Electrographic status epilepticus in sleep in an adult with cerebral folate deficiency

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Practical Implications

Consider electrographic status epilepticus in sleep alone or in combination with cerebral folate deficiency as a cause of neurocognitive, behavioral, and motor regression in adults. Identification of etiology is important because etiology-focused treatment may lead to improvement of the seizures and neurologic function.

A 27-year-old woman was evaluated for developmental delay and intractable epilepsy. She was born via cesarean section at 42-week gestational age. Developmental delay for gross motor skills, fine motor skills, and language was noted since infancy. She was hypotonic and walked by age 3 years. She began speaking at age 2 years. Her social skills were preserved.

Her epilepsy began at age 4 years as generalized tonic seizures. Seizures were well controlled between 4 and 8 years of age. She was able to walk, say a few words, and participate in performances at the special education school. Seizures increased during adolescence but did not affect her overall level of cognitive functioning. At age 22 years, seizures became daily (5–10 per day), despite multiple antiepileptic drugs (AEDs) (figure 1). She became less verbal and developed excessive drooling, inability to walk independently, and urine incontinence.

Video-EEG evaluation at our center at age 27 years showed abundant epileptiform discharges occupying >85% of 10-second epochs during slow-wave sleep, consistent with electrographic status epilepticus in sleep (ESES) (figure 2, A and B). At that time, treatment included perampanel, levetiracetam, clobazam, oxcarbazepine, and folic acid. Treatment with diazepam 20 mg at bedtime was started. A considerable reduction in spikes during sleep and in seizure frequency was achieved for a few months (figure 2C). She became more alert and her speech improved. Four months later, seizures increased again.

Brain fluid-attenuated inversion recovery MRI showed several nonspecific small foci of hypersignal involving the deep and periventricular white matter (figure 2D). Genetic workup showed several mutations of unclear significance. Metabolic workup showed low levels of 5-methyltetrahydrofolate (5MTHF) in the CSF. Genetic causes (*ALDH7A1*, *FOLR1*) for low CSF 5MTHF and mitochondrial diseases were excluded.¹ Serum folate level was normal. She tested positive for anti-folate receptor antibodies (>5.7 pmol of folate blocked per milliliter of serum; range 0–1.55).² Treatment with folinic acid, an active form of folic acid that bypasses the blocked folate transport mechanism, was initiated with a single daily dose of 1 mg/kg/day.

At 4-month follow-up, she had a major reduction in seizure burden, with a more than 65% decrease in seizures and occasional seizure-free days (figure 1). Neurocognitive improvements included independent ambulation, increased expressive language, and reduced drooling.

DISCUSSION

Our case demonstrates the occurrence of ESES, severe neurocognitive deterioration, and frequent seizures in an adult, at least partly related to cerebral folate deficiency (CFD). Although

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Figure 1 Exponential growth curve

Exponential growth curve was fit to data between 2009 and initiation of folinic acid, yielding a growth rate in seizure frequency. Patient age 20.8–27.9 years. Colored lines show the initial treatment with diazepam and folinic acid. There was a transitory improvement in seizure frequency after treatment with diazepam. (A) Monthly seizure frequency showing a sharp drop after start of folinic acid treatment (November 7, 2014, month circled). (B) Weekly seizure frequency, weeks numbered from the start of folinic acid treatment; note the frequency decrease apparent 8–10 weeks after beginning folinic acid.

ESES has been described as a childhood condition, 2 cases have been reported in adults.^{3–5} One patient with epilepsy was diagnosed with ESES at the age of 21 years.⁴ Treatment with adrenocorticotrophic hormone and multiple AEDs did not improve seizures or cognition. Another patient was diagnosed at age 61 years.⁵ His seizures began at age 41 years after a pituitary adenoma resection. Treatment and outcomes are unknown.

Our case also ties the etiology of ESES to CFD. The presence of ESES in a patient with autoimmune CFD has been reported in a 15-year-old child. Our case demonstrates an adult with autoimmune CFD with documented ESES.

CFD can be defined as any neurologic condition associated with low CSF 5MTHF in the presence of normal folate metabolism outside the nervous system.⁶ 5MTHF, the active folate metabolite in the brain and CSF, is essential for brain maturation and function. In 2005, Ramaekers et al. found autoantibodies against cerebral folate receptor in some children with CFD.² The clinical features of CFD usually manifest at about 4–6 months of age and symptoms include marked irritability, slow head growth, psychomotor retardation, cerebellar ataxia, pyramidal signs, dyskinesias, central visual disturbances, and seizures.^{2,6}

The treatment for CFD includes oral folinic acid. The initial dose is 0.5–1 mg/kg/day, but doses up to 5 mg/kg/day have been used. The goal of treatment is normalization of 5MTHF levels in the CSF and neurocognitive clinical improvement, especially if the treatment is started early in the disorder.⁶ Additional treatment with a milk-free diet may be helpful.⁷

In our case, it will be difficult to prove whether CFD is the cause of her early developmental delay and seizures. Her initial presentation is not inconsistent with autoimmune CFD. The possible contribution of folate-depleting AEDs was ruled out given the presence of normal serum folate levels.

Our hypothesis is that ESES in our case represents a more severe clinical form of untreated CFD, as noted in a previous report. This may have important diagnostic implications when evaluating children and adults with ESES. Further studies are needed to strengthen this association.

Figure 2 Imaging

(A, B) EEG recording during admission. (A) Patient awake with normal posterior background and focal epileptiform discharge in the right frontocentral region. (B) Patient asleep with continuous spike-and-wave discharges covering the whole tracing and occupying >85% of slow-wave sleep, consistent with electrographic status epilepticus in sleep. (C) EEG recording after treatment with diazepam. (D) Brain MRI.

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