



MITO 101- Epilepsy and Paroxysmal Spells

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- Key points
 - Epilepsy is very common in patients with mitochondrial disease, especially with defects of the electron transport chain.
 - As a group, over 50% have epilepsy.
 - Although most patients have multiple seizure types, the most common seizure semiology is myoclonia and myoclonic seizures.
 - There are multiple epilepsy syndromes found in patients with mitochondrial disease.
 - The most common epilepsy syndromes are Infantile spasms or West syndrome in infants and Severe Epilepsy with Multifocal Independent Spike Foci in children and adolescents.
 - Most seizures remain refractory to anti-seizure medications and vagus nerve stimulator implantation.
 - Valproic acid should be used with extreme caution as it might induce liver failure in some patients with a specific type of mitochondrial disease.

- Mitochondrial disease and epilepsy frequency
 - Epilepsy is relatively common in patients with mitochondrial disease. Several studies have shown that as many as 50% have epilepsy.^{1,2} In our patient population, about 50% (76/130 cases) of children with electron transport chain deficiencies have epilepsy. Seizures presented between 2 years and 6 years, with a median of 3 years.
 - Epilepsy can present at any age,³ however early onset seems to be common in patients with electron transport chain disorders.

- Epilepsy and paroxysmal events
 - Seizures are defined as transient clinical events that result from abnormal excessive electrical activity within a population of cerebral neurons.
 - The clinical manifestations are not always positive events. Many seizures are characterized by negative phenomena, such as a 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 paroxysmal 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.^{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. A group of our mitochondrial patients (8/67) fit the diagnosis of less severe epilepsy with mainly partial seizures (PE-MISF).⁷
 - Myoclonus epilepsy with ragged-red fibers (MERRF) is one of the "classic" progressive myoclonic epilepsies and is part of a typical mitochondrial syndrome.^{8, 9, 10} More than 80% of patients have the A8344G mutation within the mitochondrial DNA (mtDNA).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.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 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 in a patient with an electron transport chain defect.^{12, 15}

- 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}
 - 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 1 hour.¹⁶ Mostly seen in fixed cortical (i.e., malformation of cortical development) or progressive lesion (i.e., Rasmussen's encephalitis).^{17, 18} However, 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.^{19, 20, 21, 22} Unlike other mitochondrial diseases, a high percentage of patients with Alpers syndrome present with EPC.²³
- 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 defects,¹⁵ 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.²⁴ 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 gamma 1 (POLG).^{23, 25, 26, 27} Patients harboring mutation in POLG suggestive of Alpers syndrome, have a high risk of liver failure if exposed to VPA.^{23, 25} We have noted acute encephalopathy with worsening seizure frequency in some patients without POLG mutation and electron transport chain defects. Several cases of a rare disorder of nonhyperammonemic, reversible mental deterioration with brain pseudoatrophy in epilepsy children exposed to VPA have been described.²⁸ The underlying mechanisms are not completely understood.

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