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

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?
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) × 10^9/L, and leukocytes 18.7 (6–11) × 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 transaminis (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-
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 (TPPI gene) were negative. POLG1 (pol-γA) 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?
DNA polymerase—

- the brain and liver cirrhosis.\(^3\),\(^5\)

include neuronal loss in the cerebral gray matter in
cased by recessive mutations in pol-

rophy, white matter changes, or basal ganglia lesions
lobes, are seen in most cases.\(^3\),\(^4\) Pathologic findings
polyspikes, often most prominent over the occipital
waves mixed with lower amplitude
of fresh-frozen plasma. He subsequently died sec-
ary 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 Alpers\(^1\) 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 epi-
lepsia partialis continua), developmental regression, hy-
potonia, ataxia, cortical blindness, and hepatic
dysfunction. The typical presentation involves a develop-
mentally normal infant who, in the setting of inter-
current illness, develops myoclonic seizures, generalized
seizures, or epilepsia partialis continua.\(^2\)

Typical MRI findings include severe cerebral at-
rophy, white matter changes, or basal ganglia lesions mimicking stroke.\(^3\) 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.\(^5\)

Most cases of Alpers-Huttenlocher disease are
caused by recessive mutations in pol-γA (POLG1). DNA polymerase-γ (pol-γ) is the only polymerase re-
sponsible for the synthesis and repair of mitochondrial
DNA in mammalian cells. Pol-γ is encoded by the nu-
clear POLG1 gene; mutation of this gene results in pro-
foundly 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 asso-
ciated with progressive external ophthalmoplegia;
mitochondrial recessive ataxia syndrome; sensory
ataxic neuropathy, dysarthria, and ophthalmoparesis;
some forms of Charcot-Marie-Tooth disease; and id-
iopathic 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 adult-
hood has been described.\(^9\) Liver failure and intractable
seizures are the most common causes of death.

**DISCLOSURE**

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