Clinical Reasoning:

A 2-day-old baby girl with encephalopathy and burst suppression on EEG

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SECTION 1

A 2-day-old baby girl was transferred to our facility for evaluation and management of seizures. She was born to nonconsanguineous parents from Somalia at 41 $\frac{5}{7}$ weeks of gestation. The pregnancy was uneventful. The mother was group B streptococcus-positive and was appropriately treated with antibiotics during labor. Labor and vaginal delivery were uncomplicated (no history of prolonged rupture of membranes or birth trauma). The baby's Apgar scores were 9 at 1 and 5 minutes. The baby appeared to be well on the first day of life but began having seizures on the second day.

On presentation to our facility, the patient exhibited rhythmic jerking movements of her extremities, consistent with myoclonic seizures. She also had multiple apneic episodes and was therefore intubated and mechanically ventilated. EEG recording showed an asynchronous burst suppression pattern with occasional

generalized epileptiform discharges that were associated with body jerking, consistent with severe encephalopathy with seizures. On general physical examination, she was normocephalic and nondysmorphic. There were no abnormal skin findings and no hepatosplenomegaly. Neurologic examination revealed diffuse hypotonia with symmetrically hypoactive reflexes in all 4 extremities. Bedside funduscopic examination revealed normal Moro; suck and rooting reflexes were poor, but palmar grasp reflex was present bilaterally.

There was no family history of neurologic or metabolic disorders (including seizures).

Questions for consideration:

1. What is the differential diagnosis for neonatal seizures?
2. Does the burst suppression pattern on EEG limit the differential diagnosis?
3. Can this infant's presentation be classified as an epilepsy syndrome?

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SECTION 2

The diagnostic possibilities for neonatal seizures are broad and include common causes such as electrolyte imbalance (hypocalcemia, hypomagnesemia, hyponatremia, or hypoglycemia), hypoxic ischemic encephalopathy, neonatal stroke (ischemic or hemorrhagic), maternal drug withdrawal, benign neonatal seizures, and infectious diseases (e.g., group B streptococcus sepsis or meningitis) and less common but important causes such as metabolic encephalopathies (e.g., mitochondrial disease, organic acid disorders, amino acid disorders, sulfite oxidase deficiency, molybdenum cofactor deficiency, and glucose transporter 1 deficiency), storage diseases (including neuronopathic Gaucher disease, Tay-Sachs disease, and neuronal ceroid lipofuscinosis), CSF tetrahydrobiopterin, folate deficiency, pyridoxine deficiency, and a supratentorial structural lesion (table e-1 on the *Neurology*[®] Web site at www.neurology.org). The presence of burst suppression on EEG suggests severe encephalopathy

and either a significant hypoxic-ischemic insult or a severe metabolic disorder.

The patient's hemoglobin was 15.3 (10–20) g/dL, platelet count was 281 (150–450) $\times 10^9$ /L, and leukocyte count was 11.2 (5–20) $\times 10^9$ /L. Blood glucose was 102 mg/dL. The patient underwent lumbar puncture for CSF examination; this revealed a white blood cell count of 3 cells/ μ L, glucose of 54 mg/dL, and protein of 50 mg/dL. Results of blood and CSF cultures were negative. Liver function tests showed that aspartate transaminase, alanine transaminase, and total bilirubin levels within normal limits. Serum ammonia and lactate levels and values for a complete electrolyte panel were normal. Given the initial normal electrolytes and no evidence of hypoxic-ischemic encephalopathy or infection at birth, a metabolic disorder was considered. Urine organic acid levels, serum biotinidase activity, a serum acyl-carnitine panel, a chromosomal microarray, and a serum peroxisomal panel composed of very-long-chain fatty acids, phytanic acid, and pristanic acid were all normal. Serum and CSF amino acid profiles showed markedly elevated glycine, with a CSF/serum ratio of 0.138 (normal <0.03), which was diagnostic for nonketotic hyperglycinemia.

The infant's seizures can be classified as early myoclonic encephalopathy, a symptomatic epilepsy syndrome characterized by seizure onset between birth and the first few weeks of life and burst suppression on EEG. The overall prognosis for this epilepsy syndrome is poor with high mortality in the first few years of life.

Results of a head ultrasound examination were normal. MRI of the brain without gadolinium done at day 3 of life showed agenesis of the corpus callosum and an immature sulcation pattern. There was no evidence of hypoxic-ischemic injury on diffusion-weighted imaging or any evidence of intracranial hemorrhage. Magnetic resonance spectroscopy revealed no elevation of brain lactate or *N*-acetylaspartate and normal creatine but showed an elevated glycine peak (figure).

Questions for consideration:

1. What are the medications used to treat this condition?
2. Which specific antiepileptic medications should be avoided in this condition?
3. What is the overall prognosis?

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(A) MRI (T1 sagittal) shows agenesis of corpus callosum (arrow). (B) Magnetic resonance spectroscopy shows a glycine peak (G), *N*-acetylaspartate (NAA), choline (Cho), creatine (Cr), and myoinositol (ml). (C) EEG shows burst suppression.

SECTION 3

The elevated ratio of CSF to serum glycine (>0.08) confirms the diagnosis of nonketotic hyperglycinemia (NKH). Patients with atypical NKH can have ratios between 0.03 and 0.08. A liver biopsy was not performed in our patient for confirmatory enzymatic analysis because the parents did not consent. Our patient's seizures were initially controlled with IV phenobarbital but then recurred. A ketamine (NMDA receptor antagonist) drip and sodium benzoate (an agent that binds excessive glycine in the CSF) were started, which resulted in control of seizures. High doses of sodium benzoate can lower the serum carnitine concentration and thus blood levels of carnitine should be measured and supplemented accordingly.

She was weaned off phenobarbital, given its potential to cause respiratory suppression, and transitioned to topiramate. She was slowly weaned off mechanical ventilation. A gastric tube was placed, given her continued poor feeding.

Valproate should be avoided in infants with NKH because it increases blood and CSF glycine concentrations by further inhibiting the glycine cleavage enzyme and increases seizure frequency.¹ As a general rule, valproate should not be used in any child with an undiagnosed suspected metabolic disorder because it can worsen seizures due to urea cycle disorders, fatty acid oxidation defects, and mitochondrial disorders. Given the higher likelihood of a metabolic disorder being the underlying cause of seizures in younger children, valproate is typically avoided in children younger than 2 years.

The overall prognosis for NKH is dismal. Most patients die in infancy of central apnea, if they are not supported by mechanical ventilation. Intractable seizures and feeding problems are common. Those who survive are left with severe intellectual disability.

At the last follow-up at 4 months of age, our patient continues to have diffuse hypotonia, no social smile, and poorly controlled seizures and is dependent on a gastric tube for feeding.

DISCUSSION NKH, also known as glycine encephalopathy, is an autosomal recessive metabolic disorder characterized by the accumulation of glycine in the brain due to a defect in the glycine cleavage enzyme system. The neonatal form presents in the first few days of life with progressive lethargy, hypotonia, hiccups, and seizures, and progresses to central apnea and often death. Surviving infants often have profound developmental delay and intractable seizures. The infantile form presents in the first few months of life and is also characterized by hypotonia, developmental delay, and seizures. An increased CSF glycine

level (typically 20–30 times normal) along with an elevated CSF/plasma glycine ratio suggests the diagnosis. Enzymatic confirmation can be done by measurement of glycine cleavage (GCS) enzyme activity in liver obtained by biopsy and is clinically available. The 3 genes known to be associated with NKH are *GLDC* (encoding the P-protein component of the GCS complex, accounting for 70%–75% of disease), *AMT* (encoding the T-protein component of the GCS complex, accounting for ~20% of disease), and *GCSH* (encoding the H-protein component of the GCS complex, accounting for <1% of disease). Mutations associated with residual enzyme activity seem to be associated with a milder outcome and infantile presentation, and 2 mutations with no residual enzyme activity seem to be associated with severe outcome and neonatal onset.^{2–4}

The initial EEG typically shows a burst-suppression pattern that evolves into hypsarrhythmia or multifocal spikes over the next few months. MRI can be normal or show agenesis of the corpus callosum. Delayed myelination can be seen later in life. Agenesis of the corpus callosum is not specific and can be seen in various migrational and structural disorders of the CNS (e.g., Dandy-Walker malformation and lipoma of the interhemispheric fissure).⁵ Less common findings include retrocerebellar cysts with subsequent hydrocephalus.⁶ A glycine peak on magnetic resonance spectroscopy is seen in the most severely affected infants and carries a poor prognosis.

No effective treatment exists for this disorder. Therapy is focused on managing seizures by using sodium benzoate to reduce the plasma concentration of glycine. NMDA receptor antagonists (ketamine, dextromethorphan, felbamate, and topiramate) are also used in this condition.⁷

AUTHOR CONTRIBUTIONS

R.D. provided the study concept or design. R.D. acquired data. R.D. and K.J.M. drafted/revised the manuscript. K.J.M. supervised the study.

DISCLOSURE

Dr. Dhamija reports no disclosures. Dr. Mack serves on the editorial board of *Pediatric Neurology*, *Journal of Child Neurology*, and *Brain and Development* (2006–present) and is Book Review Editor for *Neurology*®.

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Neurology 2011;77:e16-e19

DOI 10.1212/WNL.0b013e318225aae3

This information is current as of July 18, 2011

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