Mitochondrial Disease and Epilepsy Frequency
Russell P. Saneto, DO, PhD
Division of Pediatric Neurology, Children’s Hospital and Regional Medical Center/University of Washington, Seattle, Washington

Address correspondence to:
Russell P. Saneto, DO, PhD
Division of Pediatric Neurology
Children’s Hospital and Regional Medical Center
4800 Sand Point Way NE
Seattle, WA 98105
Email: russ.saneto@seattlechildrens.org
Studies suggest that as many as 50% of patients with mitochondrial disease have epilepsy.\textsuperscript{1,2} In our patient population, about 50% (76/130 cases) of children with electron transport chain deficiencies have epilepsy and present between the ages of 2 months and 6 years, with a median of 3 years of age (unpublished data). Although epilepsy can occur at any age,\textsuperscript{3} early onset seems to be common in patients with electron transport chain disorders.

Epilepsy and Paroxysmal Events

Epileptic seizures are transient clinical events that result from abnormal excessive activity within a population of cerebral neurons. The clinical manifestations are not always positive motor events. Many seizures are characterized by negative phenomena, such as loss of awareness, muscle tone, or language. However, an epileptic seizure always results from electroencephalogram (EEG) changes, as opposed to other types of paroxysmal attacks. Patients with mitochondrial disease can have a variety of involuntary movements that may confuse the diagnosis. A patient with new-onset seizure requires a full EEG evaluation to verify that the events are epileptic seizures and that appropriate medication is needed.

Mitochondrial Disease and Epilepsy Syndromes

We have found that the most common form of epilepsy in children with electron transport chain defects is severe epilepsy with multiple independent spike foci (SE-MISF). SE-MISF is characterized by intractable seizures of various types, severe developmental delay, and by an EEG pattern of multifocal independent spikes with background slowing.\textsuperscript{4,5,6} In our series, 42/67 patients with electron transport chain defects were classified as having SE-MISF. In another study, 9/17 children but only 1 adult had SE-MISF.\textsuperscript{3} A group of our mitochondrial patients (8/67) fit the diagnosis of less severe epilepsy with mainly partial seizures (PE-MISF).\textsuperscript{7}

Myoclonus epilepsy with ragged-red fibers (MERRF) is one of the “classic” progressive myoclonic epilepsies and is part of a typical mitochondrial syndrome.\textsuperscript{8,9,10} More than 80% of patients have the A8344G mutation within the mitochondrial DNA (mtDNA).\textsuperscript{11} As a rule, patients have normal early development, with disease onset ranging from 3 years to adulthood. Patients eventually display the canonical features of myoclonus, generalized seizures (myoclonic), ataxia, and ragged-red fibers in muscle, but they often have other symptoms.

West syndrome or Infantile spasms consists of the triad of hypsarrhythmia pattern on EEG, epileptic spasms, and developmental retardation or deterioration.\textsuperscript{12} Some infants with mtDNA mutations, electron transport chain
deficiencies or pyruvate dehydrogenase deficiencies have been shown to have West syndrome.13, 14, 15 In our series, 12/67 or 18% of patients with electron transport chain defects and epilepsy presented with West syndrome.

Other epilepsy syndromes are rarely seen. Four patients with Lennox-Gaustaut syndrome and mitochondrial disease have been reported.15 However, this is likely uncommon, as none of our 67 patients nor the 31 patients described by Canafoglia et al.3 had this syndrome. There are also isolated reports of Ohtahara syndrome with Leigh syndrome and Landau-Kleffner syndrome in a patient with an electron transport chain defect.12, 15

Alpers-Huttenlocher or Alpers syndrome is one of the mitochondrial syndromes within the spectrum of polymerase gamma 1 (POLG) disease.16 Although not a true epilepsy syndrome, this disorder manifests seizures in most all patients.17 Seizures are very difficult to control with medications, and if given Valproic acid, liver failure can occur.18 There are some characteristic symptoms that may help the practitioner avoid giving Valproic acid. Early development is normal and seizures are usually explosive in onset and have an occipital predominance in epileptiform discharges.19,20 Any ethnic group can be involved (Saneto et al., in preparation). There are frequent bouts of epilepsia partialis continua or frank status epilepticus with seizure semiology suggesting occipital lobe seizures; focal clonic seizures and/or secondarily generalized seizures, hallucinations, and eye nystagmus.19,20 Progressive psychomotor regression is almost universal from the initiation of seizures, although there is a wide variation depending on mutation and other factors that are still unclear. Sequencing of POLG should be performed as multiple mutations may be responsible.

Seizure Types

Most mitochondrial patients have more than one seizure type. In our series, the most common types were myoclonic seizures and segmental myoclonus. Almost all patients had other seizure types, including atypical absence, epileptic spasms, or short tonic seizures. Other commonly reported seizure types are versive, postural, and secondarily generalized tonic-clonic.12, 15 Generalized myoclonic, tonic-clonic and atonic seizures have been noted in some studies.12, 15 Excluding patients with MERRF, pure generalized epilepsy is rare. Canafoglia et al.3 reported only two patients with pure generalized, and in our series only 12/67 had predominant generalized seizures.

Epilepsia partialis continua (EPC) consists of regular/irregular clonic muscular twitches affecting a limited part of the body that last at least for 1 hour.22 Mostly seen in fixed cortical (i.e., malformation of cortical development) or progressive lesions (i.e., Rasmussen’s encephalitis),23,24 patients with mitochondrial disease can express EPC. Case reports of patients with Leigh syndrome, electron transport chain defects, MERRF, and mitochondrial myopathy, encephalopathy,
lactic acidosis, and stroke-like episodes (MELAS) have been reported. Unlike other mitochondrial diseases, a high percentage of patients with Alpers syndrome present with EPC.

Treatment

In our series, response to anti-seizure medication (AED) is invariably poor in patients with SE-MISF. Although response to AEDs is somewhat better in patients with PE-MISF and generalized seizures, most patients remain refractory to AEDs. In one study, the ketogenic diet produced seizure freedom in 6/14 patients with electron transport chain deficiencies but we have had the same response in only 1/8 patients. It is not clear why some patients respond to the diet and others do not. A non-pharmacological modality, vagus nerve stimulation (VNS) did not alter myoclonic seizures in 5 patients. Although this was a small study; it clearly suggests that VNS may not be effective in controlling myoclonic seizures in children with electron transport defects.

The use of sodium valproate (VPA) deserves special mention. There are numerous reports describing acute neurological and hepatic deterioration with VPA exposure in both children and adults having mutations in polymerase , POLG). Patients harboring mutation in POLG suggestive of Alpers syndrome, have a high risk of liver failure if exposed to VPA. We have noted acute encephalopathy with worsening seizure frequency in some patients without POLG mutations and electron transport chain defects. The underlying mechanisms are not completely understood.

Summary

Epilepsy is very common in patients with mitochondrial disease, especially with defects of the electron transport chain. As a group, about 50% of patients have epilepsy. Partial seizures are predominant with myoclonic seizures most common, but most patients have multiple seizure types. West syndrome is common in infants, while in children the most common syndrome is SE-MISF. Unfortunately, treatment is unsatisfactory and most patients fail to respond to medications and VNS placement. VPA should be used with caution and is contraindicated in patients with POLG mutations. There are some clinical findings that may be helpful in detecting those infants, children and adolescents with possible POLG mutations that may help the clinician with medication management. The ketogenic diet may be an option for selected children.

Clearly the study of epilepsy and mitochondrial disease is in its infancy. Much work remains to be done and better treatment options are needed.

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