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Epilepsy and Mitochondrial Dysfunction: A Single Center's Experience

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Abstract

Epilepsy is a common manifestation of mitochondrial disease. In a large cohort of children and adolescents with mitochondrial disease (n = 180), over 48% of patients developed seizures. The majority (68%) of patients were younger than 3 years and medically intractable (90%). The electroencephalographic pattern of multiregional epileptiform discharges over the left and right hemisphere with background slowing occurred in 62%. The epilepsy syndrome, infantile spasms, was seen in 17%. Polymerase γ mutations were the most common genetic etiology of seizures, representing Alpers-Huttenlocher syndrome (14%). The severity of disease in those patients with epilepsy was significant, as 13% of patients experienced early death. Simply the loss of energy production cannot explain the development of seizures or all patients with mitochondrial dysfunction would have epilepsy. Until the various aspects of mitochondrial physiology that are involved in proper brain development are understood, epilepsy and its treatment will remain unsatisfactory.

Keywords

epilepsy, seizures, mitochondrial disease, electroencephalogram, infantile spasms, Alpers-Huttenlocher syndrome, status epilepticus, treatment

Introduction

Mitochondria are essential organelles involved in the proper operation of the highly controlled cellular energetic processes of brain function, including amino acid and fatty acid synthesis and metabolism, heme synthesis, and control of intracellular calcium fluxes. Central to the cellular controls of these processes is mitochondrial energy production. Compromise of the organelle's ability to produce energy, adenosine triphosphate (ATP), can disrupt the intricate controls of the mitochondrial multiple functions and can lead to excitation and inhibition of communication between neurons and glia. The deficit in energy production alters the balance of neuronal excitation and inhibition, which can lead to seizures.

Mitochondria contain their own genome that gives rise to mitochondrial-specific protein translational components of 22 tRNAs, 2 rRNAs, and 13 polypeptides involved in the oxidative phosphorylation (OXPHOS) production of ATP.[1] However, the replication, maintenance, and expression of mitochondrial DNA (mtDNA) and the other mitochondrial processes are nuclear-encoded products from nuclear DNA (nDNA). The proper combination of mtDNA- and nDNA-encoded gene products is required for normal mitochondrial function.[2] When compromised, the unique properties of organelle-specific mtDNA and dependence of nDNA-encoded gene products can give rise to a wide variety of clinical phenotypes, including the high prevalence of seizures and encephalopathy in mitochondrial diseases. Several studies have shown that approximately 35% to 60% of individuals with biochemically confirmed mitochondrial disease have epilepsy.[3–7]

The available data suggest the prevalence of seizures is higher in the mitochondrial disease population compared to the general population in children.[3–9] However, the reasons for such a predominance of early-onset seizures is unclear. The literature is variable, with some studies describe few patients with early seizures, whereas others suggest early-onset seizures to be more common.[7–10] The aim of this study is to describe the age of onset, electroencephalogram (EEG), seizure semiologies, response to medical management, and outcomes in a large

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cohort of infants, children, and adolescents with mitochondrial disease from a single center.

Methods

This is a chart review cohort study from the years 2001 to 2016 of patients younger than 20 years who were diagnosed and managed at Seattle Children's Hospital. Our institutional review board (#11445) has approved this study. Mitochondrial disease confirmed whether the patient met the Bernier et al's criteria for definitive mitochondrial disease and/or possessed an mtDNA-encoded or nDNA-encoded pathological mutation.[11] When available and approved by insurance, mtDNA and nDNA gene sequencing was performed. All patients underwent 1 or more video EEG studies at Seattle Children's Hospital. Seizure semiologies were noted by video EEG and/or parental description of the events and adapted to the current International League Against Epilepsy (ILAE) classification, unless otherwise indicated.[12] Seizure frequency was determined by seizure diaries on sequential clinic visits. The author reviewed all studies and clinical reports.

Routine clinic appointments occurred at intervals of 3 to 6 months. Assessment of seizure types and their frequency and possible medication side effects took place at each visit. Seizure counts from patient seizure diaries were assessed at each visit. Families often would call the clinic's nurse line between clinic office visits to indicate seizure frequency changes and possible side effects. The author reviewed all notes recorded in the electronic medical record.

Prior to genetic testing, the determination of classically defined mitochondrial disease relied on the constellation of clinical, biochemical, and radiological signs and symptoms in the OXPHOS system. Over time, the enhanced knowledge of mitochondrial physiology, commercial availability in the identification of candidate genes involved in mitochondrial functioning, and a large number of defects outside the OXPHOS system that directly or indirectly affect mitochondrial energy production have been identified. Thus, any study examining patients described over time has bias to the diagnostic dilemma of imprecise diagnostic tools at the time of diagnosis and changing landscape of mitochondrial function elucidation.

Results

Patients

A total of 174 patients were identified as having primary mitochondrial disease, with 83 males and 91 females. Overall, the age of onset of symptoms was 3.72 years in patients without seizures (data not shown; 44.6 months; range: 1 week to 19 years). In those patients with epilepsy (n = 85; males = 41), the average age of symptom onset was earlier, as defined by seizures, with seizure onset at 2.86 years (34.3 months; range: 1 week to 19 years).

The age of onset of seizures: 40 (46%) patients had seizure onset during infancy, ≤1 year; 37 (44%) had onset during childhood, 1 to <10 years; and 8 (10%) had onset during adolescence, 10 to 19 years (Table 1). Seizures developed in 58 (68%) children younger than 3 years.

Earlier death was strongly associated in the seizure population compared to the nonseizure population. There were 5 patients who did not have seizures who died during the course of this study; average age of death was 25.4 months or about 2 years (data not shown; range: 5-60 months). In contrast, 26 patients had seizures and died (Table 1). The average age of death was 79.6 months or 6.6 years (data not shown; range: 7-168 months). Patients with infantile spasms or genetic etiologies of mitochondrial disease died earlier compared to patients with epilepsy outside these 2 categories. In patients with infantile spasms (n = 6), the time to death was earlier than the patient population with seizures (mean = 44 months; range: 8-60 months vs 79.6 months; Table 2). Only 2 patients with a history of infantile spasms were thought to have died due to sudden unexplained death due to epilepsy (SUDEP; Table 1). Patients with childhood Alpers-Huttenlocher syndrome who have died (n = 9) also had a shorter life span (Table 3). The mean time to death was 57 months (range: 9-103 months). Only 2 patients with Alpers-Huttenlocher syndrome died due to liver failure (mean = 216 months; range: 144-288 months). The other 7 patients died during status epilepticus, of which 6 died due to withdrawal of care by the parents. The other patient died of a cardiac arrest.

Twenty-six patients had pathological genetic mutations (Table 3). The most common genetic etiology of patients with epilepsy was *polymerase γ 1* (*POLG*) mutations. Twelve patients had mutations in *POLG* and seizures. Those patients with childhood Alpers-Huttenlocher syndrome (n = 9) developed seizures at an average of 21.2 months (range: 8-36 months). Three patients with juvenile Alpers-Huttenlocher syndrome developed seizures at an average of 16 years (range: 14-17 years). Fourteen patients with other pathological genetic mutations in a variety of mtDNA or nDNA genes developed seizures at an average of 59.7 months (range: 3-228 months). Only 3 of these latter patients developed seizures before the age of 1 year. Ten of the other patients with genetic epilepsy developed seizures from 1 to 10 years, while a single patient developed seizures at the age of 19 years.

There were 56 patients without identified genetic mutations with electron transport chain (ETC) enzymatic defects and who met the Bernier et al's criteria for definitive mitochondrial disease (Table 1).[11] Forty patients had single ETC enzymatic defects. The most common single ETC defect was in complex I (n = 22). Thirteen patients had multiple ETC defects. There was a single patient with enzymatic defects suggesting an E3/lipoic acid dehydrogenase defect.[14]

Electroencephalogram Findings

The patient's age of the first EEG limited the EEG patterns of epilepsy onset. The timing of the initial study was dependent on the referral age or clinic discovery and time to arrange the initial EEG. However, once diagnosis occurred, all further evaluations occurred in 1 single center with multiple studies

Table 1. Demographics, Age of Seizure Onset, Seizure Semiology, Electron Transport Chain (ETC), and Molecular Abnormalities, and the Electroencephalograph Findings.[a]

Patient (Sex)	Age of Seizure Onset	Semiology	EEG Findings	ETC Abnormalities	Molecular Abnormality
1 (m)	1 month	Myo/tonic	MISD	IV	
2 (m)[b]	1 month	Myo/myoC/SE	SI	NA	*POLG*
3 (f)	1 month	F-motor	MISD	I, II/III	
4 (m)	1 month	ES > myo/F-motor	Hyps > MISD	III	
5 (m)	1 month	ES > myo/Tonic	Hyps > MISD	I	
6 (m)	2 months	F-motor	MISD	III	
7 (m)	2 months	ES > myo/tonic	Hyps > MISD	IV	*MTO1*
8 (f)	2 months	Myo/tonic/F-motor	MISD	I	
9 (f)[b]	2 months	ES > tonic	BS > MISD	NA	*E3/Lipoic acid*
10 (m)	2 months	Myo/tonic/clonic	MISD	NA	m.11778G>A
11 (m)	3 months	F-motor/dys	MISD	NA	m.8993T>G
12 (m)	3 months	ES > myo/tonic	Hyps > MISD	I	
13 (f)	3 months	ES > myo/tonic/myoC	Hyps > MISD	III	
14 (f)[b,c]	4 months	ES > myo/tonic	Hyps > MISD	I	
15 (f)	4 months	ES > myo/tonic	Hyps > MISD	II, III, IV	
16 (f)	4 month	ES > myo/tonic	Hyps > MISD	I	
17 (f)[b,c]	4 months	ES > F-motor	Hyps > MISD	I	
18 Female	4 months	Myo/tonic/F-motor	MISD	I	
19 (f)	4 months	ES > myo/tonic	BS > Hyps > MISD	IV	
20 (f)[b]	5 months	Myo	MISD	IV	
21 (m)	5 months	ES > myo/tonic	Hyps > MISD	I, IV	
22 (m)	5 months	Myo/tonic/F-motor	MISD	I	
23 (m)	6 months	Myo/tonic	MISD	I	
24 (m)	6 months	Myo/tonic/days	GSW	III	
25 (f)	6 months	Myo/tonic/atonic	MISD	I	
26 (f)	6 months	Myo/tonic	MISD	III	
27 (m)	6 months	Myo/tonic	MSID	I	
28 (m)[b]	7 months	Myo/tonic/GTC/myoC/EPC[c]	MISD	NA	*POLG*
29 (m)	8 months	F-motor	MISD	III	
30 (f)	8 months	Myo/2-GTC/F-motor	GSW	I	
31 (m)	8 months	Myo/2-GTC/F-motor	GSW	IV	
32 (f)[b]	9 months	Myo/EPC/F-Clonic/MyoC	MISD	NA	*POLG*
33 (m)[b]	9 months	Myo/F-clonic/myoC/EPC[c]	MISD	NA	*POLG*
34 (m)[b]	11 months	F-motor	MISD	I, III	
35 (m)	11 months	Myo/tonic/clonic	MISD	III, IV	
36 (m)[b]	12 months	ES/myo/tonic	Hyps > MISD	IV	*TANGO 2*
37 (m)	12 months	Myo/tonic	MISD	NA	m.8993T>G
38 (f)[b]	12 months	Myo/tonic	MISD	I	
39 (m)[b]	12 months	Myo/tonic	MISD	III	
40 (f)[b]	12 months	Myo/tonic/F-motor	MISD	NA	*PDHC* deficiency
41 (f)	15 months	Myo/tonic/F-motor	MISD	I, II/III	
42 (m)	15 months	ES/myo/tonic	Hyps > MISD	I	
43 (m)	18 months	Dys	MISD	IV	
44 (f)	18 months	Atonic/myo	MISD	IV	
45 (m)	20 months	F-motor/dys	Focal	I	
46 (m)	20 month	Myo/tonic	MISD	I	
47 (m)	2 years	Dys/myo	MISD	NA	m.8363G>A
48 (f)	2 years	Myo/tonic/F-motor	MISD	NA	*PDHA1*
49 (f)	2 years	Myo	MISD	I, III, IV	
50 (f)	2 years	Dys/atonic	GSW	II/III	
51 (f)	2 years	GTC (febrile)	SI	IV	
52 (f)	2 years	Dys/atonic	GSW	I	
53 (f)[b]	2 years	ES/tonic	Hyps > MISD	I, III, IV	
54 (f)	2 years	Myo/tonic/F-motor	MISD	I, IV	
55 (f)	2 years	Myo/tonic	MISD	I	
56 (f)	2 years	Myo/tonic	MISD	I, III, IV	

(continued)

Table 1. (continued)

Patient (Sex)	Age of Seizure Onset	Semiology	EEG Findings	ETC Abnormalities	Molecular Abnormality
57 (f)	2 years	EPC/myo/tonic	MISD	Normal	*RARS 2*
58 (f)[b]	2 years	Myo/F-clonic/EPC[c]	MISD	NA	*POLG*
59 (f)	3 years	F-motor	MISD	I	
60 (m)	3 years	F-motor/2-GTC	GSW > MISD	I/III, II/III	
61 (m)	3 years	Dys	MISD	I	
62 (m)	3 years	Myo/tonic	GSW	III	
63 (f)[b]	3 years	F-motor/F-clonic/myo/EPC[c]	MISD	NA	*POLG*
64 (f)	3 years	Myo/F-motor	MISD	IV	
65 (f)	4 years	Myo/2-GTC	MISD	I	
66 (f)	4 years	Tonic	MISD	I	
67 (m)	4 years	Dys/F-motor	GSW	I	
68 (f)[b]	4 years	F-motor/Myo/F-clonic/EPC[c]	MISD	NA	*POLG*
69 (m)	4 years	F-motor/myo/2-GTC/SE	MISD	NA	m.3243A>G
70 (m)[b]	5 years	F-motor/myo/F-clonic/EPC[c]	MISD > GSW > SI	Normal	*POLG*
71 (m)	5 years	F-motor/dys	MISD	III	
72 (m)	5 years	F-motor	Focal	I/III, II/III	
73 (m)	5 years	Myo/tonic	MISD	III, IV	
74 (f)[b]	6 years	F-motor/myo/SE	MISD	NA	*POLG*
75 (f)	7 years	Dys	MISD	NA	m.3243A>G
76 (f)	8 years	Dys	MISD	III	
77 (f)	9 years	Myo/F-motor	MISD	I	
78 (m)[b]	10 years	F-motor/myo	MISD	I	
79 (m)	10 years	F-motor/myo	MISD	NA	m.14478T>C
80 (m)[b]	11 years	Dys (NCS)	MISD	NA	m.14459A>G
81 (f)[b]	14 years	F-motor/myo/EPC+	MISD	III	*POLG*
82 (m)	14 years	F-motor/2-GTC	MISD	NA	m.3243A>G
83 (f)	17 years	F-motor/2-GTC/myo/SE	MISD	NA	*POLG*
84 (f)	17 years	F-motor/myo/SE	MISD	NA	*POLG*
85 (f)	19 years	Myo/tonic	MISD	NA	*SLC19A3*

Abbreviations: BS, burst suppression; dys, disconjugate; ES, epileptic spasm; EPC, epilepsy partialis continua; EPC[b], combination of epilepsy partialis continua; f, female; F-motor, focal motor; focal, epileptiform discharges over just a single region of 1 hemisphere; 2-GTC, secondary generalized tonic clonic; GSW, generalized spike and wave discharges; hyps, hypsarrhythmia; m, male; motor, minor motor movements that do not fall into category of focal or generalized; MISD, multifocal epileptiform discharges over the left and right hemisphere with background slowing; *MTO1*, mitochondrial-tRNA translation optimization factor; myo, myoclonic; myoC, myoclonus; NA, not tested for ETC activity; *PDHA 1*, pyruvate dehydrogenase alpha subunit gene; *PDHC*, pyruvate dehydrogenase complex gene; *POLG*, polymerase γ 1 gene; *RARS2*, arginyl-tRNA synthetase gene; SI, background slow for age; *SLC19A3*, solute carrier family 19 member 3 (thiamine transporter) gene; *TANGO 2*, transport and Golgi organization 2 homolog gene.

[a]After the age of 2 years, age of onset was rounded to the nearest year.

[b]Patients who have passed away.

[c]Patients who passed away to sudden unexplained death due to epilepsy.

obtained, which minimized the loss of EEG changes over time. The author reviewed all studies. The most common first EEG findings (n = 58) was an interictal pattern of multifocal spike discharges (MISD) over the left and right hemispheres with background slowing (Figure 1). Only a single patient presenting with MISD (n = 57) evolved into a different EEG pattern over the course of this study. Twenty-eight patients presented with other EEG patterns (see below). Sixteen of these patients evolved into an MISD pattern on EEG. Patients with *POLG* mutations initially presented with spikes/polyspikes over the occipital region (left and/or right), with slowing over the regions of epileptiform discharge. Only a single patient evolved from presenting with an MISD pattern to generalized slowing without epileptiform discharges. The MISD EEG pattern has also been described as multiple independent spike foci (MISF).[15] The MISD EEG pattern is epileptiform discharges arising from multiple cerebral lobes, including at least 1 area of both hemispheres.[13,15] The EEG pattern of MISD may or may not be associated with background slowing. All of the patients in this series who had MISD had background slowing, which corresponds to the Severe Epilepsy-MISF description.[13,15] To avoid confusion, the term used in this report to describe the pattern of multifocal epileptiform discharges over the left and right hemispheres with background slowing will be labeled MISD.

Fourteen patients had an EEG pattern of hypsarrhythmia, and all 14 evolved into the EEG pattern of MISD (Table 2). The onset of hypsarrhythmia on average was 6.75 months (range: 2.5 months to 2 years). Once the pattern of MISD was established, none of these patients developed other EEG patterns over time, with examination of repeat EEGs ranging from 1 to 12 years.

Generalized spike wave pattern was seen in 6 patients with their first EEG study. Interictal discharges did not evolve into the slow spike and wave pattern described in Lennox-Gastaut syndrome.[16] Most interictal discharges were single, with some

Table 2. Mitochondrial Patients With Infantile Spasms: Hypsarrythmia on EEG, Epileptic Spasms, and Developmental Delay.[a,b,c]

Patient (Sex)	Age Onset	ETC/Genetic Defect	Medications	Age of Death
1 (m)	2 months	C-IV; *MTO1*	ACTH, VGB, TPM, FBM, CLB, LEV, LTG, KD	
2 (m)	3 months	C-I	ACTH, VGB, LTG, TPM, LEV, GAN	
3 (m)	3 months	C-III	ACTH, KD, LTG, RFM, LEV	
4 (f)	3 months	E3/lipoic acid	VGB, Prednisone, ZNS	8 months
5 (m)	3 months	C-I	PB, ACTH, VGB, LAC, LTG, LEV, KD	
6 (f)	4 months	C-I	ACTH, ZNS, LTG	5 years
7 (m)	4 months	C-II, C-III, C-IV	ACTH, ZNS, LTG, RFM, LAC, VPA, CLB	
8 (f)	4 months	C-I	ACTH, ZNS, VGB	4 years
9 (f)	4 months	C-I	ACTH, VGB, LTG, CLB, RFM, GAN	
10 (f)	4 months	C-IV	PB, ZNS, B6/LEV/KD	4 years
11 (m)	5 months	C-I, C-IV	ACTH, ZNS, TPM, LEV, LTG, KD	
12 (m)	12 months	C-IV; *TANGO 2*	ACTH, ZNS, VPA, CLB, CBD	3 years
13 (m)	15 months	C-I	Prednisone, ZNS, LTG	
14 (f)	23 months	C-I, C-III, C-IV	ZNS, TPM, KD	5 years

Abbreviations: ACTH, adrenocorticotrophic hormone; B6, pyridoxine; C, electron transport chain complex; CBD, cannabidiol; CLB, clobazam; ETC, electron transport chain; f, female; FBM, felbamate; GAN, ganaloxone; KD, ketogenic diet; LAC, lacosamide; LEV, levetiracetam; LTG, lamotrigine; m, male; *MTO1*, mitochondrial-tRNA translation optimization factor 1 gene; PB, phenobarbital; RFM, rufinamide; E3/lipoic acid[13]; *TANGO 2*: transport and Golgi organization 2 homolog gene; TPM, topiramate; VGB, vigabatrin; VPA, valproic acid; ZNS, zonisamide.

[a]The demographic of sex, age of infantile spasms onset, electron transport chain or genetic defect, medications used and age of death (if occurred) are given.

[b]Patients 8 and 10 presented with an EEG pattern of suppression-bursts before evolving into hypsarrhythmia.

[c]Patient 3 became seizure free on monotherapy of ketogenic diet (4:1 ratio) but had to discontinue due to parental concerns.

occurring in runs of 3 to 4 Hertz with a short duration of 2 to 3 seconds. The spike pattern did not change over time, 4 to 10 years. The age of onset was 1.7 years (range: 6 months to 4 years). A single patient who presented with a generalized spike and wave pattern developed an EEG pattern of MISD over time. The other 5 patients continued to have generalized discharges over time.

There were 2 patients who presented with only independent focal discharges and did not meet the criteria of MISD. The interictal EEG pattern of focal discharges occurred in only 1 hemisphere. The age of presentation was 20 months and 5 years. Both patients' EEG pattern has remained with only focal discharges arising from the same hemisphere. Two patients presented with a suppression burst pattern. The age of onset was 2 and 4 months. Both patients evolved into the MISD pattern over time, with one of the patients evolving into hypsarrhythmia before MISD (patient 19: Table 1; patient 10: Table 2).

Those patients with *POLG* mutations (n = 12) all presented with independent focal discharges over the posterior head regions. Over time as the disease progresses, the EEG findings evolved into either a generalized spike and wave pattern, MISD pattern, generalized slowing of the background without epileptiform discharges; if frank liver failure occurred then a periodic epileptiform pattern occurred.[16–18] However, in some patients, care was withdrawn after genetic diagnosis was made, usually in the context of status epilepticus or severe neurological decompensation. In these patients, the natural history of EEG evolution could not be made.

Seizure Semiology

The 14 patients with hypsarrhythmia on EEG had epileptic spasms (Table 2). Spasms continued after the EEG had evolved into the interictal MISD pattern, but seizures eventually evolved into multiple seizure types. Patients progressed from epileptic spasms into tonic seizures. When captured on EEG, tonic seizures demonstrated background attenuation with overriding paroxysmal fast activity in a generalized distribution (Figure 1). In addition to tonic seizures, patients had both generalized and focal myoclonic seizures, the latter mostly involving the upper body. Focal myoclonic seizures were cortical in origin and seen with generalized and focal onset (Figure 1). The myoclonus events, when captured on video EEG, were not time-locked to EEG epileptiform discharges (data not shown).[19,20] Electrodiagnostic testing was not pursued to define etiology of spinal cord or peripheral nerve due to age of the population. Only 2 patients had persistent focal seizures arising from 1 hemisphere, either motor or dyscognitive (formerly described as partial complex or atypical absence).[14]

Six patients with interictal generalized spike discharges had a variety of seizure types. Four of the patients had periods of dyscognitive seizures. Two of the four patients had dyscognitive and atonic seizures. Another patient had dyscognitive and focal motor seizures. The 3 remaining patients had multiple seizure types, including generalized myoclonic seizures, tonic, and tonic–clonic seizures, and secondarily generalized tonic–clonic seizures. One of the latter patients also had focal motor seizures in addition to generalized seizures.

The seizure types in patients with MISD varied. Most patients presenting with this interictal EEG pattern had a combination of multiple seizure types (n = 57). In this population, the most common seizure type combination was generalized tonic and myoclonic seizures. Twelve of these patients only had tonic and myoclonic seizures, with another 12 patients having other seizure semiologies, in addition to tonic and myoclonic seizures. The next combination of

Table 3. Patients With Mitochondrial DNA- and Nuclear DNA-Encoded Mutations and Epilepsy.[a]

Patient (Sex)	Age Onset	Gene	Mutation	Status Epilepticus	Number Seizure Medications	Death
1 (m)	1 month	*POLG*	c.428C>T/c.679C>T	Yes	3	1 year
2 (m)	2 months	*ND5*	m.11778G>A	No	3	
3 (m)	2 months	*MTO1*	c.176C>G/c.922A>G	No	9	
4 (m)	3 months	*MT-ATP6*	m.8993T>G	No	4	7 years
5 (m)	7 months	*POLG*	c.2740A>C/c.3286C>T	Yes	4	2 years
6 (f)	9 months	*POLG*	c.1399G>A/c.2897T>G	Yes	5	
7 (m)	9 months	*POLG*	c.1399G>A/c.3313G>C	Yes	8	1 year
8 (m)	12 months	*TANGO2*	c.711-3C>G/del exon 3-9	Yes	5	4 years
9 (m)	12 months	*MT-ATP6*	m.8993T>G	No	4	
10 (m)	24 months	*MT-TK*	m.8363G>A	No	4	
11 (f)	24 months	*RARS2*	c.472_474delAAA/c.772C>A	Yes	7	
12 (f)	24 months	*PDHA1*	c.904C>A	No	2	
13 (f)	3 years	*POLG*	c.1399G>A/c.202C>T	Yes	5	3 years
14 (f)	3 years	*POLG*	c.2242G>C/c.2554C>T	Yes	4	8 years
15 (f)	4 years	*POLG*	c.2242G>C/c.2542G>A	Yes	6	7 years
16 (m)	4 years	*MTTL1*	m.3243A>G	Yes	4	
17 (m)	5 years	*MtDNA*	7.4 kb deletion	No	3	
18 (m)	5 years	*POLG*	c.1399G>A/c.2542G>A	Yes	5	12 years
19 (f)	6 years	*POLG*	c.229C>G/c.2243G>C	Yes	6	8 years
20 (f)	7 years	*MTTL1*	m.3243A>G	Yes	3	
21 (m)	10 years	*ND6*	m.14487T>C	Yes	3	
22 (m)	11 years	*ND6*	m.14459T>G	Yes	1	15 years
23 (f)	14 years	*POLG*	c.1399G>A/c.1399G>A	Yes	6	24 years
24 (f)	17 years	*POLG*	c.1399G>A/c.1399G>A	Yes	5	
25 (f)	17 years	*POLG*	c.1399G>A/c.1399G>A	Yes	6	
26 (f)	19 years	*SLC19A3*	c.1228A>G/c.223G>A	Yes	4	

Abbreviations: f, female; m, male; *MTO1*, mitochondrial-tRNA translation optimization factor 1 gene; *PDHA1*, pyruvate dehydrogenase E 1 gene; *POLG*, polymerase γ 1 gene; RARS 2, arginyl-tRNA synthetase gene; *SLC19A3*, solute carrier family 19 member 3 (thiamine transporter); *TANGO* 2, transport and golgi organization 2 homolog gene.

[a]After the age of 24 months, the age of onset was rounded up/down to reflect years.

seizure types was myoclonic and focal motor seizures (n = 6). The other 16 patients had multiple seizure types including mixtures of generalized atonic, tonic–clonic, and clonic seizures. Some patients also had secondarily generalized tonic–clonic seizures. There were patients who only had a single seizure type (n = 14). Four patients had dyscognitive seizures, 2 had myoclonic seizures, 6 had focal motor seizures, 1 patient had generalized tonic seizures, and 1 patient had generalized tonic–clonic seizures.

The most frequent overall seizure semiology in the cohort was myoclonic seizures (n = 61) followed by generalized tonic seizures (n = 39). Focal seizures were also common, and the most common was focal motor seizures (n = 34). Patients with mitochondrial disease demonstrate both generalized and focal seizures and the majority have multiple seizure types (n = 71).

Status Epilepticus

Twenty-one patients developed episodes of status epilepticus. Interestingly, 19 of these patients possessed either mtDNA-encoded or nuclear-encoded gene mutations (Table 3). The majority were patients with Alpers-Huttenlocher syndrome (n = 12), with 7 other patients having a mixture of mtDNA-encoded and nuclear-encoded mutations. Two patients without a molecular diagnosis had status events. One patient had the biochemical findings of E3/lipoic acid biosynthesis defects and the other patient had a complex I defect with magnetic resonance imaging (MRI) findings compatible with mitochondrial encephalomyopathy, lactic acidosis, and stroke-like syndrome (MELAS).

There were 12 patients with *POLG* mutations and Alpers-Huttenlocher syndrome. All 12 of these patients developed status epilepticus. Seven patients presented with epilepsy partialis continua (EPC) as their initial seizure.[21] Three of these 7 patients also later developed motor status epilepticus. The remaining 4 patients had motor status epilepticus that occurred after seizure onset.

Three patients with mtDNA-encoded mutations developed status epilepticus. Two patients developed EPC in the context of metabolic strokes, with 1 patient having the classic m.3243A>G mutation for MELAS, while the other had the overlap syndrome of MELAS and Leigh syndrome with the m.14478T>C mutation. The third patient developed nonconvulsive status epilepticus and carried the m.14459A>G mutation. A third patient with the m.3243A>G mutation did not evolve into status epilepticus.

Status epilepticus was seen in 2 patients who possessed a nuclear-encoded mutation. One patient had motor status epilepticus with compound heterozygous mutations in the

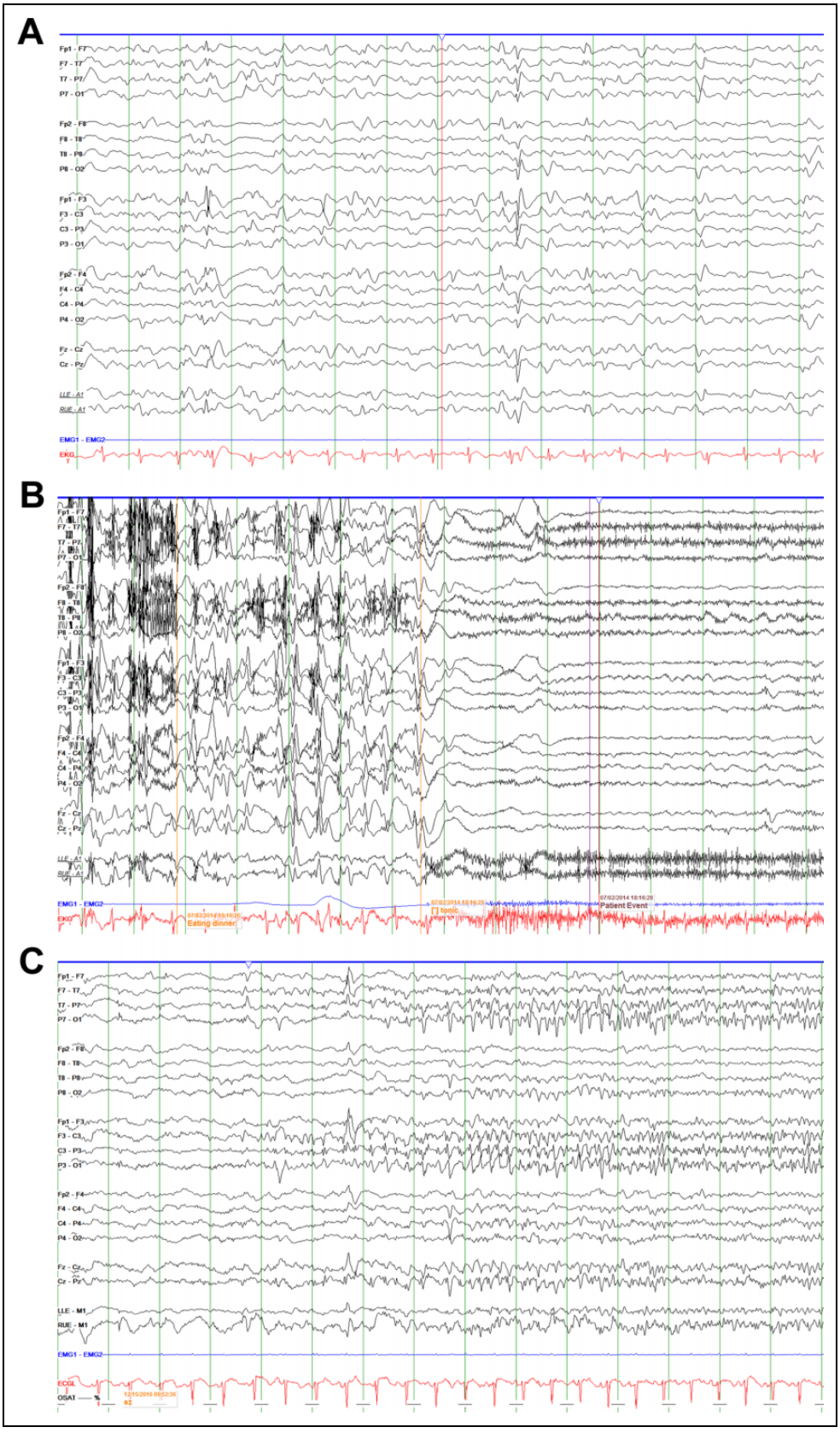

Figure 1. A, The electroencephalogram (EEG) pattern in panel A shows interictal epileptiform discharges over the left and right hemispheres with background slowing (multifocal spike discharges [MISD]). This EEG epoch is taken from a patient who had infantile spasms at 4 months of age. This EEG epoch represents the findings at age 12 years. Panel B: This EEG epoch is from the same patient at age 12 years showing a

Table 4. Seizure Medications Used for Seizure Control.[a,b]

Medication	Patients
Adrenocorticotrophic hormone	11
Carbamazepine	12
Clobazam	11
Ethosuximide	10
Felbamate	3
Ketogenic diet	21
Lacosamide	8
Lamotrigine	57
Levetiracetam	53
Oxcarbazepine	9
Phenobarbital	10
Prednisone	2
Phenytoin	4
Topiramate	24
Rufinamide	7
Valproic acid	18
Vigabatrin	9
Zonisamide	30

[a]This table indicates the individual seizure medications that each patient used during the course of this study.
[b]The range of seizure medications listed does not include those medications used to control status epilepticus or experimental medications used in clinical trials.

TANGO2 gene. The other patient developed nonconvulsive status epilepticus and had compound heterozygous mutations in the arginyl tRNA gene, *RARS 2*. Mutations were in trans for both patients with alterations segregating to biological parents.

Treatment

Treatment for seizure control is unsatisfying. No patient obtained seizure control with the initial seizure medication and multiple medications, both singly and in combination (Table 4). Currently, only 6 patients are in seizure control on medications with 0.5 to 14 years of seizure freedom. Two patients are taking monotherapy of lamotrigine. Both patients presented with MISD on the EEG. One of the patients had events described as dyscognitive with postictal behavioral changes, while the other had solely dyscognitive changes. The older patient has been seizure-free for 14 years. She initially failed ethosuximide and then transitioned onto topiramate therapy. Unfortunately, although seizures were controlled, she had behavioral side effects of cognitive slowing and regression in cognitive performance and subsequently switched to monotherapy of lamotrigine (Figure 2). She has remained in seizure control and her cognitive abilities greatly recovered. She has since won art contests, graduated from college, and is currently doing well in business. The second patient became seizure-free for the last 4 years on lamotrigine monotherapy. The third patient has been in seizure control on monotherapy of levetiracetam. This latter patient developed seizures at 1 month of age in the context of a fever and corona viral infection. Initially started on phenobarbital, he became-seizure free and switched to levetiracetam. He has been seizure-free for the last 6 months; he is currently 9 months of age. He was found to possess the mtDNA mutation, m.11778G>A. The other patients are on multiple antiseizure medications. Two of these latter patients are on the ketogenic diet and 2 traditional antiseizure medications. The other patient is on 3 antiseizure medications.

One patient was diagnosed with pyruvate dehydrogenase complex deficiency and was on the monotherapy of the ketogenic diet (4:1 ratio) until she died. She was already on the ketogenic diet when she transferred to our center. She was not completely seizure-free, but breakthrough seizures were infrequent, 2 to 3 per month.

The other 78 patients with seizures remain either uncontrolled or have died. Each has been on multiple medications, average of $4.3 + 0.9$ (range: 3-5) at any one time (Table 4). The range of medication numbers trialed was 1 to 11. Alternative methods of seizure control occurred due to poor control with traditional seizure medications. Twenty-one patients tried the ketogenic diet (varying ratio: 2:1-4:1). Seven of the 21 patients on the ketogenic diet had a favorable response with >75% seizure reduction (as noted on seizure diaries). Three of the responders were seizure-free, but due to compliance or quality of life issues were withdrawn from the diet. Two of the patients remaining on the diet are to date seizure free as noted above, while 2 others remain with seizures but with a reduction in seizure frequency.

There were 8 patients implanted with the vagus nerve stimulator. Five of these patients were previously reported by our group.[22] Three additional patients were eventually implanted with this device in hopes of gaining seizure control. As with the other 5 patients, these 3 patients had a limited response to vagal nerve stimulation. All 3 patients had multiple electron transport complex deficiencies.

There were 14 patients with infantile spasms (Table 2). Video EEG captured epileptic spasms in all patients. Three patients had seizures prior to epileptic spasm onset and started phenobarbital as the initial medication. Eleven of the patients received adrenocorticotropic hormone (ACTH) when spasms and hypsarrhythmia started. Five of the patients had resolution of epileptic spasms and hypsarrhythmia on EEG; however upon weaning ACTH, epileptic spasms returned. In the other

Figure 1. (*Continued*) generalized tonic seizure. At the onset of the seizure, the background becomes attenuated with the evolution of low amplitude theta frequencies after several seconds. The total time of the tonic seizure was 25 seconds (not shown). During the seizure, the patient stiffened all limbs. Panel C: An epoch taken from a patient who developed infantile spasms at the same age of the patient whose EEG is shown in Panel A. The EEG epoch was from a video EEG study at 14 years of age and demonstrating a focal motor seizure that begins over the left frontocentral region with the seizure increasing the distribution to the left lateral hemisphere. The seizure remained focal throughout the course of the seizure. The patient developed right upper extremity stiffening with a head turn to the left. Prior to the seizure, the EEG demonstrated a similar background of MISD as the patient shown in A (data not shown).

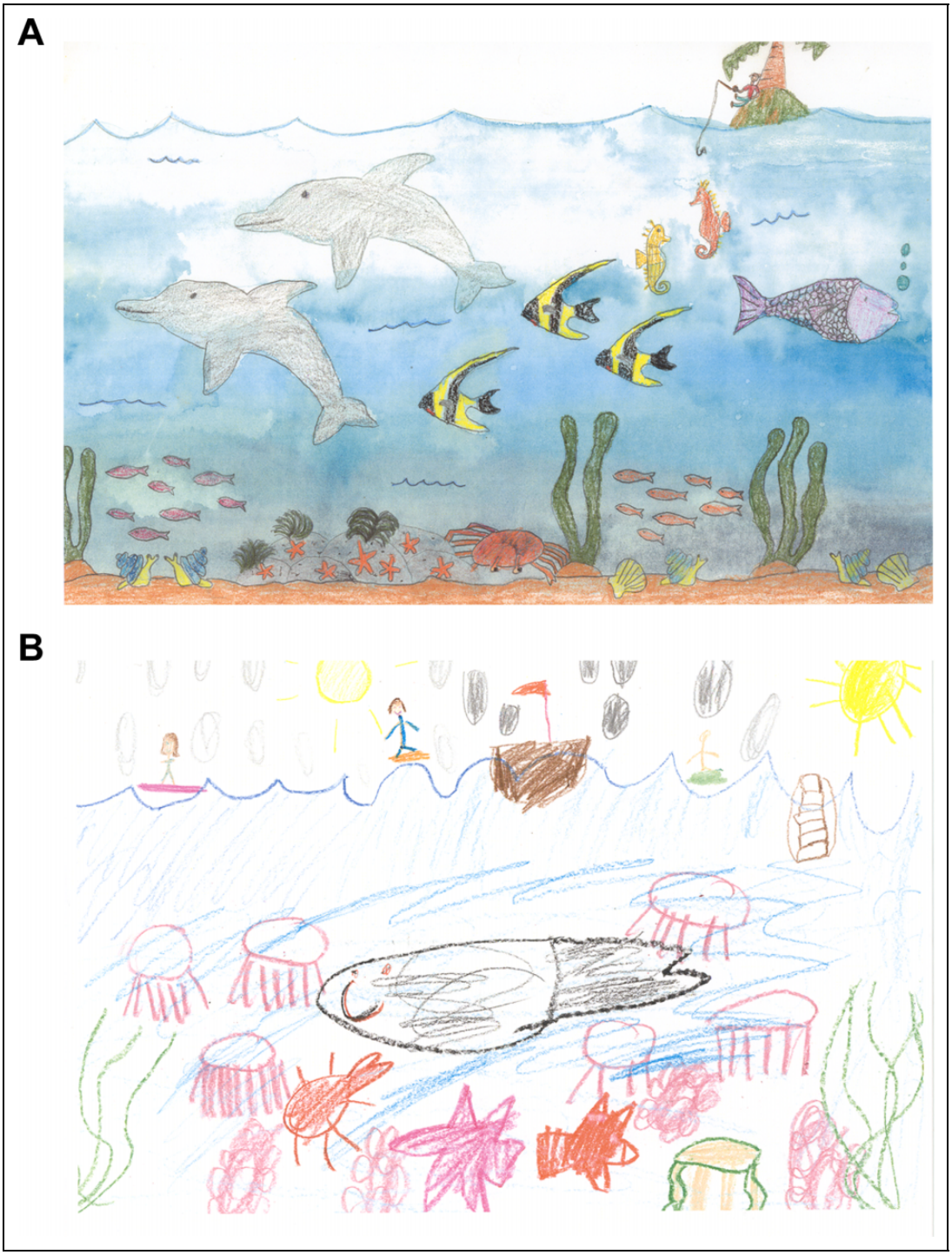

Figure 2. A, This picture shows a drawing by patient before being placed on topiramate monotherapy. At the time of this drawing, she was having dyscognitive seizures (atypical absence episodes with postictal changes). B, This picture shows a drawing by the same patient several months after starting topiramate monotherapy. Her seizures were well controlled at the time of the drawing. At the time of this drawing, the mother had noted that her daughter was cognitively slower and had difficulty in word finding.

6 patients given ACTH, there was no response. In all of these patients, vigabatrin was trialed without efficacy and was eventually withdrawn in all but a single patient, who had a mild reduction in seizure frequency. In the 3 patients who were not exposed to ACTH, vigabatrin, corticosteroids, zonisamide, and topiramate were initially trialed but without effect, and these medications were eventually stopped. Two patients enrolled in the Marinus Infantile Spasm Study, and neither patient responded to ganaxolone with epileptic spasm control. Six patients with epileptic spasms tried the ketogenic diet, with

currently only 2 patients on the diet. Of interest, 1 patient with complex III dysfunction became seizure-free on the monotherapy of the ketogenic diet for 5 years, but had to discontinue due to family issues (also described above). He, like all the other patients, currently remains with seizures. The average number of medications trialed was 6 (range: 3-9). Six patients in this population died during the course of this study, average age of death was 3.7 years (range: 1-5 years). The only patients who died of SUDEP were in the group with infantile spasms (Table 1).

The use of valproic acid is contraindicated in patients with Alpers-Huttenlocher syndrome.[17] Exposure to valproic acid can induce hepatopathy and progression to frank liver failure within as little as 4 to 6 weeks of exposure. Two patients with Alpers-Huttenlocher syndrome exposed to valproic acid died of liver failure. Another patient with Alpers-Huttenlocher syndrome progressed to liver failure without exposure to valproic acid. A second patient (Table 3; patient 1) with *POLG* mutations but with the syndrome of myocerebrohepatopathy spectrum died due to liver failure without exposure to valproic acid. Given the sensitivity to liver dysfunction with *POLG* mutations, valproic acid should be avoided in this patient population.

Discussion

In a single-cohort study of infants and children, of 174 patients with definite mitochondrial disease, over 48% had epilepsy. The prevalence of epilepsy was higher in the patients younger than 3 years compared to the older children and adolescents, 68% versus 32%. The high percentage of epilepsy and young age of seizure onset in mitochondrial disease have been seen in other studies.[4,5] Two studies have demonstrated rates of 65% (30 of 65 patients) and 55% (38 of 56 patients). Although in an adult cohort of patients with mitochondrial disease, only 23.1% had epilepsy with a mean age of onset at 29.4 years.[23] These data suggest that onset of epilepsy in patients with mitochondrial disease would follow the trend of other types of epilepsy presenting with higher prevalence during infancy and young childhood, compared to the adult population.[24]

There is a suggestion from the Seattle cohort that patients with epilepsy and mitochondrial disease have more severe disease. Earlier onset seizures coexisted with increased mortality compared to patients without epilepsy. Twenty-four patients with early-onset seizures died compared to only 5 patients without epilepsy. Using onset of seizures as the first clinical symptom, earlier onset of symptoms occurred in patients with epilepsy compared to patients without seizures, 2.9 versus 3.7 years, respectively. However, evidence exists that onset of other symptoms occurs earlier in patients with epilepsy than those without seizures.[5] Assuming the other symptoms besides epilepsy is occurring in our population, the likelihood for onset of disease is even more pronounced. Although our study had the limitation of insurance approval for obtaining genetic testing, more patients with early epilepsy onset had nuclear-encoded mutations compared to the overall group of patients with epilepsy (Table 3). Nuclear-encoded mitochondrial diseases are usually expressed earlier in life and are clinically more severe in nature.[7,25–27] Taken together, there is a strong suggestion that early-onset epilepsy in patients with mitochondrial disease portends more severe involvement of the disease. The more severe disease involvement early in life may be, in part, the decreased presence of epilepsy in the adult population.[23] Further investigations are needed to confirm this suggestion.

The age-dependent epileptic encephalopathy syndrome, infantile spasms, was seen in 14 patients (Table 2). The incidence in the general population has been estimated to be 1 per 3225.[28] It appears that this epilepsy syndrome is more common in mitochondrial disease than the general population. Infantile spasms was one of the most common of the classic epilepsy syndromes seen in the Seattle cohort; 17% of the patients with epilepsy developed infantile spasms. In this cohort, 13 patients had normal MRI scans of the brain; the exception was the patient with E3/lipoic acid deficiency with cortical dysplasia (data not shown). Although no mtDNA-encoded mutations were found, there were 2 nuclear-encoded pathological mutations found in our cohort. One patient had compound heterozygous mutations in *MTO1*, which has previously been reported.[29] The other patient had compound heterozygous mutations in *TANGO2*, which has been shown to be present in patients with seizures, but our patient would be the first one to be reported with infantile spasms.[30,31] Eleven of the other patients had defects in the ETC. Eight patients had single complex and 3 patients had multiple ETC complex defects (Table 2). One patient had an enzymatic profile and biochemical abnormalities consistent with E3/lipoic acid deficiency (noted above). Treatment was unsatisfying and all patients developed intractable seizures with an average of 5.4 medications per patient trialed. Mortality was high, and 6 patients died before the age of 6 years. Previous studies have been mixed with some showing a high percentage of patients with mitochondrial disease expressing infantile spasms, while others only limited numbers or none at all.[3,4,32] Given the data presented, as noted a decade ago, mitochondrial disease is most likely an underrecognized etiology of infantile spams and clinicians need to be aware of this possibility.[33]

The EEG pattern found in the cohort crossed genetic abnormalities, mtDNA or nDNA-encoded, seizure semiology, and age. The most common EEG pattern is MISD (84%), which in the vast majority remains a constant pattern over time and unchanging. Surprisingly, the EEG pattern seen in infantile spasms, hypsarrhythmia, evolved into the MISD pattern and did not change over time. Other studies have shown that the slow spike and wave pattern seen in Lennox-Gastaut syndrome can be seen in patients with mitochondrial disease; this was not seen in our cohort.[4] The reasons the slow spike and wave pattern not being seen in our cohort is unclear but suggests that Lennox-Gastaut syndrome is uncommon in mitochondrial disease. The patients in this study had mixed seizure types of focal seizures, generalized seizures, and noncerebral involuntary movements (eg myoclonus) with the same interictal pattern of MISD. The suggestion is that dysfunctional mitochondrial

physiology within the brain produces a predictable electrical interictal EEG pattern that is capable of heterogeneous ictal clinical expression.

One of the striking findings of our cohort is the high frequency of status epilepticus. Both EPC and status epilepticus were common (~24%). A high percentage was found in patients with Alpers-Huttenlocher syndrome, which is well described.[16,17] Most patients with MELAS or MELAS overlap syndrome developed status epilepticus. The single patient with the m.3243A>G mutation who did not develop status was treated during the initial stroke-like episode with L-arginine therapy. As with patients with Alpers-Huttenlocher syndrome, patients with MELAS develop status epilepticus multiple times.[34] In the other 3 patients who developed status epilepticus, the etiology of status epilepticus is unclear but, likely in part, relates to acute energy deprivation.

Treatment of seizures in mitochondrial disease is unsatisfying. Only a few patients gained seizure control by medical management and high-fat diet, but most were not. No patient had significant benefit from vagus nerve stimulation in our study. Clearly, the medications and electrostimulation currently available have little benefit to control seizures completely. Furthermore, certain medications had organ-specific toxicity. Valproic acid has been shown to induce liver hepatopathy and can lead to frank liver failure in patients with Alpers-Huttenlocher syndrome.[16,17,25] Further research is needed in seizure management and awaits novel agents to be discovered and trialed.

Seizure semiologies varied; both focal and generalized events coexisted in the same patient. There were multiple seizure types in most patients, including myoclonic, tonic, epileptic spasms, focal motor, atonic, dyscognitive, and tonic–clonic. Most all of the patients in this study have cognitive delay/intellectual disability (data not presented, paper in preparation). Combined with the EEG pattern of MISD, the findings in this study are very compatible with the epilepsy syndrome named Markand-Blume-Ohtahara syndrome. This epilepsy syndrome has been described as demonstrating an EEG showing MISD, very frequent multiple types of seizures, mental retardation, and poor prognosis for seizure control.[35] This syndrome is not part of the current ILAE list of epilepsy syndromes but would be classified as "structural–metabolic."[14] There are few patients who have exclusively generalized or focal seizures, suggesting that the seizure phenotype of mitochondrial disease can be quite variable. The etiology of the differences between generalized and focal seizures remains unclear. However, the variation in energy demand likely plays a part of seizure semiology expression.

One of the dilemmas concerning epilepsy and mitochondrial disease is that not all patients have seizures. If seizures are strictly due to energy depravation, then all patients with mitochondrial disease would have seizures. The reasons for the variable expression of epilepsy within similar abnormalities and common biochemical and/or genetic mutations, remain unclear. Epilepsy has been related to multiple genetic mutations, both mtDNA- and nDNA-encoded, that are involved in the direct energy production machinery, calcium maintenance, oxidative radical formation, and immunological and vitamin deficiencies.[36] The other influences on phenotypic expression of epilepsy remain unclear, which are environmental, risk/permissive genes, and other yet undiscovered factors. How the combination of factors alters the vulnerability of the young developing brain remains unclear. Hopefully, as our understanding of how these factors are integrated in producing the epileptic state and with possible new therapeutic agents entering into the field, the control of seizures will get better.

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