**Epilepsy**

The prevalence of epilepsy in mitochondrial disease is not accurately known. Seizures have been reported to occur in 35% – 60% of infants, children and adolescents with biochemically confirmed disease (Debray et al., 2007; Khurana et al. 2008; Lee et al. 2011). The prevalence in adults with mitochondrial disease is more obscure with few large population studies describing seizures. However, in mixed aged studies, the development of seizures in adult patients appears to be less than in the younger populations. In one study, in 54 adult patients with *polymerase gamma 1* (*POLG*) mutations, epilepsy started early in the course of disease (13/54) but only a single patient developed seizures after 28 years of age (Tchikviladze et al. 2015). In another study, of 60 patients with seizures and mitochondrial disease, only 17 had seizures were older than 18 years of age (Chevallier et al. 2014).

Recent reviews of the topic include one by Rahman (Rahman, Developmental & Child Neurology, 2012) and Steele & Chinnery (Seiminars in Neurology2015).

In the Seattle pediatric aged cohort, there were 81/178 patients with defined mitochondrial disease with epilepsy (Saneto, unpublished data). Onset of epilepsy varied by age: onset before 1 year of age was 49%; onset between 1 – 5 years was 33%; and onset greater than 5 years was 18%. In a published cohort of 56 patients, the peak onset of seizures in patient with mitochondrial disease was 1 year of age (El Sabbagh et al., 2010). In another study, 65% (30/65 patients) developed seizures before the age of 1 year (Lee et al., 2011). In another study, only 1% of patients with seizures and mitochondrial disease had onset younger than 2 years of age (Chevallier et al., 2014).

Mitochondrial Genetics & Epilepsy

Over 169 seizure causing genes that have been identified to alter mitochondrial function (Zsurka and Kunz, 2015). Both mitochondria-encoded and nuclear-encoded genes that induce mitochondrial disease have been shown to also cause seizures. Almost all the mitochondrial-encoded genes associated with epilepsy are parts of mitochondrial syndromes (Table I, below). On the other hand, nuclear-encoded genes associated with seizures are not routinely associated with syndromes. The exceptions would be Alpers-Huttenlocher syndrome, Leigh syndrome, Infantile-onset Spinocerebellar Ataxia, Bjornstad Syndrome-GRACILE syndrome, Myocerebrohepatopathy Spectrum, Pontine Cerebellar Hypoplasia 6, and Myoclonus Epilepsy Myopathy Sensory Ataxia. Most of the nuclear-encoded genes associated with seizures (>100) do not fall neatly into a mitochondrial syndrome. There are also seizures in mitochondrial diseases for which genetic etiologies have not yet been discovered, which are based on clinical, biochemical and structural criteria (Lee et al., 2011).

Predicting which patient will develop seizures presents a clinical and genetic dilemma. To further compound the problem of genetic diagnosis are phenocopies and genocopies. For example, *POLG* gene mutations may produce seizures in one patient but not in another (Saneto and Naviaux, 2010). Classic mitochondrial syndromes may present in patient with the additional symptom of seizures while another patient with the identical heteroplasmy does not (Yatsuga et al., 2012). Furthermore, many more patients have abnormal EEG studies that do not have frank clinical seizures (Chevallier et al., 2014). Seizures may declare the onset of a syndrome but also may occur later during the disorder (Saneto et al., 2013). The clinician must have a high index of suspicion for the possibility of any patient with mitochondrial disease to have seizures and patients who have seizures who might have a mitochondrial disorder.

Many of the classic epilepsy syndromes occur in particular developmental ranges in infants and children (Berg et al., 2010). Infantile spasms is one of the most common epilepsy syndromes in patients with mitochondrial disease presenting from 4-months to 1-year of age. Mitochondrial disease syndromes such as Leigh syndrome due to the mtDNA m. 8993T>G has been associated with Infantile spasms (Desguerre et al., 2003). In addition, nuclear-encoded genetic diseases such as PDH deficiency have also been report in patients with Infantile spasms (Otero et al. 1995). Other nuclear-encoded genes have been associated with the syndrome of Infantile spasms; tRNA synthetase, RARS2, and tRNA modifying gene, MTO1 (Nogh et al., 2016 and Saneto, 2016). In a large population of patient with Electron-Transport-Chain abnormalities, 10 of the 56 patients with epilepsy, presented with Infantile spasms (El Sabbagh et al. 2010). In the Seattle cohort, 18% of the patients with mitochondrial disease developed infantile spasms (Saneto, unpublished data).

Other epilepsy syndromes associated with mitochondrial disease include Ohtahara syndrome, Neonatal epileptic encephalopathy with suppression bursts, Lennox-Gastaut syndrome, Landau-Kleffner syndrome and occipital idiopathic epilepsy (Kang et al., 2007; Lee et al. 2007; Castro-Gago et al., 2009; El Sabbagh et al. 2010). Both MELAS and Alpers syndrome may present with epilepsia partialis continua (EPC) or status epilepticus. Patients may present with focal neurologic symptoms (such as visual auras or visual field defects). There are many mitochondrial patients who do not have an epilepsy syndrome that have seizures. Therefore, the clinician needs a high index of suspicion of a patient with seizures to pursue a work-up for possible mitochondrial disease.

Evaluation

The work-up for a mitochondrial patient with possible seizures is similar to anyone who may have seizures. It is essential, if possible, to have the full description of the events from a witness. In infants and children, the parents or caregivers are usually the witness. But, in adults this can be problematic unless there is a spouse or other person who spends time with the patient. A first seizure event may not have a reliable witness to fully describe the event. The circumstances surrounding the seizure event are important as this may give clues to what type of seizure may have occurred. A video of the event recorded on a “smart phone” may be helpful in discerning focal versus generalized onset. A detailed history can give significant hints to the possible etiology of the seizure events. For example, a history of a difficult birth may signal possible hypoxic event, prematurity at birth may indicate possible central nervous insults such as hydrocephalus or intracranial bled or sudden loss of motor function may signal a metabolic stroke. A low threshold for EEG monitoring is needed, especially in patients with underlying cognitive regression, disability or dementia, as the state change from their baseline mental status may not be as easily ascertained.

An EEG should be performed, and if needed a prolonged Video-EEG to capture seizure event if several events have not been witness and the routine EEG studies have been normal. Although rare, non-epileptic paroxysmal events (pseudoseizures) have been reported in the mitochondrial population (Saneto, 2016). Nuclear magnetic resonance imaging (MRI) should be done to help characterize possible structural abnormality giving rise to the seizure event. If seizure semiology changes drastically, then repeating the EEG may be helpful to characterize seizure event.

Treatment

Treatment of seizures is similar to non-mitochondrial disease patients who have seizures. However, there are several caveats to treatment based on type of epilepsy and genetic mutation. Valproic acid should be avoided in patients with *POLG1* mutations, as valproic acid exposure has been linked to liver failure (Saneto et al., 2010). Vigabatrin should be avoided in seizures due to mutations in 4-aminobutyrate aminotransferase. Vigabatrin exposure inhibits the conversion of dNDP to dNTP in the mitochondrial nucleoside salvage pathway and can induce mtDNA depletion (Besse et al. 2015). Therefore, it is possible that vigabatrin should be avoided in mtDNA depletion syndromes, but confirmation of untoward effects has not been well reported. However, there is one epileptic syndrome, neonatal epileptic encephalopathy with suppression bursts that the use of vigabatrin should be avoided as the conversion of dNTP to dNTP is already inhibited (Besse et al., 2015). The use of vagus nerve stimulator implantation was not found to be highly successful in reducing seizure frequency in one small study (Arthur et al., 2007). However, large populations have not been studied.

Certain epilepsy syndromes have known specific treatments based on treatment studies. One such syndrome is Infantile spasms. The consensus of experts is using ACTH as first line and vigabatrin as second line treatment in (Pellock et al., 2010). In the Seattle cohort, ACTH controlled epileptic spasms and reversed the EEG hypsarrhythmia pattern in 16/18 patients with Infantile spasms. Unfortunately, all 18 patients have gone on to have intractable seizures with only limited response to seizure medications (Saneto, unpublished data).

Other epilepsy treatments have only been studied in small populations of mitochondrial disease patients. In two small studies, a group of patients with Infantile spasms and Lennox-Gaustaut syndrome responded to the Ketogenic Diet with 6/14 and 12/24 children becoming seizure-free (Kang et al., 2007b, Lee et al., 2008). For most reports, patients with mitochondrial disease represent populations unresponsive to most traditional seizure medications with 49% - 95% intractable to seizure medications (El Sabbagh et al., 2010; Lee et al., 2011). Patients with mitochondrial disease and seizures are often prescribed multiple individual and combinations of seizure medications without a clear consensus of data from clinical research studies. To date, no single or combination of seizure medications has been found highly effective to control seizures.

**Summary**

The prevalence of epilepsy in mitochondrial disease is not accurately known. In several mitochondrial syndromes such as Myoclonus, epilepsy with ragged-red fibers (MERRF) and Alpers-Huttenlocher syndrome (AHS), seizures are a cardinal feature. There are many non-syndromic patients who also have seizures as well. Several population studies in infants and children with mitochondrial disease, suggest that the prevalence of seizures reaches upwards to 35% - 60%. In contrast, in limited reported studies in adult populations, only a few syndromes are reported to have a high incidence of seizures (MERRF and MELAS-Mitochondrial encepahalomyopathy, lactic acidosis, and stroke-like episodes). Overall, the data suggests that within the mitochondrial disease patient population, at any age the incidence of seizure is higher than the general population and onset of seizures is higher in the younger age ranges and decreases with age. In general, no one seizure type is seen more commonly in mitochondrial disease and both generalized and focal epilepsies are seen. MELAS and Alpers syndrome may more commonly present with epilepsia partialis continua (EPC) or status epilepticus. Both mitochondrial-encoded and nuclear-encoded gene mutations have been found in mitochondrial disease patients with epilepsy.

With certain specific exceptions, the evaluation and management of seizures in this patient population resembles that in patient without mitochondrial disease. Infantile spasms are the most common epilepsy syndrome encountered in the infant (4 months to 1 year) mitochondrial disease population (El Sabbagh et al., 2010). As with non-mitochondrial patients, Adrenal Corticotrophin Hormone (ACTH) is first line for the treatment of epileptic spasms (Pellock et al., 2010). In other types of seizures, anti-seizure medications used for focal and generalized seizure onset should mirror what is used for patients without mitochondrial disease. There have been no clinical trials looking at medication use and seizure control in this population. Definition of focal versus generalized epilepsy should be defined by electroencephalograph (EEG) and possible structural etiologies need to be investigated by nuclear magnetic resonance imaging (MRI). Video-EEG may be required to fully define focal versus generalized onset and help to determine seizure type. A low threshold for EEG monitoring is needed, especially in patients with underlying cognitive regression, disability or dementia, as the state change from their baseline mental status may not be as easily ascertained.

There are two medications to avoid in the treatment of mitochondrial disease related seizures. Valproic acid has been shown to induce severe hepatopathy in AHS patients due to *POLG* mutations. However, before the connection between valproic acid and *POLG*-related AHS, this medication has been used for seizure control in other mitochondrial diseases. Clinical judgement and particular patient characterization need to be considered before attempting to use valproic acid in a mitochondrial disease patient. Vigabatrin may also need to be avoided in the treatment of specific types of mitochondrial patients, in particular neonatal epileptic encephalopathy with suppression bursts syndrome due to mutations in the 4-aminobutyrate aminotransferase gene. This gene converts dNDP to dNTP in the mitochondrial nucleoside salvage pathway. Vigabatrin inhibits this enzyme and could compound the loss of dNTP in mitochondria and hence induce an mtDNA depletion disorder (Besse et al., 2015). Given vigabatrin’s mechanism of action, one may need to avoid it for any patient with a mtDNA depletion syndrome.

**Reader comments**

The authors mention Arthur et al 2007 study on VNS in patients with mitochondrial disease. No patient had a molecular diagnosis. Patients were characterized biochemically. I think that better data is needed with contemporary diagnostic paradigms before anything can be said about efficacy

 I think it would be important to mention which drugs should be considered more safe than others in mito-patients (i.e. Levetiracetam). Moreover, topiramate is known to increase lactic acidosis, and it should be mention. Finally, I do not agree with the recommendation on valproic acid; in my experience it is commonly a toxic drug also in other mitochondrial disorders (not only POLG Alpers), and it should always be avoided or -if strongly necessary- to be used in association of Carnitine and other mitochondrial vitamins.

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**Recommendations**

* Mitochondrial disease patients are at a higher risk of epilepsy Score 4.85
* There should be a low threshold to obtain EEG monitoring in mitochondrial patients with recurrent stereotypical spells, spells of behavior arrest or alterations of state from baseline, especially in those with underlying cognitive disability or dementia Score 4.91
* Evaluation and treatment of epilepsy in mitochondrial disease is similar to patients without mitochondrial disease Score 4.41
	+ Caveats include avoiding the use of valproic acid in patients with POLG-related disease. Score 4.41
* Patients with select mitochondrial diseases are at a high-risk for epilepsia partialis continua (EPC) Score 4.65
	+ EPC, when present, should raise the concern of a metabolic stroke Score 4.32
* Vigabatrin may need to be avoided in patients with mtDNA depletion syndromes due to inhibition of 4-amino butyrate aminotransferase and a reduction in mitochondrial nucleoside salvage Score 4.35

Second survey/reader recommendation

* Valproic acid should be avoided in mitochondrial disease patients when possible (including as treatment for HA, psychiatric disease, epilepsy, movement disorders and others) Score 4.76
* Caution is needed with Topiramate as it may worsen acidosis Score 3.89

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Table 1: Pathological genetic mutations encoded in mitochondrial DNA reported to cause seizures.

 Clinical Phenotype Gene (n=distinct genes)

Myoclonus, Epilepsy with Ragged-Red Fibers MT-tRNAs (n=5)

Atypical Myoclonus, Epilepsy with Ragged-Red Fibers MT-tRNAs (n=6)

 MT-ND3 (complex I)

 MT-ND5 (complex I)

 MT-CYB (complex III)

Mitochondrial Encephalomyopathy, Lactic Acidosis MT-tRNAs (n=5)

 and Stroke-like Episodes MT-ND5 (complex I)

 MT-ND5 (complex I)

 MT-CYB (complex III)

 MT-CO1 (complex IV)

Epilepsy and Deafness MT-tRNA (n=1)

Seizures, PEO, Diabetes, and Deafness MT-tRNA (n=1)

Deafness, Retinal Degeneration, Myopathy and MT-tRNA (n=1)

 Epilepsy

Cardiomyopathy, Deafness, and Seizures MT-tRNA (n=1)

Encephalopathy with Recurrent Episodes of MT-tRNA (n=1)

 Epilepsia Partialis Continua

Leigh syndrome MT-tRNA (n=2)

 MT-ND3 (complex I)

 MT-ND5 (complex I)

 MT-ND6 (complex I)

Mitochondrial Myopathy, Lactic Acidosis, and MT-ATP6 (complex V)

 Sideroblastic Anemia

Optic Atrophy with Epilepsy MT-ND6 (complex I)

Leber Hereditary Optic Neuropathy MT-ND1 (complex I)

 MT-ND4 (complex I)

 MT-ND6 (complex I)