

Folinic Acid–Responsive Seizures Presenting as Breakthrough Seizures in a 3-Month-Old Boy

ABSTRACT

Neonatal seizures associated with white-matter changes on neuroimaging suggest an etiology of hypoxic-ischemic encephalopathy. Metabolic and idiopathic etiologies are also considerations but are less likely. Despite the fact that two disorders associated with neonatal seizures are diagnosed by cerebrospinal fluid neurotransmitter analysis, such an analysis is not standard in the work-up for idiopathic neonatal seizures. We describe an infant who had a prolonged delivery, seizures on the first day of life, and white-matter changes on neuroimaging. A progressive seizure disorder that was refractory to standard antiepilepsy medications developed at 2 months of age. Analysis of cerebrospinal fluid neurotransmitters at that time demonstrated a pattern consistent with folinic acid–responsive seizures. Seizures ceased 24 hours after starting folinic acid. Serial neuroimaging, electroencephalograms, and metabolic changes from this patient are presented. This case illustrates the importance of cerebrospinal fluid neurotransmitter analysis as part of the work-up for idiopathic neonatal seizures. (*J Child Neurol* 2003;18:562–569).

Neonatal seizures are a distinctive signal of neurologic disease.¹ Hypoxic-ischemic encephalopathy is the most common on the list of possible diagnoses, especially if neuroimaging demonstrates abnormalities in the white matter or deep nuclei of the brain. Although diffusion-weighted imaging and magnetic resonance spectroscopy have improved the differentiation between hypoxic-ischemic encephalopathy and metabolic diseases, these examinations are often equivocal. A comprehensive metabolic work-up is standard in such situations but can also be equivocal. Often the neurologist has no choice but to follow a patient clinically.

New syndromes based on cerebrospinal fluid analysis of neurotransmitters have been described.² For example, aromatic L-amino acid decarboxylase deficiency can present with intractable seizures on the first day of life. Cerebrospinal fluid must be obtained for neurotransmitter analysis to detect the diagnostic increase in 3-O-methyldopa.³ Since the first description of folinic acid–responsive seizures in 1995,⁴ only a handful of cases have been reported.^{5,6} The incidence and etiology of this disorder are still unknown. However, in 40 neonates with seizures, 8 cerebrospinal fluid samples were found to have the distinctive pattern of unknown compounds suggestive of folinic acid–responsive seizures.⁶ Thus, this disorder might not be as rare as previously believed.

In this case report, we describe an infant with a history of neonatal seizures and white-matter changes on neuroimaging. Although the infant did well immediately after the neonatal period, a recurrent progressive seizure disorder refractory to standard antiepilepsy medications developed at 2 months of life. An analy-

sis of the patient's cerebrospinal fluid neurotransmitters at 3 months of life identified the distinctive pattern seen in folinic acid–responsive seizures. Addition of folinic acid to the patient's treatment regimen resulted in cessation of seizures. However, 10 days later, a multisystem illness, including enteroviral meningitis, evoked status epilepticus. A subsequent episode of status epilepticus eventually led to the patient's demise. This case illuminates the importance of cerebrospinal fluid testing for neurotransmitters in the setting of neonatal seizures of unknown etiology. In addition, serial magnetic resonance imaging (MRI), electroencephalograms (EEGs), and metabolic tests demonstrate the nonspecific findings of this disorder.

Case Description

Birth History

The patient was born at 39 weeks' gestation to a 25-year-old gravida 2, para 1 mother after a pregnancy complicated by spotting at 8 weeks' gestation. The patient's mother denied use of alcohol, tobacco, or medications during the pregnancy. Fetal movements were normal, but fetal hiccoughing for several weeks prior to the delivery was reported in retrospect. Membranes were ruptured 15 hours prior to delivery. Group B streptococcus screening was positive, and clindamycin was given 4 hours prior to delivery. The patient was born via nonemergent cesarean section owing to failure of labor to progress. Apgar scores were 8 and 9 at 1 and 5 minutes, respectively, and birthweight was 3.6 kg (35th percentile). Bilateral lower-extremity clonic movements with associated apnea and cyanosis began at 9 hours of life, prompting transfer to the special nursery.

Phenobarbital 30 mg/kg was given to control the seizures. Complete blood count, electrolytes, calcium, magnesium, phosphorus, ammonia, toxicity screen, cerebrospinal fluid cell count (18 red blood cells/ μ L, 4 white blood cells/ μ L), protein (126 mg/dL), and glucose (56 mg/dL, 76% of blood glucose) were normal. However, bicarbonate was low (10 mEq/L), serum lactic acid was high (9.7 mmol/L), and aspartate transaminase was slightly high (85 U/L). Arterial pH (7.32), carbon dioxide partial pressure (32 mm Hg), and oxygen partial pressure (87 mm Hg) were low, and a base deficit (9.6) was present. An EEG demonstrated excessive discontinuity for age and frequent multifocal sharp waves in the frontotemporal and central regions bilaterally. The patient was transferred to the neonatal intensive care unit at Children's Hospital Boston on the third day of life.

Neonatal Intensive Care Unit

Vital signs and growth parameters were normal on admission (weight 3.6 kg, 35th percentile; length 53 cm, 75th percentile, head circumference 36 cm, 50th percentile). The patient was alert, irritable, and extremely jittery. General physical examination demonstrated large right preauricular and small left cheek skin tags and micrognathia. Cranial nerves were normal, but extremity tone and deep tendon reflexes were increased with bilateral ankle clonus. Moro's reflex was hyperactive, with all other primitive reflexes intact.

The family history was significant for progressive neurosensory hearing loss in the father, paternal grandfather, and paternal great-grandfather. The patient's ethnic background was mixed, with no known consanguinity.

An EEG on the third day of life demonstrated frequent electrographic seizures arising from the left temporoparietal region and periods of discontinuity (Figure 1, A and B). Phenobarbital was maintained at a level of 40 μ g/mL, and fosphenytoin was added and kept at a level of 20 μ g/mL. Repeat EEG on the fifth day of life revealed significant discontinuity, which was not sufficiently explained by the anticonvulsant levels (Figure 1C). MRI on the sixth day of life (Figure 2, A–E) demonstrated T₂-weighted prolon-

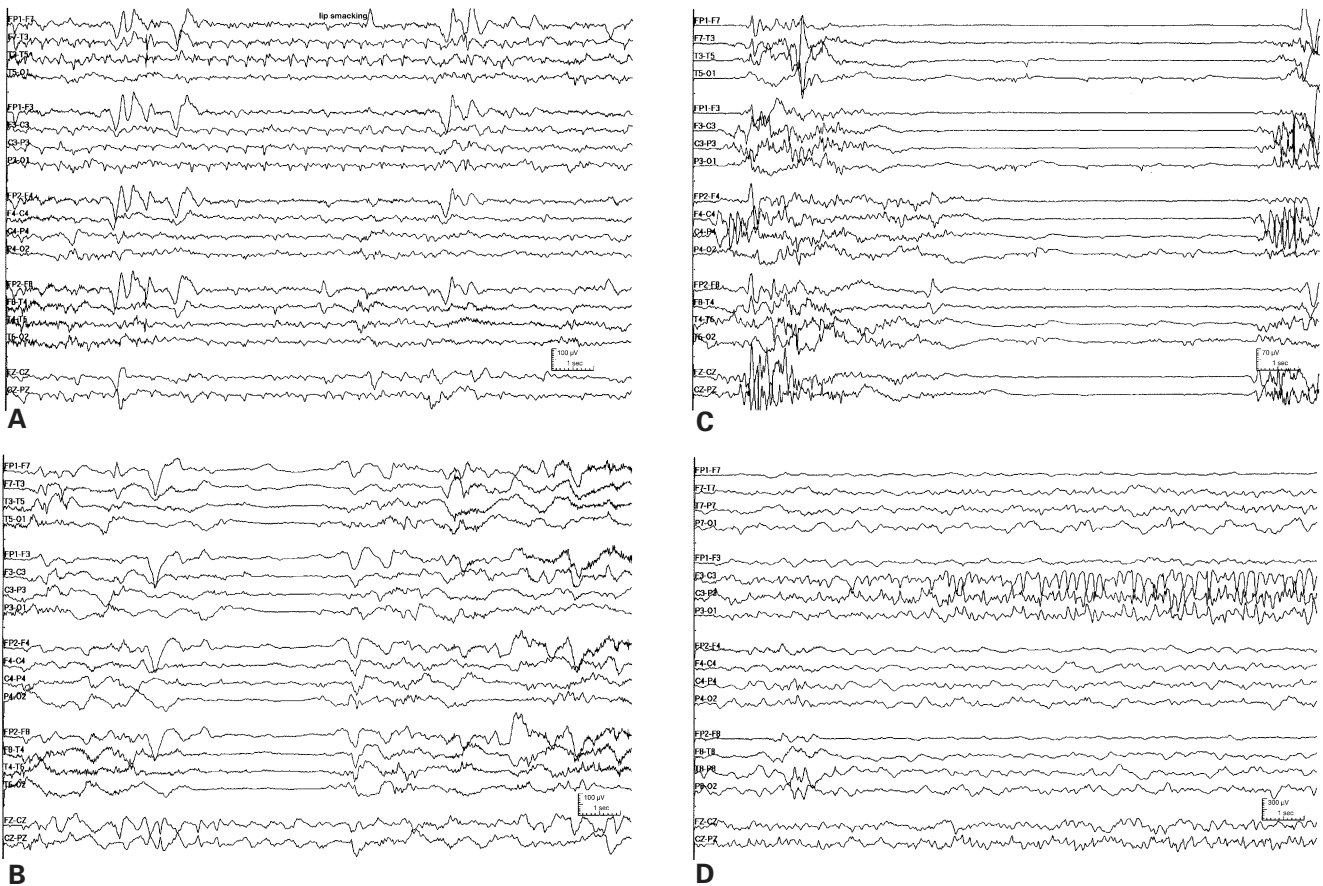


Figure 1. Electroencephalograms. *A*, Left hemisphere seizure, age 3 days. *B*, Discontinuity, age 3 days. *C*, Excessive discontinuity, age 5 days. *D*, Left hemisphere seizure, age 2.5 months.

gation in the white matter diffusely. There was also evidence of a partial lack of myelination within the periorlandic region and posterior limb of the internal capsule bilaterally. Prolonged T_1 - and T_2 -weighted signal, without susceptibility artifact on gradient images, was identified superolateral to the posterior aspect of the right lateral ventricle. Subtle foci of abnormal T_1 -weighted signal were present within the subcortical parietal white matter, left greater than right. Ventricles were slightly asymmetric. Diffusion-weighted images were normal. Magnetic resonance spectroscopy obtained from the left basal ganglia and right parietal white matter demonstrated a small lactate peak of unclear significance. EEG on the eighth day of life demonstrated frequent epileptiform discharges in the bilateral temporal areas and excess discontinuity with hemispheric asynchrony. However, no seizures were noted, and state changes, previously absent, were present. Fosphenytoin was stopped. The degree of jitteriness decreased throughout the hospital stay and was minimal at discharge. The patient was discharged on 5 mg/kg/day of phenobarbital.

Ampicillin, gentamicin, and acyclovir were given until bacterial cultures and cerebrospinal fluid, herpes simplex virus, and polymerase chain reaction were negative. Electrolytes and complete blood count remained normal. Brain auditory evoked response demonstrated possible mild left neurosensory hearing loss. A genetics evaluation, which included cervical spine films, renal sonograms, and karyotype, was normal.

A metabolic work-up on the sixth day of life revealed a normal serum ammonia, acylcarnitine profile, and newborn screen. Urine organic acids contained unknown compounds. Serum and cerebrospinal fluid lactate were normal, but pyruvate was low in both serum and cerebrospinal fluid, and the lactate-to-pyruvate ratio was high in both serum and cerebrospinal fluid (Table 1). Serum amino acids were normal except for low aspartic acid (1 $\mu\text{mol/L}$, normal = 3–17 $\mu\text{mol/L}$), methionine (10 $\mu\text{mol/L}$, normal = 14–61 $\mu\text{mol/L}$), isoleucine (7 $\mu\text{mol/L}$, normal = 14–91 $\mu\text{mol/L}$), tyrosine (18 $\mu\text{mol/L}$, normal = 19–131 $\mu\text{mol/L}$), and lysine (36 $\mu\text{mol/L}$, normal = 54–271 $\mu\text{mol/L}$). Cerebrospinal fluid glycine and ratio

of cerebrospinal fluid to plasma glycine were high (23.9 nmol/mL, normal = 5.8–9.5 nmol/L; and 0.1, normal < 0.06, respectively). Several other cerebrospinal fluid amino acids were abnormal (Table 2). On the eighth day of life, cerebrospinal fluid glycine was slightly high (10.1 nmol/mL), but the ratio of cerebrospinal fluid to plasma glycine normalized (0.03) (see Table 2). Serum amino acids on that same day were normal.

Outpatient Course After Neonatal Intensive Care Unit Admission

At 1 month of age, the patient had no further seizures, was feeding and growing well, and established a normal sleep-wake cycle. He visually fixed, smiled, cooed, and recognized voices but did not visually track well. Mild hemifacial microsomia with the right mandible being slightly smaller than the left was noted. Neurologic examination was significant for mild axial weakness, minimal jitteriness, and brisk deep tendon reflexes. The phenobarbital was weaned over the next month.

The patient's jitteriness increased as the phenobarbital was tapered. At 2 months of age, a 5-minute generalized seizure, characterized by rhythmic twitching of slightly flexed arms and legs with right head and eye deviation, occurred. The patient was reloaded with phenobarbital at a local hospital. Two weeks later, a similar 3-minute generalized seizure occurred. Following this seizure, the infant became unusually irritable during the day. A repeat EEG was normal in the awake and sleep states.

Approximately 1 week later, the patient had another generalized seizure that was stopped with diazepam 2.5 mg by rectum. Two days later, another generalized seizure was again stopped with diazepam 2.5 mg by rectum. Three days prior to admission, an MRI (Figure 2, F and G) demonstrated an asymmetry in the size of the lateral ventricles and diffuse white-matter volume loss surrounding the lateral ventricles without evidence of delayed myelination. Magnetic resonance spectroscopy of the left basal ganglia and the right posteroparietal white matter was normal. On the day of admis-

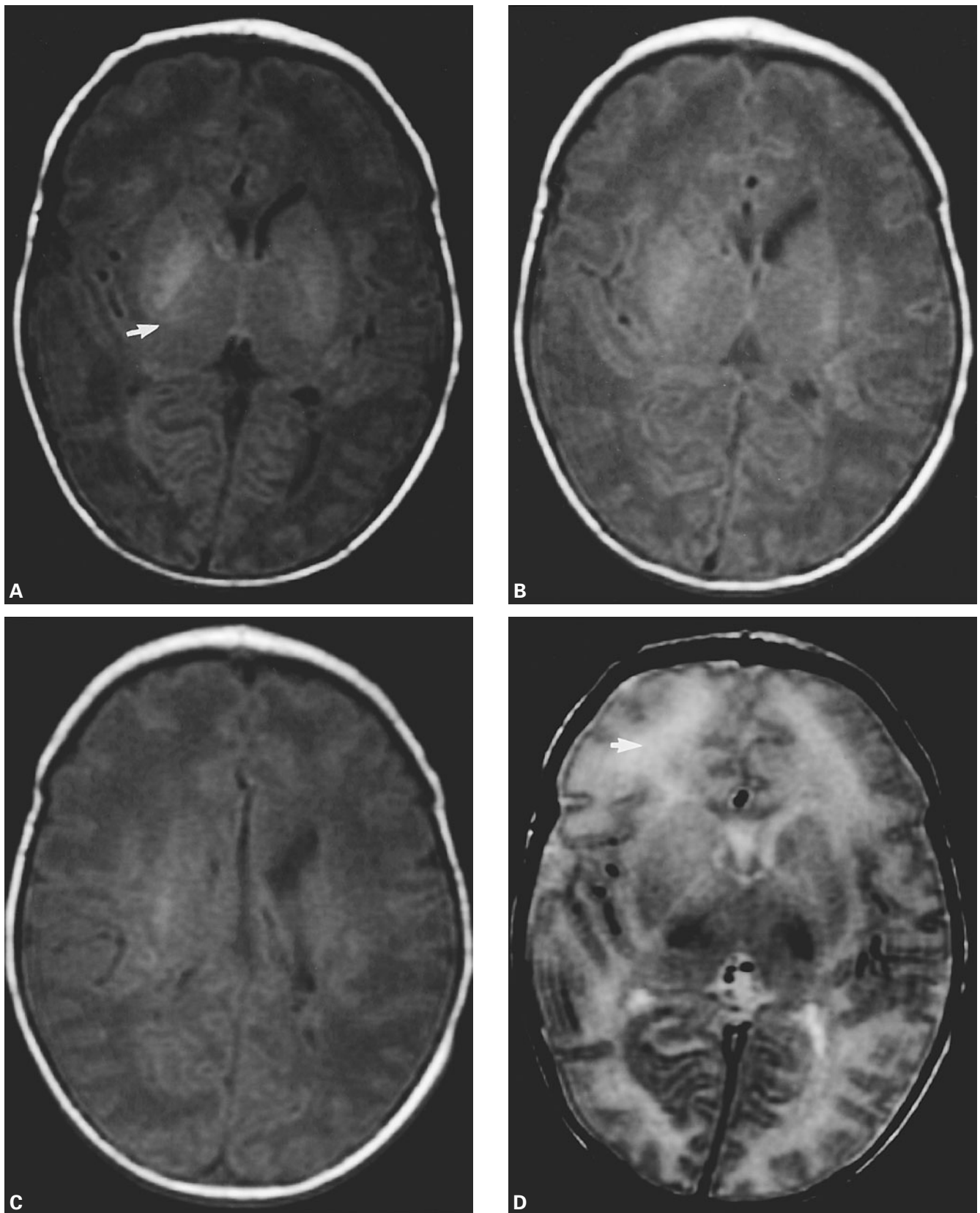


Figure 2. Magnetic resonance imaging. *A to C*, Axial T_1 -weighted images of the brain obtained at 5 days of age. Lateral ventricle asymmetry, left greater than right, is noted, as well as bilateral hypomyelination in the posterior limb of the internal capsule, basal ganglia, lateral thalamus (*white arrow*), and periorlandic white matter. *D to F*, Axial fast spin-echo T_2 -weighted images of the brain obtained at 5 days of age. Diffuse subtle T_2 -weighted hyperintensity is present throughout the frontal and parietal white matter (*white arrow*). Again noted is asymmetry in the size of the lateral ventricles and hypomyelination bilaterally in the posterior limb of the internal capsule and periorlandic white matter.

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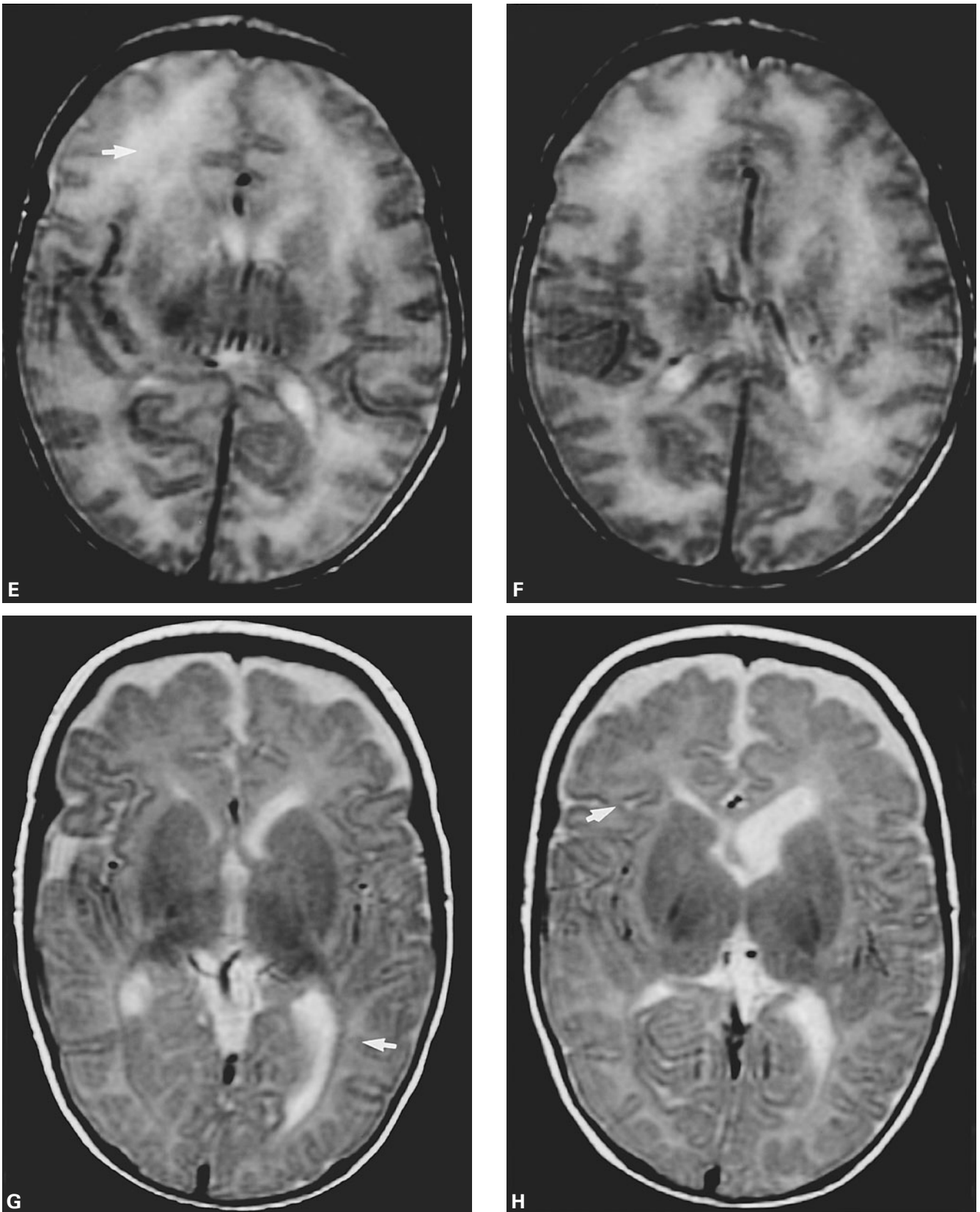


Figure 2. (Continued) G to J, Axial fast spin-echo T_2 -weighted images of the brain obtained at 3 months of age. Previously appreciated subtle diffuse white-matter T_2 -weighted hyperintensity is no longer seen, consistent with progressive myelination, but new evidence of volume loss within the periventricular white matter is present since the prior examination. Loss of white-matter volume is present in multiple areas, with the gray matter closely approximating the lateral ventricles (*white arrows*). The lateral ventricles remain asymmetric, and there has been a slight interval increase in their size. Prominence of the sulci is also seen. *Continued on next page*

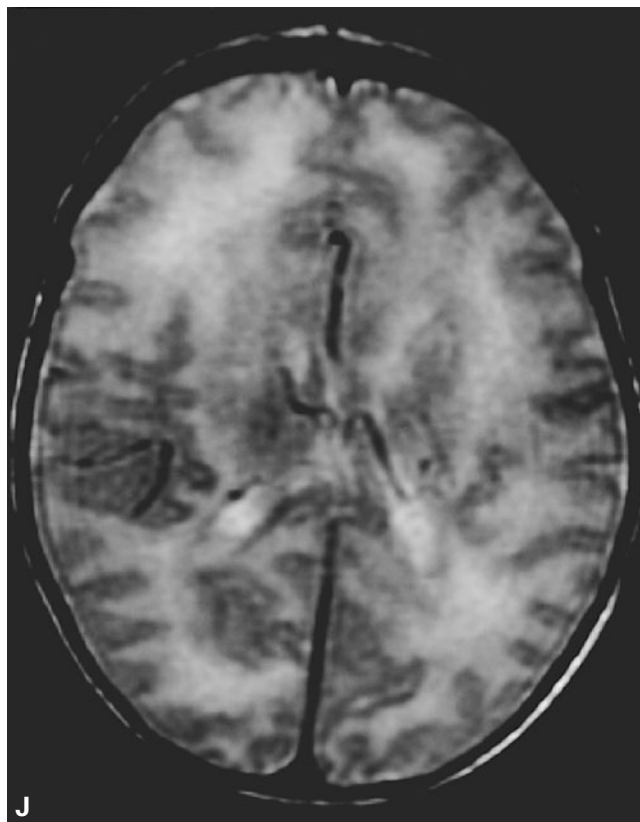
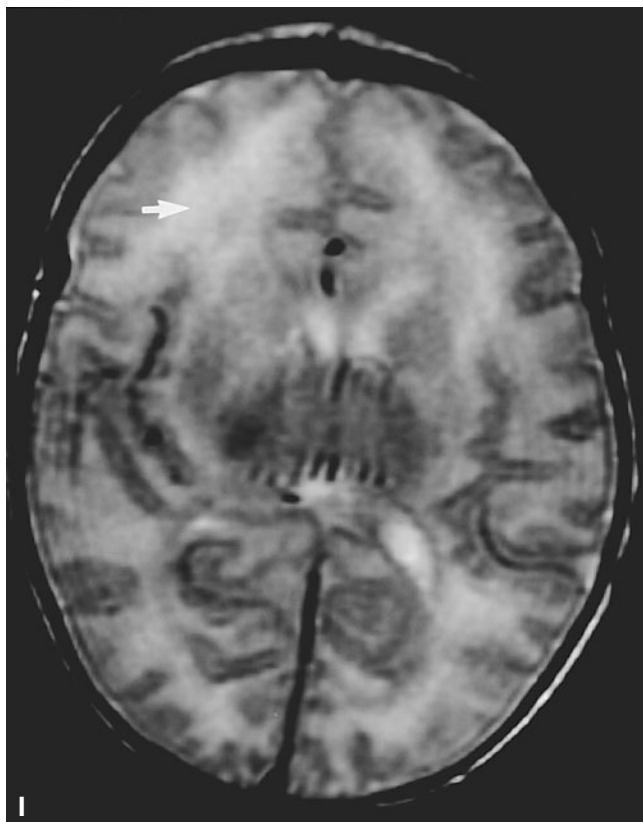


Figure 2. (Continued)

sion, the patient developed a focal seizure with right arm twitching and right eye deviation.

Hospital Admission at 3 Months

The patient's growth was greater than expected (weight 8.3 kg, > 95th percentile; length 62 cm, 95th percentile; head circumference 42.5 cm, 80th percentile). The patient was awake and alert, smiling and cooing, but did not visually track well and responded inconsistently to auditory stimulation. Examination of the cranial nerves revealed preferential deviation of the head and eyes to the right but full extraocular movements without nystagmus. The left nasolabial fold was slightly flattened with cry, but sucking and rooting reflexes were normal. Motor examination revealed greater quality and quantity of movements in the left extremities compared with the right. The right leg was kept externally rotated, and the right hand was kept closed without cortical thumbing. Axial tone was decreased more than appendicular tone, and strength was mildly reduced throughout. Deep tendon reflexes were normal except for sustained right ankle clonus. Moro's reflex was inconsistent, and step and place reflexes were present only on the left.

A comprehensive metabolic work-up was initiated (Table 3). An EEG demonstrated slow background activity, multifocal sharp waves, and an electrographic seizure arising from the left central region. Clinically, the seizure was characterized by rhythmic jerking of the right hand with right eye deviation, which progressed to tonic stiffening of the right side (see Figure 1D).

Supplemental vitamins were started: thiamine 50 mg by mouth every day, riboflavin 50 mg by mouth every day, pyridoxine 5 mg by mouth every day, and cyanocobalamin 1 mg by mouth every day. Increasing the serum phenobarbital level to 40 $\mu\text{g}/\text{mL}$ controlled the seizures for several days, prompting discharge.

Postadmission Course

Seizures manifested by leftward eye deviation with either lip smacking or generalized tonic-clonic activity of the arms and legs continued. Phenytoin

by mouth with levels maintained between 12 $\mu\text{g}/\text{mL}$ and 20 $\mu\text{g}/\text{mL}$ did not decrease the seizure frequency. The results of the cerebrospinal fluid collected during the previous admission revealed the distinctive pattern of unknown compounds diagnostic for folinic acid-responsive seizures. Seizures stopped within 24 hours of starting folinic acid 4 mg/kg/dose by mouth divided twice a day.

Subsequent Development and Progression of Epilepsy

With complete seizure control, the patient's development progressed. The patient was more interactive and began to fix and follow appropriately. However, approximately 10 days after initiation of folinic acid, status epilepticus developed in the setting of acute gastroenteritis and enteroviral meningitis. Status epilepticus was initially controlled with midazolam infusion. After 3 days of seizure control, the midazolam was weaned, and the patient was without seizures for approximately 24 hours after cessation of the midazolam infusion. However, status epilepticus resumed thereafter. A pentobarbital coma with an EEG pattern of burst suppression was maintained for approximately 1 week, during which time topiramate was initiated and folinic acid was increased. Following pentobarbital weaning, the patient remained seizure free in the hospital for 2 weeks. During this time, phenytoin was tapered, owing to abnormally elevated liver function tests, without an increase in seizure activity. Enoxaparin was started for bilateral external iliac deep venous thrombosis, presumably resulting from femoral central line placements.

Prior to discharge, at approximately 5 months of age, flash visual evoked potentials demonstrated a reproducible negative-positive-negative waveform response, and a brain auditory evoked potential demonstrated possible relative prolongation of the left III to V and right I to III interwave latencies. Repeat MRI demonstrated mild interval atrophic change, delayed myelination, a thin corpus callosum, and bifrontal hygromas. An EEG prior to discharge demonstrated multifocal independent sharp waves, runs of bicentral intermittent alpha, and generalized background slowing but no seizures. Serum copper was abnormally high (207 $\mu\text{g}/\text{dL}$, normal =

Table 1. Serum and Cerebrospinal Fluid Ammonia, Lactate, and Pyruvate at Three Time Points

	Day of Life		Months of Life	
	6	8	3	7
Serum				
Ammonia	49	51 (28–80)		
Lactate	1.1	(0.5–2.2)		
Pyruvate	0.04	(0.03–0.08)		
L:P ratio	27.5			
Cerebrospinal fluid				
Lactate	1.7 (0.05–2.8)		0.8	0.91.5 (0.5–2.8)
Pyruvate	0.04 (0.06–0.19)	0.03	0.06	0.08 (0.06–1.9)
L:P ratio	42.5	26.7	15	18.8

Lactate and pyruvate units are mmol/L; ammonia units are $\mu\text{g/dL}$. Abnormal values are represented in bold with italic values representing abnormally low values and nonitalic values representing abnormally high values. Normal ranges for age are in parentheses. L:P = lactate to pyruvate.

85–150 $\mu\text{g/dL}$). At discharge, antiepilepsy medications included phenobarbital 55 mg by mouth at bedtime (6 mg/kg/day), topiramate 25 mg by mouth twice a day (5.4 mg/kg/day), and folinic acid 25 mg by mouth three times a day (8 mg/kg/day).

With elimination of the seizures, development began to slowly progress. At 6 months of age, the patient was able to sit supported with his head steady, roll over, grasp objects, and babble. However, seizures resumed at a frequency of one to two per day when croup and bronchiolitis developed. Initially, seizures were controlled with increases in topiramate to 25 mg by mouth in the morning and 50 mg by mouth in the evening (7.8 mg/kg/day) and phenobarbital to 36 mg by mouth twice a day (7.5 mg/kg/day). Approximately 1 week later, generalized seizures developed, prompting readmission. Seizure control was achieved by increasing the morning dose of topiramate to 37.5 mg (9.2 mg/kg/day) and initiating lorazepam 0.5 mg three times per day (0.15 mg/kg/day). A work-up for immunodeficiency demonstrated normal immunoglobulin levels and normal T- and B-cell subsets except for an increased number of CD19 B cells (22%, normal = 5–10%).

Unfortunately, seizures resumed, and EEG demonstrated status epilepticus. After variable control of status epilepticus with pentobarbital over a 2-week period, care was withdrawn after detailed consultation with the fam-

ily. The patient succumbed to respiratory failure soon after the withdrawal of support. The family declined skin biopsy, muscle biopsy, and autopsy. Prior to death, multiple serum amino acids were abnormally low, including aspartic acid, 1 $\mu\text{mol/L}$ (normal = 2–8 $\mu\text{mol/L}$); threonine, 16 $\mu\text{mol/L}$ (normal = 43–189 $\mu\text{mol/L}$); serine, 28 $\mu\text{mol/L}$ (normal = 58–191 $\mu\text{mol/L}$); asparagine, 12 $\mu\text{mol/L}$ (normal = 22–90 $\mu\text{mol/L}$); glutamine, 266 $\mu\text{mol/L}$ (normal = 427–907 $\mu\text{mol/L}$); proline, 39 $\mu\text{mol/L}$ (normal = 68–412 $\mu\text{mol/L}$); alanine, 64 $\mu\text{mol/L}$ (normal = 121–578 $\mu\text{mol/L}$); valine, 66 $\mu\text{mol/L}$ (normal = 105–407 $\mu\text{mol/L}$); cystine, 6 $\mu\text{mol/L}$ (normal = 18–52 $\mu\text{mol/L}$); methionine, 4 $\mu\text{mol/L}$ (normal = 11–45 $\mu\text{mol/L}$); isoleucine, 8 $\mu\text{mol/L}$ (normal = 24–124 $\mu\text{mol/L}$); leucine, 30 $\mu\text{mol/L}$ (normal = 46–228 $\mu\text{mol/L}$); tyrosine, 17 $\mu\text{mol/L}$ (normal = 32–134 $\mu\text{mol/L}$); phenylalanine, 29 $\mu\text{mol/L}$ (normal = 30–93 $\mu\text{mol/L}$); ornithine, 11 $\mu\text{mol/L}$ (normal = 18–91 $\mu\text{mol/L}$); lysine, 21 $\mu\text{mol/L}$ (normal = 63–242 $\mu\text{mol/L}$); histidine, 24 $\mu\text{mol/L}$ (normal = 46–109 $\mu\text{mol/L}$); and arginine, 10 $\mu\text{mol/L}$ (normal = 29–116 $\mu\text{mol/L}$). Several cerebrospinal fluid amino acids were again abnormal. Serum ceruloplasmin was normal but copper was increased 210 $\mu\text{g/dL}$ (normal = 85–150 $\mu\text{g/dL}$). Repeat cerebrospinal fluid neurotransmitter analysis demonstrated the two peaks representing unknown compounds diagnostic of folinic acid-responsive seizures. No unusual cerebrospinal fluid organic acids were found.

Table 2. Cerebrospinal Fluid Amino Acid Levels at Three Time Points

	Day of Life		Months of Life	
	6	8	3	7
Low in neonatal period				
Produces acetyl-CoA				
Isoleucine	1.8	9.3 (4.7–11.7)	3.4 (4.2–8.9)	4.3 (1.8–6.3)
Tyrosine	14.9	5.0 (8.1–24.3)	5.9 (6.9–20.5)	6.1 (2.2–15.5)
Tryptophan	0.6	2.6 (2.1–7.5)	0.9 (2.1–7.5)	1.7 (0.0–6.9)
Lysine	9.9	5.6 (10.7–27.7)	11.2 (9.4–29.4)	10.4 (8.3–23.9)
Produces α -ketoglutarate and NADH				
Glutamic acid	0.00	0.00 (0.8–10.6)	7.3 (0.8–10.6)	0.0 (0.0–3.8)
Produces oxaloacetate				
Aspartic acid	0.00	0.00 (3.7–10.5)	0.00 (0.2–1.1)	0.0 (0.1–1.1)
High during neonatal period				
Produces pyruvate but requires NADH				
Alanine	41	54.1 (24.7–39.0)	25.2 (16.2–40.6)	22.8 (12.6–34.7)
High during neonatal period but low at 3 months				
Produce ammonia				
Asparagine	18.0	15.4 (4.2–16.3)	0.9 (6.6–12.3)	0.0 (2.7–8.9)
Glutamine	902	893 (385–771)	397 (417–627)	603 (293–601)
Glycine	23.9	10.1 (5.8–9.5)	1.3 (5.8–9.5)	2.8 (1.8–8.4)
Histidine	32.0	19.7 (9.7–27.3)	9.6 (10.5–20.3)	9.4 (5.5–18.7)
Taurine	17.6	18.8 (6.2–16.7)	4.4 (6.2–16.7)	6.1 (3.7–9.5)
Ornithine	15.4	24.6 (1.7–16.1)	12.4 (3.0–12.2)	11.2 (1.4–9.8)

Only amino acids with at least two abnormal values are depicted. Abnormal values are represented in bold with italic values representing abnormally low values and nonitalic values representing abnormally high values. Normal ranges for age are in parentheses. Note that several amino acids with initially abnormally high values were abnormally low when the patient was 3 months old. Amino acids units are nmol/mL. CoA = coenzyme A; NADH = reduced nicotinamide adenine dinucleotide.

Table 3. Differential Diagnosis of Progressive White-Matter Abnormalities and/or Seizures in the Newborn Period

<i>Disorder</i>	<i>Test</i>
Aromatic L-amino acid decarboxylase deficiency	Cerebrospinal fluid 3-O-methyldopa level
Adrenoleukodystrophy	Very-long-chain fatty acid analysis, phytanic acids
β -Mannosidosis	β -Mannosidase activity
Congenital disorder of glycosylation	Isoelectric focusing of transferrin
Fatty acid oxidation deficiency	Serum acylcarnitine, urine acylglycine
Folinic acid-responsive seizures	Cerebrospinal fluid neurotransmitter analysis
Globoid cell leukodystrophy	Galactocerebroside β -galactosidase activity
Glycine encephalopathy	Serum and cerebrospinal fluid amino acid analysis, urine ketones
G _{M1} gangliosidosis	β -Galactosidase activity
Homocystinuria	Serum amino acids
Metachromatic leukodystrophy	Arylsulfatase A activity, urine sulfatides
Mitochondrial encephalopathy	Cerebrospinal fluid and serum lactate and pyruvate
Molybdenum cofactor deficiency	Urine sulfatide analysis
Neuronal ceroid lipofuscinoses	Linoleic acid
Pelizaeus-Merzbacher disease	Proteolipid protein-1 mutation
Tay-Sachs/Sandhoff's disease	β -Hexosaminidase A Activity
Urea cycle defects	Ammonia, serum amino acids

Our patient was evaluated for the disorders listed with the indicated tests.

Discussion

This case report describes an infant who presented at 3 months of age with a progressive seizure disorder refractory to standard antiepilepsy medications. Investigation to determine the etiology of seizures in the neonatal period was unrevealing, but the MRI was consistent with probable hypoxic-ischemic encephalopathy. In light of good seizure control and adequate development, antiepilepsy medication was discontinued at 1 month of age. A second metabolic investigation at 3 months of age revealed a cerebrospinal fluid pattern consistent with folinic acid-responsive seizures. Administration of folinic acid stopped the seizures. Two illnesses heralded seizures that evolved to status epilepticus. Development resumed only during periods of seizure control. During the first episode of status epilepticus, discontinuation of a pentobarbital coma was possible after starting topiramate and increasing folinic acid. Unfortunately, the second episode of status epilepticus was medically refractory for 2 weeks, at which point care was withdrawn.

Folinic acid-responsive seizures was discovered serendipitously. Folinic acid (5-formyltetrahydrofolate) was given as part of a vitamin cocktail for neonatal seizures because of its effectiveness in another patient with dihydropteridine reductase deficiency. To date, cerebrospinal fluid samples from eight patients, not including ours, have demonstrated the characteristic unknown compounds consistent with folinic acid-responsive seizures. Although four patients have responded to folinic acid therapy, one later died and the others survived with significant global developmental delay. Two patients were deceased when their cerebrospinal fluid samples were analyzed. Additionally, two other infants have been reported to respond to folinic acid therapy without analysis of their cerebrospinal fluid.⁶ The concentration of the unknown cerebrospinal fluid compounds appears to decrease during periods of good seizure control.⁶

This case has findings consistent with those reported from other patients with folinic acid-responsive seizures, but we have demonstrated some additional findings that occurred throughout the early course of this disease. Like other reported cases, this patient had a waxing and waning course of seizures, including

several episodes of status epilepticus. Indeed, at one point, the infant's seizure disorder was well controlled without taking any antiepilepsy medication, and after reloading him with phenobarbital, the EEG was normal. Several of the previously reported patients were well controlled for many months before their seizure disorder became refractory to antiepilepsy medication; in fact, recurrent episodes of status epilepticus, despite folinic acid therapy, appear to be common in this disorder. Like previously reported cases, both cortical atrophy and white-matter changes were found on MRI (see Figure 2). Similar to previously reported cases, the EEG was discontinuous early in life (see Figure 1, B and C). Unlike previously reported cases, serial EEGs are presented and demonstrate the progressive and episodic nature of this disorder, from a normal EEG at just over 2 months of age to a grossly abnormal EEG several weeks later (see Figure 1D).

The etiology of folinic acid-responsive seizures remains elusive. Folinic acid is best known for rescuing chemotherapy patients from the antagonistic effects of methotrexate on folate production, although it is used with other drugs that antagonize folate metabolism and in dihydropteridine reductase deficiency where conversion of dihydrofolate to tetrahydrofolate can be reduced.^{7,8} However, there is no evidence of a folate pathway abnormality or activation of the folate pathway with folinic acid treatment in patients with folinic acid-responsive seizures. Indeed, cerebrospinal fluid 5-methyltetrahydrofolate is normal in patients with folinic acid-responsive seizures. Multiple metabolites from pathways in which folate is essential do not coelute with the unknown cerebrospinal fluid compounds when analyzed with the same technique used to analyze cerebrospinal fluid neurotransmitters.⁶ Folic acid has also been used as a nontoxic single-carbon donor for the elimination of toxic metabolites in nonketotic hyperglycinemia.⁹ Thus, folinic acid could help eliminate toxic substances through production of folate compounds. In this manner, other compounds that stimulate the elimination of the toxic unknown cerebrospinal fluid compounds might also be effective in controlling seizures, and folinic acid might not be a specific treatment for folinic acid-responsive seizures. Indeed, one patient with cerebrospinal fluid containing the

distinctive compounds diagnostic of folinic acid-responsive seizures is well controlled with pyridoxine monotherapy.⁴

The cerebrospinal fluid concentrations of amino acids, pyruvate, and lactate detected in this patient might add information regarding the etiology of folinic acid-responsive seizures. Although previous reports mention selective aminorachia, the specific changes in amino acid levels were never reported. In this case, the serum lactate and pyruvate values were normal, but the lactate-to-pyruvate ratio was elevated. Similarly, in the cerebrospinal fluid, the lactate-to-pyruvate ratio was also elevated, but the pyruvate was consistently low. In the setting of high lactate, an increased lactate-to-pyruvate ratio can suggest a disorder involving reduced nicotinamide adenine dinucleotide (NADH) reduction. In this case, these data suggest a disorder of use of the energy derived from NADH reduction, thus requiring the overproduction of NADH through an overactive tricarboxylic acid cycle. The cerebrospinal fluid amino acid abnormalities support this hypothesis. Amino acids that were abnormal on at least two cerebrospinal fluid samples are listed in Table 2. These are divided into three groups. Amino acids that were consistently low in the neonatal period are all tricarboxylic acid cycle intermediate precursors that do not require the production of NADH or ammonia. The amino acid alanine, which was high during the neonatal period but normal at 3 months, is a pyruvate precursor but requires NADH for the conversion to pyruvate. The amino acids increased in the neonatal period but reduced at 3 months all require the production of ammonia for transformation into tricarboxylic acid cycle intermediates. If the tricarboxylic acid cycle is overactive, central nervous system ammonia can be increased initially until production of urea cycle enzymes responsible for ammonia disposal in the liver is increased. Thus, these laboratory values suggest an overactivation of the tricarboxylic acid cycle for the production of NADH. Thus, rather than a defect in the production of energy intermediates, it appears that the use of energy produced by these intermediates, possibly in the electron transport chain, can be defective.

A mitochondrial defect is supported by the clinical course of folinic acid-responsive seizures. For example, the pattern of progressive cortical atrophy and white-matter changes found on MRI is not uncommon in mitochondrial defects. The family history of hearing loss in this patient and the history of cardiomyopathy in previous case reports would also be consistent with a mitochondrial disorder. A mitochondrial disorder resulting in an energy deficiency could explain the poor response to phenobarbital because this drug inhibits transport of glucose into the cerebrospinal fluid.¹⁰

In the future, a more comprehensive work-up should be performed on patients with folinic acid-responsive seizures. The pattern of the cerebrospinal fluid amino acids at birth suggests increased cerebrospinal fluid ammonia, but this was never tested. If it is assumed that folinic acid-responsive seizures involve a defect in the electron transport chain, the function of mitochondrial complexes should be examined. Although a muscle biopsy is the gold standard for such examination, heteroplasmy could result in this defect being isolated to the central nervous system. The pos-

sibility of a mitochondrial disorder must be regarded with caution because a defect in ammonia disposal from the central nervous system could result in secondary mitochondrial dysfunction. The tests outlined might be of use in the future to help delineate the etiology of folinic acid-responsive seizures. In addition, this case illustrates the importance of testing cerebrospinal fluid neurotransmitters in neonates with seizures of unknown etiology. Identification of folinic acid-responsive seizures in the neonatal period could lead to the commencement of an alternative treatment plan that could control seizures.

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