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J Child Neurol 2008 23: 1460 originally published online 14 October 2008

DOI: 10.1177/0883073808318546

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Progressive Encephalopathy in a Child With Cerebral Folate Deficiency Syndrome

Joshua L. Bonkowsky, MD, PhD, Vincent T. Ramaekers, MD, PhD,
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Cerebral folate deficiency syndrome, a recently recognized cause of developmental delay, regression, and seizures, is associated with autoantibodies against folate receptors. A female child with developmental delay and a history of seizures who presented with seizures and unexplained coma is reported. Extensive testing to evaluate the patient's coma and subsequent developmental regression were unrevealing until the results of her cerebrospinal fluid neurotransmitter analysis

returned. These showed low levels of methyltetrahydrofolate, the active metabolite of folate in the cerebrospinal fluid; subsequently, elevated titers of autoantibodies against folate receptors were found. Despite treatment with folinic acid, she developed intractable epilepsy and severe developmental delay.

Keywords: encephalopathy; coma; seizures; developmental delay; cerebral folate deficiency

Cerebral folate deficiency syndrome is a rare but potentially treatable cause of developmental delay and seizures. Although other disorders have been associated with low cerebrospinal fluid (CSF) levels of folate (such as Rett syndrome, Aicardi-Goutieres syndrome, and some mitochondrial disorders),¹⁻⁵ cerebral folate deficiency syndrome is notable for the presence of autoantibodies against membrane-associated folate receptors of the choroid plexus. The blocking antibodies prevent uptake of folate across the blood-spinal fluid barrier.⁶ Importantly, successful treatment of cerebral folate deficiency syndrome has been reported using high-dose folinic acid.^{2,6,7}

We report a child with a history of seizures and developmental delay who presented with seizures followed by a prolonged episode of coma lasting 5 days. After extensive testing, the diagnosis of cerebral folate deficiency syndrome was established. Despite treatment with folinic acid, the patient developed intractable epilepsy and profound developmental delay.

Case Report

A 17-month-old female was brought to the emergency department following a one-minute generalized tonic-clonic seizure. In the emergency department, the patient had 6 additional generalized tonic-clonic seizures and was treated with lorazepam and phenobarbital. She had a head computed tomography scan, complete blood count, lumbar puncture, and blood chemistries, all of which were normal. Physical and neurological exam revealed coma, normally reactive pupils, and ankle clonus. Head circumference was normal (25% percentile).

The patient remained comatose for 5 days. She had no further seizures during the hospitalization. An electroencephalogram (EEG) obtained 2 days after admission showed high amplitude, polymorphic delta and theta activity, with irregular periods of relative attenuation, but no epileptiform features. Her hospitalization was complicated by fevers and hyponatremia, both of which were resolved. Brain magnetic resonance imaging (MRI) studies (including with contrast) were performed on hospital days 2 and 9; no abnormalities were noted. Because of the unexplained coma, history of seizures and developmental delay, and fevers, an extensive laboratory evaluation was performed, including studies for infectious, endocrine, metabolic, and genetic causes of her encephalopathy (Table 1). A repeat EEG 8 days later consisted of high-amplitude delta activity most prominent over the posterior regions, poorly formed sleep spindles during sleep, and no epileptiform features.

At the time of discharge (11 days following admission), the patient had no verbal output, did not follow any commands, would not reach for objects or hold them, and

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Bonkowsky JL, Ramaekers VT, Quadros EV, Lloyd M. Progressive encephalopathy in a child with cerebral folate deficiency syndrome. *J Child Neurol*. 2008;23;1460-1463.

Table 1. List of Testing Which Yielded Normal Results

General	Infectious	Metabolic/Genetic
CBC with differential	Blood culture	Lactate
Chemistry 10 panel	Urine culture	Ammonia
AST, ALT, bilirubin	CSF culture	Serum very-long chain fatty acids
ESR, CRP	Chest X ray	Carnitine profile
CSF (glucose, protein, cell count)	ASO, anti-DNase B	Ceruloplasmin
TSH, free T4	HSV PCR (CSF)	Uric acid
ANA	HHV6 PCR (CSF)	Urine organic acids
Lead	EBV PCR (CSF)	Serum amino acids
Homocysteine	Enterovirus PCR (CSF)	Urine amino acids
Vitamin B12	Mycoplasma PCR (CSF)	CSF amino acids
Antimicrobial antibody	Mycoplasma IgG/IgM	CSF lactate
Antithyroglobulin antibody	Toxoplasma IgG/IgM	Leukocyte lysosomal enzymes
Cortisol	Varicella IgG/IgM	Biotinidase
	CSF AFB culture	Methyltetrahydrofolate reductase
	HIV1/2 antibodies	Rett syndrome (methylation studies)
	Arbovirus panel (IgG/IgM for California	Palmitoyl-protein thioesterase I
	equine virus, St Louis encephalitis,	Tripeptidyl-peptidase I
	Eastern equine encephalitis, Western	
	equine encephalitis)	

NOTE: AST = aspartate aminotransferase; ALT = alanine transaminase; ASO = antistreptolysin O; ANA = antinuclear antibody; AFB = acid-fast bacilli; CSF = cerebrospinal fluid; CRP = C-reactive protein; CBC = complete blood count; ESR = erythrocyte sedimentation rate; EBV = Epstein-Barr virus; TSH = thyroid stimulating hormone; HSV = herpes simplex virus; HHV = human herpesvirus; HIV = human immunodeficiency virus; PCR = polymerase chain reaction.

had to be fed by her parents. However, she was visually attentive and would track objects and could smile or laugh interactively with her parents.

The patient's medical history was significant for generalized tonic-clonic seizures starting at the age of 5 months for which she was treated with phenobarbital (which was stopped by her parents at the age of 12 months). Evaluation at the age of 6 months was normal, including a routine EEG, head computed tomography scan, and brain MRI. Family history, pregnancy and birth history, and other medical history were unremarkable. There was no known consanguinity. She had 2 older healthy siblings.

In addition, the patient had a history of mild developmental delay; she did not begin to cruise along furniture until the age of 15 months and was not walking independently at the time of admission. Although she babbled, she was not saying any specific words at the time of admission, and her parents felt that her receptive language skills were delayed compared with other children her age.

Cerebrospinal fluid neurotransmitter analysis (for biogenic monoamine metabolites, pterins, and 5-methyltetrahydrofolate) was also done during her hospitalization, and results (obtained after discharge) revealed low levels of 5-methyltetrahydrofolate (28 nmol/L, normal = 40-187 nmol/L). Testing for folate receptor autoantibodies in the serum was subsequently performed and showed elevated levels (1.95 pmol folate receptor blocked per mL serum, normal = 0). She was then started on folinic acid replacement at a dose of 5 mg bid (1 mg/kg/day).

Over the next 2 years, the patient developed intractable seizures that were resistant to 5 different antiepileptic drugs, both singly and in combinations (including gabapentin, levetiracetam, lorazepam, oxcarbazepine, phenobarbital, phenytoin, and topiramate), and placement of a vagal nerve stimulator. Her seizures included a mixture of partial complex, absence, tonic, and tonic-clonic seizures. She had no recovery of her developmental milestones and had continued deterioration in her neurological status. Repeat cerebrospinal fluid 5-methyltetrahydrofolate levels were normal (91 nmol/L) while on folinic acid. The patient remained on folinic acid treatment for 6 months and had her dose increased to 2 mg/kg/day before the parents discontinued it. During this time, she had 3 admissions for status epilepticus. Repeat EEGs showed bitemporal sharp waves with seizures arising from the left temporal or temporal-occipital regions with secondary generalization (Figure 1A). A brain MRI at the age of 2 years was notable only because of mild cerebellar atrophy (Figure 1B). Magnetic resonance spectroscopy showed decreased N-acetylaspartate levels, likely due to loss of neurons. She also required a Nissan and gastrostomy tube placement because of bulbar dysfunction.

The patient's most recent neurological exam at the age of 3 years showed a severe static encephalopathy and normal head circumference (25th percentile). She has limb spasticity, positive Babinski signs, and axial hypotonia. Her current seizure frequency is >30 seizures/day. The patient functions at the level of a 2-month-old and does not visually track.

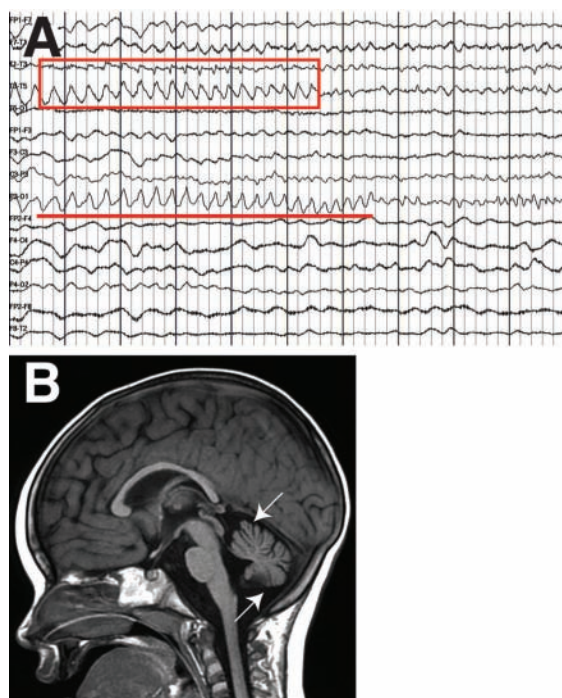


Figure 1. (A) Routine electroencephalogram obtained at the age of 3 years, bipolar montage. The pattern in the boxed region and underline are part of the same discharge, consisting of left hemisphere 3-4 Hz spike and wave discharges maximal in the temporal-occipital region. (B) Brain magnetic resonance imaging, sagittal view, T1 series. Mild cerebellar atrophy is seen (arrows).

This study was reviewed and a waiver granted by the University of Utah Institutional Review Board.

Discussion

This report describes a child with a progressive encephalopathy and intractable epilepsy. The patient did have a preceding history of mild developmental delay and prior seizures, but her presentation was remarkable for her prolonged unexplained coma. Despite extensive investigations during her initial admission, no explanation for her seizures or coma was found until the results of her cerebrospinal fluid neurotransmitter analysis returned.

The patient was diagnosed with cerebral folate deficiency syndrome based on low cerebrospinal fluid levels of 5-methyltetrahydrofolate, the central nervous system metabolite of folate, and the presence of autoantibodies in the blood against folate receptors. Folate is actively transported from the blood to the cerebrospinal fluid and brain by folate receptors, and the antibodies presumably inhibit transport of folate, leading to decreased cerebrospinal fluid levels.

Cerebral folate deficiency syndrome has been reported in 30 patients.^{2,7,8} Typical symptoms include irritability,

developmental delay or regression, hypotonia and ataxia, seizures, and dyskinesias.⁶ Magnetic resonance imaging findings are variable between patients. Cerebellar atrophy has been reported in 3 of 20 patients with cerebral folate deficiency syndrome² although cerebellar symptoms are reported in nearly all patients. In some patients, no MRI changes were noted,^{2,7,8} whereas in other cases, moderate demyelination or supratentorial or infratentorial atrophy was found.²

The etiology of cerebral folate deficiency syndrome is unknown, and it is unknown whether it is primarily genetic or is autoimmune with an interaction with environmental triggers. Some support for the latter hypothesis has been shown by a reduction in the titer of folate receptor autoantibodies by adoption of a milk-free diet.⁹ Marked responses to treatment with folinic acid have been reported,^{2,6-8} and it has been suggested that starting treatment at an earlier age may be associated with an improved response.² Treatment with immunomodulatory agents has not been reported.

This case underlines the importance of cerebrospinal fluid neurotransmitter analysis in cases of unexplained coma, intractable epilepsy, or episodic progressive developmental regression. Correct and timely diagnosis is important because of the potentially treatable nature of this disorder.⁶⁻⁸ Starting folinic acid therapy immediately at diagnosis may be necessary to prevent irreversible central nervous system sequelae. Unfortunately, our case suggests that folinic acid treatment, even when started early, may not be an adequate treatment for all patients.

Acknowledgments

The authors report no conflicts of interest. Edward V. Quadros holds a patent (US 20060127955 and WO/2004/043233) issued to State University of New York Research Foundation describing methods for the detection of folate receptor autoantibodies. This work is supported in part by funding from the National Institutes of Health (HD051880 to Edward V. Quadros and K12 HD001410 to Joshua L. Bonkowsky) and by a grant from the Children's Health Research Center, University of Utah, to Joshua L. Bonkowsky.

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