

Clinical Reasoning: A 10-month-old boy with myoclonic status epilepticus

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SECTION 1

A 10-month-old boy was transferred to our facility for workup and treatment of myoclonic status epilepticus. He was product of a healthy term pregnancy, born to nonconsanguineous parents, and was developmentally normal until the onset of myoclonic seizures at 8 months. Following this, developmental regression was noted. His myoclonic seizures were preceded by a febrile upper respiratory tract infection and involved the right upper and lower extremities for the first 5 weeks. However, all 4 extremities were eventually affected. His myoclonic seizures were reported to be resistant to IV lorazepam, levetiracetam, fosphenytoin, phenobarbital, IV immunoglobulin, a midazolam infusion, and pyridoxine. High-dose steroids (IV methylprednisolone for 4 days, followed by an oral prednisone taper) were subsequently initiated, with mild but unsustained attenuation of seizures. The ketogenic diet was also tried; this was discontinued secondary to intractable vomiting.

On presentation to our facility, the patient was observed to have nearly continuous myoclonic jerks,

predominantly involving the right upper extremity. EEG recording showed continuous generalized epileptiform discharges associated with body jerking, consistent with myoclonic status epilepticus. The myoclonic jerks persisted despite administration of prednisone, pyridoxal 5-phosphate, and lorazepam. The examination was limited due to medication effects; however, he was normocephalic and nondysmorphic. Funduscopic examination was normal. He was able to fixate and follow visually. Motor examination revealed diffuse hypotonia, although his reflexes were preserved and symmetric in all 4 extremities. General physical examination showed no skin findings and absence of hepatosplenomegaly. Family history was negative for neurologic disorders (including seizures).

Questions for consideration:

1. What is a myoclonic seizure?
2. What tests would you order?
3. What is the differential diagnosis of myoclonic status epilepticus in an infant?

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SECTION 2

Myoclonic seizures are defined as sudden, brief, involuntary jerking movements of the extremities arising secondary to a discharge from the brain. Our patient's history was suggestive of progressive myoclonic epilepsy which culminated in myoclonic status epilepticus.

The diagnostic possibilities for refractory myoclonic status epilepticus are metabolic encephalopathies (e.g., mitochondrial disease, multiple carboxylase deficiency, GLUT1 deficiency), storage diseases (including neuronopathic Gaucher disease, Tay-Sachs disease, Sandhoff disease, Canavan disease, and neuronal ceroid lipofuscinosis [NCL]), CSF tetrahydrobiopterin deficiency, genetic syndromes such as Angelman syndrome and Aicardi-Goutières syndrome, a supratentorial

structural lesion, and acute inflammatory encephalopathies.

The patient's hemoglobin was 10.9 (10.5–13.5) g/dL, platelet count 433 (150–450) $\times 10^9/L$, and leukocytes 18.7 (6–11) $\times 10^9/L$. The patient underwent lumbar puncture for CSF examination; this revealed a cell count of 2 cells/ μL , glucose of 69 mg/dL, and protein of 65 mg/dL. Liver function tests showed mild transaminitis (aspartate transaminase 168 U/L, alanine transaminase 87 U/L; reference range <50 U/L) and elevated total bilirubin at 8.1 mg/dL (normal 0.1–0.9 mg/dL). Serum ammonia and electrolytes were within normal limits. Lactate was elevated at 6.9 mmol/L in the serum (reference range 0.6–3.2 mmol/L) and 4.2 mmol/L in the CSF (reference range <2.2 mmol/L). Serum amino acid profile was normal and urine organic acid profile showed elevated secretion of lactic acid. This ruled out major disorders of amino acid metabolism and organic acidurias but raised the possibility of a mitochondrial disorder. CSF neurotransmitters (including tetrahydrobiopterin), pyridoxal 5-phosphate, and paraneoplastic panel were normal. Peroxisomal panel comprising very long chain fatty acids, phytanic acid, and pristanic acid was normal. Blood and CSF cultures were negative.

The patient underwent an MRI of the brain with gadolinium; this revealed no abnormalities. Magnetic resonance spectroscopy (MRS) revealed no elevation of brain lactate or NAA and normal creatine. Elevated NAA peak on MRS, macrocephaly, and loss of acquired skills are the characteristics seen in Canavan disease, also called Canavan-Van Bogaert-Bertrand disease (aspartoacylase deficiency). MRS results on our patients ruled this possibility out. Angelman syndrome is a genomic imprinting disorder (chromosome 15) characterized by abnormal facies, developmental delay, sleep disturbance, seizures, jerky movements, and usually a happy demeanor. We did not test our patient for this disorder as it usually presents a little later in life with developmental delay. Aicardi-Goutières syndrome is characterized by early-onset encephalopathy, hepatosplenomegaly, thrombocytopenia, abnormalities on cranial CT (calcification of the basal ganglia and white matter) and MRI (leukodystrophic changes), CSF pleocytosis, and mutations in one of the 4 known causative genes (*TREX1*, *RNASEH2A*, *RNASEH2B*, and *RNASEH2C*). Our patient lacked many of the clinical manifestations of this syndrome. Normal CSF glucose and lack of micro-

Figure Routine scalp EEG recording during myoclonic status epilepticus



(A) EEG (mastoid referential montage) showing 1- to 2-Hz generalized spike and wave discharges corresponding with myoclonic jerks (red arrows). (B) A longitudinal bipolar montage revealed that the discharges were maximal over bicentro-parieto-occipital regions.

cephaly in our patient made the possibility of GLUT1 deficiency unlikely.

His EEG revealed 1- to 2-Hz slow spike and wave discharges in a generalized distribution during his myoclonic jerks (figure, A), maximal over bicentroparieto-occipital regions (figure, B). No mutations or deletions were detected in the mitochondrial DNA. Genetic testing for NCL1 (*PPT1* gene) and NCL2 (*TPP1* gene) were negative. *POLG1* (pol- γ A) gene

testing showed 2 heterozygous mutations: c.1399G>A (P.A467T) in exon 6 and c.2740A>C (p.T914P) in exon 17.

Questions for consideration:

1. What is the diagnosis?
2. What other complications can develop in this condition?
3. Which medications should be avoided in this condition?
4. What is the overall prognosis?

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SECTION 3

The presence of 2 heterozygous mutations in the *POLG1* gene, along with the clinical picture of severe epileptic encephalopathy and liver disease, is suggestive of Alpers-Huttenlocher disease. The overall prognosis of this condition is poor. Most patients die by age 5 years, typically due to hepatic failure or intractable seizures. Valproic acid is contraindicated in these patients, as exposure to this medication can precipitate hepatic failure. Furthermore, carbamazepine, phenytoin, and vigabatrin should be avoided as they can exacerbate myoclonic seizures.

Our patient was started on antiepileptic medications topiramate and clonazepam and a mitochondrial cocktail comprising of coenzyme Q-10, levocarnitine, and riboflavin. These medications diminished (but did not eliminate) his myoclonic seizures. He was discharged home on hospital day 10. He was readmitted at age 12 months for intractable bleeding at his gastric tube site. His coagulopathy failed to respond to multiple infusions of fresh-frozen plasma. He subsequently died secondary to complications of hepatic failure. The parents did not consent for an autopsy.

DISCUSSION While the differential diagnosis of myoclonic seizures in infancy is broad, the combination of myoclonic status epilepticus, elevated lactate in both CSF and blood, and transaminitis suggested Alpers-Huttenlocher disease. This disorder was first described as a diffuse progressive degeneration of gray matter of cerebrum by Bernard Alpers¹ in 1931. It is also known as progressive neuronal degeneration of childhood and progressive infantile poliodystrophy. It is a rare autosomal recessive hepatocerebral disorder starting in infancy or childhood characterized by epilepsy (particularly epilepsy partialis continua), developmental regression, hypotonia, ataxia, cortical blindness, and hepatic dysfunction. The typical presentation involves a developmentally normal infant who, in the setting of intercurrent illness, develops myoclonic seizures, generalized seizures, or epilepsy partialis continua.²

Typical MRI findings include severe cerebral atrophy, white matter changes, or basal ganglia lesions mimicking stroke.² However, MRIs can be normal early in the course, as in our patient's case.

While the EEG pattern may vary, high-amplitude generalized slow waves mixed with lower amplitude polyspikes, often most prominent over the occipital lobes, are seen in most cases.^{3,4} Pathologic findings include neuronal loss in the cerebral gray matter in the brain and liver cirrhosis.^{3,5}

Most cases of Alpers-Huttenlocher disease are caused by recessive mutations in pol- γ A (*POLG1*). DNA polymerase- γ (pol- γ) is the only polymerase responsible for the synthesis and repair of mitochondrial

DNA in mammalian cells. Pol- γ is encoded by the nuclear *POLG1* gene; mutation of this gene results in profoundly decreased mitochondrial DNA copy numbers in affected tissues.^{6,7}

The spectrum of *POLG1* mutations is diverse. To date, approximately 150 mutations in this gene have been identified. Recessive mutations have been associated with progressive external ophthalmoplegia; mitochondrial recessive ataxia syndrome; sensory ataxic neuropathy, dysarthria, and ophthalmoparesis; some forms of Charcot-Marie-Tooth disease; and idiopathic parkinsonism. Dominant mutations have also been linked to PEO. The A467T mutation found in our patient is the most common disease causing mutation in *POLG1* and is commonly found in patients presenting with the Alpers phenotype.^{5,6}

There is no specific treatment for Alpers-Huttenlocher disease.⁸ Valproic acid is contraindicated in these patients, as exposure to this medication can precipitate hepatic failure.⁴ This can manifest several weeks after starting therapy and is often irreversible. As our case demonstrates, the prognosis in Alpers-Huttenlocher disease is poor. Most patients die by the age of 5 years, although rare survival into early adulthood has been described.⁹ Liver failure and intractable seizures are the most common causes of death.

DISCLOSURE

Dr. Dhamija and Dr. Moseley report no disclosures. Dr. Wirrell serves on the editorial boards of *Epilepsia*, *Canadian Journal of Neurological Sciences*, and *Journal of Child Neurology*; and receives research support from the Mayo Foundation.

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