex spread to a joint above or below the one tested; 4 = clonus > 5 beats). Spasticity is also asses with a rapid passive movement of a limb and a “catch” is noted, usually in pronation/supination or knee flexion. Other aspects of the examination that accompany spasticity and reflect corticospinal tract involvement include the Babinski response (extension of the great toe and spread of the toes) due to scratching of the plantar lateral aspect of the foot with the reflex hammer or the same response to scratching the lateral aspect of the foot (Oppenheimer sign) or the Hoffman sign showing finger flexion in response to rapid “flicking” of the distal phalanx. Finally, spasticity if also reflected in the gait with a “bouncing” characteristic and “scissoring”. It is important to note that over time the spastic limb may become more fixed due to contractures and/or the development of rigidity as reflected in more severe grades of the qualitative modified Ashworth scale.

TYPES OF SPASTICITY:

1. Hemispasticity:

Spasticity in one arm and leg is usually reflective of a unilateral hemispheric disease which would be most commonly seen in MELAS syndrome. In the acute phases of stroke there is a loss of function in the limbs appear hypotonic but as the corticospinal tract involvement evolves, spasticity becomes a predominant feature with the often recognized on the neurological examination as described above. The differential diagnosis of unilateral spasticity would be quite broad including ischemic or hemorrhagic stroke, tumors of the brain or spinal cord, a potentially autoimmune disease (myelitis or multiple sclerosis).

1. Paraparetic spasticity:

The classic example of spasticity exclusively in the legs would be hereditary spastic paraparesis type 7 (SPG7, paraplegin mutations). The genetic cause of spastic paraparesis will have one of the many dozens of forms of autosomal recessive, X-linked recessive or autosomal dominant HSPs. This can also be seen in spinal cord injury, spinal cord tumors, spinal cord infarct and vitamin deficiencies such as vitamin B12, autoimmune disorders such as transverse myelitis, and infectious etiologies such as HTLV1.

1. Quadriparetic spasticity:

Spasticity of all four limbs is usually a manifestation of a progressive neurodegenerative disorder such as can be seen in Leigh disease, COXPD mutations and amino acyl tRNA synthetase mutations (AARS2, LARS2, HARS2, etc).

TREATMENT OF SPASTICITY:

Baclofen is a mainstay of therapy for spasticity though it’s effect on inhibiting post-synaptic spinal cord excitatory reflexes. It is generally well tolerated if initiated in low dose (5 – 10 mg) qhs and slowly titrated to effect in a tid dosing schedule with a maximal daily dose in adults of 90 mg. It is very important to slowly taper off the medication if it is not working to avoid withdrawal seizures. Severe paraparetic spasticity that does not respond to other therapies may be considered for intra-thecal baclofen pump therapy. Benzodiazepine medications such as diazepam may also be helpful for spasticity and could be considered as an early selection in patients with co-existing epilepsy due to their anti-seizure effects. Dantrolene may attenuate spasticity by reducing calcium release from the sarcoplasmic reticulum and thereby lowering the force of skeletal muscle contractions; however, generalized muscle weakness and somnolence limits the acceptance of this for treatment in patients, especially with pre-existent weakness from mitochondrial myopathy. Tizanidine is a centrally acting adrenergic agonist that may also help with spasticity. Specific experience with Tizanidine in mitochondrial disease patients has not been reported, nor have we used it for such patients. The main side effect is drowsiness that can be attenuated by a very slow titration of the dose to a maximum of 36 mg in a tid dosing schedule.

Botulinum toxin weakens skeletal muscle by inhibiting the SNAP-25/SNARE complex and thereby preventing acetylcholine quanta from being released and this leads to reversible neuromuscular junction blockade that can persist for several months. It is best used if there is a very specific muscle or muscle group that is contributing to symptomatic spasticity for widespread use can lead to off-target generalized muscle weakness. One particularly common scenario for use is severe plantar flexion spasticity that eventually leads to a rigid contracture where the botulinum toxin is injected into the gastrocnemius-soleus muscles and an ankle-foot orthosis is used to maintain the joint angle. We have used the latter approach in dozens of children with various types of mitochondrial disease and spasticity-dystonia with plantar flexion contractures and saw no significant side effects. However, caution must be used when treating muscles in the head and neck for off-target effects can be serious in patients with mitochondrial disease including aspiration from weakness induced dysphagia (Gioltzoglou *et al.*, 2005). Furthermore, we would recommend that the lowest dose within the therapeutic range be used the first time in a patient with mitochondrial disease.

RIGIDITY:

The assessment of rigidity is revealed with the tone assessment as described above but instead of a velocity dependent “catch” there is resistance to passive flexion flexion-extension of the limb that is velocity independent (the same low and high speeds) and occurs usually throughout the range of motion of the joint. Rigidity may co-exist with other basal ganglia Parkinsonian movement disorders such as tremor and this is clinically manifest as a “cog-wheeling”. In addition to the formal tone assessment, rigidity in the facial muscles can lead to a mask like expression seen on cranial nerve exam and in the limbs to decreased arm swing and “stiff” gait during ambulation and in the trunk with a stooped posture and turning that appears as though the entire body is rigid (“en block” turning). This is typically seen in idiopathic Parkinson’s disease and is sometimes referred to as the Parkinsonian gait.

Rigidity and other Parkinsonian features have been most often reported in Leigh disease , bilateral striatal necrosis and adult-onset *POLG1* associated disorders such as SANDO (Davidzon *et al.*, 2006; Hudson & Chinnery, 2006; Luoma *et al.*, 2007; Martikainen *et al.*, 2016). The dystonia seen in some mitochondrial disorders such as m.11778G>A and m.14459G>A can progress to full rigidity/Parkinsonism (Nikoskelainen *et al.*, 1995; Tarnopolsky *et al.*, 2004).

TREATMENT OF RIGIDITY:

The mainstay of drug treatment for rigidity/Parkinsonism is the use of carbiDOPA/L-DOPA and this has been used in *POLG1* associated SANDO with good long-term clinical success (Miguel *et al.*, 2014). Dopamine agonists are routinely used in classical Parkinson disease but we could find not report of their success in primary mitochondrial disease. Physical therapy with stretching and positional bracing may be of benefit especially for plantar flexion rigidity. The latter may be considered in combination with botulinum toxin injections with the caveats stated above. For severe rigidity, one may consider deep brain stimulation given some case reports of efficacy in primary mitochondrial disease (Aniello *et al.*, 2008; Pelzer *et al.*, 2012).

**Reader Comments:**

I'm not sure I agree that increased muscle stretch reflexes are a characteristic of spasticity, although the two are often found in close company. The genetic cause of spastic paraparesis is not always one of the HSPs. Baclofen does not just inhibit spinal cord-mediated spasticity; it can be given via intraventricular pump in children as well. Trihexyphyenidyl deserves mention as a first or second line anti-spasticity agent. The discussion concerning Parkinson disease should perhaps be tailored to focus on parkinsonism associated with mito diseases

The article would be improved by referencing AAN guidelines and including information in discussion. I think that comments by authors should be aligned with association guidelines. When authors have a different perspective, it needs to be carefully explained.

*Excerpt from AAN recommendations: (2013)*

For localized/segmental spasticity that warrants treatment, botulinum toxin type A should be offered as an effective and generally safe treatment (Level A). There are insufficient data to support or refute the use of phenol, alcohol, or botulinum toxin type B (Level U). For generalized spasticity that warrants treatment, diazepam should be considered for short-term treatment, with caution regarding toxicity (Level B), and tizanidine may be considered (Level C). There are insufficient data to support or refute use of dantrolene, oral baclofen, or continuous intrathecal baclofen (Level U).

RECOMMENDATIONS:

* Alterations in tone are commonly seen in mitochondrial disease with patients having any combination of hypotonia, hypertonia, rigidity and spasticity Score 4.71
* Alterations in tone can be a clinical feature in many mitochondrial disorders and should be assessed regularly (yearly or with acute clinical change) by neurological examination. Score 4.82
* New onset and rapidly progressive alterations in tone in a patient with mitochondrial disease should prompt an evaluation (including neuroimaging) for acute disease progression and secondary causes including; neuropathy, spinal cord disease, stroke, CNS tumor, multiple sclerosis, and vitamin B12 deficiency. Score 4.79
* Physiotherapy and Physiatry assessments are recommended to maximize mobility, prevent contractures and alleviate discomfort and pain. Score 4.79
* Management of abnormal tone in mitochondrial disease is similar to that in patients without mitochondrial disease. Medical, procedural (Botox) and surgical treatments should all be considered. Score 4.56
  + Caution should be used with medications that alter tone as they can selectively worsen cognitive status, decrease muscle strength and secondarily respiratory effort and impact gastrointestinal motility and urinary function Score 4.85
* The first line medication for rigidity would be carbiDOPA/L-DOPA with dopamine agonists being a second line therapy. Botulinum toxin could be considered in cases where the rigidity is severe and focal (plantar flexors, or arm flexors). Deep brain stimulation may be considered in cases of severe rigidity at centers with extensive experience with the procedure Score 4.24

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**Dystonia**

Mitochondrial disorders can present at any age, manifest as multisystem diseases, frequently with CNS involvement. Several types of movement disorders have been described in mitochondrial diseases and mostly reported as single cases and small case series.

Dystonia is a recognized component of several mitochondrial disease phenotypes and mostly in association with: Leigh syndrome, Leber hereditary optic neuropathy, various mtDNA mutations, complex I, II and IV deficiency.

Data on the frequency of dystonia in patients with mitochondrial disorders is scarce. Macaya et al., 1992 reported on 34 patients with Leigh syndrome in whom dystonia was the most frequent movement disorder (86%). Of these, 44% presented with multifocal dystonia, while 33% presented with generalized dystonia. In 33% of the patients’ dystonia progressed to being generalized within average time of 23±6 months.

Martikainen et al., 2016, report on an observational cohort study in 678 patients with mitochondrial disorders that were followed between 2000 and 2015. Of these, 42 patients (12 pediatric, 30 adult) manifested one or more extrapyramidal movement disorders. Dystonia was the most common extrapyramidal movements disorder among pediatric patients (92%) and the second most common in adult patients (37%). Of the 12 pediatric patients, 9 (75%) had a phenotype compatible with Leigh syndrome. Most adult patients with dystonia manifested generalized or multifocal dystonia (40%) while 20% presented with focal dystonia including one patient with vocal cord dystonia.

Dystonia can be part of the clinical phenotype or less frequently can be the dominant presenting feature in patients with mitochondrial disorders. Sudarsky L. et al, 1999 reported a patient with 3243 mutation presenting with focal dystonia that further on progressed to facial and lower limb dystonia. McFarland et al., 2007 reported on patients with homoplasmic mutations in mitochondrial tRNA (*MTT*) gene presenting with dystonia as primary feature. Isolated dystonia has been reported in patients with Leigh’s disease and dystonia often precedes optic atrophy in patients with Leber hereditary optic neuropathy, or it may be the sole feature, even in families with optic-only or mixed presentations. Dystonia as part of the clinical phenotype has been reported in patients with mutations in POLG (Hinnell et al., 2012).

The age of dystonia presentation in patients with mitochondrial disease can vary from early childhood age to adult age.

In patients with mitochondrial disorder presenting with new onset of dystonic movement disorder, secondary causes of dystonia such as; medications, infection, exposure to toxins, vascular, neoplastic, traumatic etiology should be excluded. Pseudo dystonia (tics, head tilt due to vestibulopathy, soft tissue mass, Dupytren’s contracture, Sandifer syndrome, orthopedic and rheumatologic causes, spasms due to hypocalcaemia, hypomagnesaemia, alkalosis) should be excluded as well.

In MD patients presenting with new onset of dystonic movement disorders neuroimaging, baseline electrophysiological testing and laboratory testing are recommended.

Treatment of dystonia in patients with mitochondrial disorders includes medications and physiotherapy. Several oral medications (L-dopa, baclofen, trihexyphenidyl) and injections of Bolutinum toxin have been used in the treatment of dystonia. Recent reports on the use of Botulinum toxin in patients with mitochondrial disorders raise concerns due to side effects. Marked bilateral ptosis, facial muscles weakness, impairment of speech and chewing, and local swelling are reported in patients treated with Botulinum toxin A for blepharospasm. Gioltzoglou et al. 2005, report on two children treated with Botulinum for sialorrhoea who developed significant dysphagia, aspiration pneumonia, leading to gastrostomy tube placement in one of the patients.

Physiotherapy assessment and support is recommended for patients with mitochondrial disorders who develop dystonia. This can include specially adapted seats for infants, walking aids and advice on appropriate exercise in children and adults. Functional assessment in the patient’s home would be of benefit as it can identify areas of difficulty and plan for future support.

Although the clinical outcome of deep brain stimulation has been the greatest in primary dystonia, new reports point to benefits in patients with secondary dystonia.

**Recommendations**

* Dystonia can be a part of the clinical phenotype or presenting feature in mitochondrial disorders. Patients with mitochondrial diseases should have regular neurologic assessment for early identification of dystonia, especially in Leigh syndrome. Score 4.82
* In patients with mitochondrial disorders presenting with new onset of dystonic movement, neuroimaging, electrophysiological testing and baseline laboratory investigations are recommended. Score 4.38
* Secondary causes of dystonia and pseudo dystonia should be excluded in mitochondrial disorder patients that present with new onset of dystonic movement disorder. Score 4.61
* Patients who develop dystonia should have regular follow in view of the progressive course of the disease. Score 4.76
* Physiotherapy assessment and support is recommended for patients with mitochondrial disorders who develop dystonia. Score 4.76
* The treatment of dystonia with oral medications in mitochondrial disease is similar to that in patients with other types of dystonia. Score 4.72
* Botulinum toxin in patients with mitochondrial disorders should be used with caution in view of reported side effects. Score 4.21

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