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Case of a Two-Year-Old Boy With Recurrent Seizures, Abnormal Movements, and Central Hypoventilation

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Anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis was first described in young women with ovarian teratoma. Typical presentations include subacute onset of neuropsychiatric symptoms, seizures, altered awareness, movement disorders, and autonomic dysfunction. Growing evidence indicates that anti-NMDAR encephalitis is one of the most common causes of encephalitis in children and young adults. We present a case of a 2 year-old boy with anti-NMDAR encephalitis to illustrate and discuss the differences in neurological presentation, frequency of symptoms, and association with underlying tumor between children and adults.
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Case History

A 2-year-old boy was transferred from another facility with recurrent seizures, abnormal movements, and failure to wean off mechanical ventilation. The patient had been healthy until approximately 4 weeks before transfer with a self-limited episode of extension and stiffening of the right arm and leg lasting for 30 minutes. He was evaluated in the emergency department at another hospital. An electroencephalogram (EEG) revealed occasional subclinical seizures. He was thought to be at high risk for recurrent unprovoked seizures and administration of levetiracetam was started.

Over the next several days, he had recurrent right-sided seizures that included right arm and leg stiffening, occasional upward eye deviation or head deviation to the left or both, and subsequent transient right-sided weakness consistent with Todd paralysis. At 2 weeks after symptom onset, the parents reported decreased interaction, spontaneous speech, and ability to feed himself. He also was observed to have had episodes of spontaneous laughing and crying without clear reason. The right-sided weakness became persistent associated with intermittent dystonic posturing of his right arm. Over the subsequent weeks, he became increasingly confused with a significantly disrupted sleep-wake cycle.

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Evaluations before transfer included repeated normal brain magnetic resonance (MR) imaging (MRI) and MR spectroscopy studies. Continuous EEG showed focal rhythmic activity in the left hemisphere but no EEG correlate for near-continuous right-sided dystonic posturing. Laboratory studies included evaluation of lactate, pyruvate, carbohydrate-deficient transferrin, biotinidase, ammonia, plasma amino acids, urine organic acids, ceruloplasmin, copper, CPK, PPT1 and TPP1 for neuronal ceroid lipofuscinosis, TSH and T4, and alpha-fetoprotein levels. Array comparative genomic hybridization (CGH) and methylation studies for Prader-Willi or Angelman syndrome were normal. Cerebrospinal fluid (CSF) analysis revealed a white blood cell count of 18 cells/μL (reference: 0-10), 91% lymphocytes, red blood cell count of 1 cell/μL, glucose of 61, and a protein of 25. Repeat CSF studies performed 3 weeks from clinical presentation showed white blood cell of 1, red blood cell of 2, glucose of 77, and protein of 37. Investigations for infectious etiologies included serum and CSF serology or polymerase chain reaction studies for *Tropheryma whipplei*, Lyme disease, La Crosse encephalitis, eastern equine encephalitis, St. Louis encephalitis, and West Nile virus. A CSF amino acid panel found mildly elevated glutamine and phenylalanine levels, but this was not felt to be consistent with a particular disorder.

Antiepileptic medications including levetiracetam, topiramate, and clobazam were titrated up to maximal doses with minimal effect for presumed seizures. A dose of prednisone (1 mg/kg/d) was initiated after an unrevealing workup for infectious etiologies. The patient was intubated and continued to have presumed seizures despite propofol or pentobarbital infusion. A third brain MRI, repeated 5

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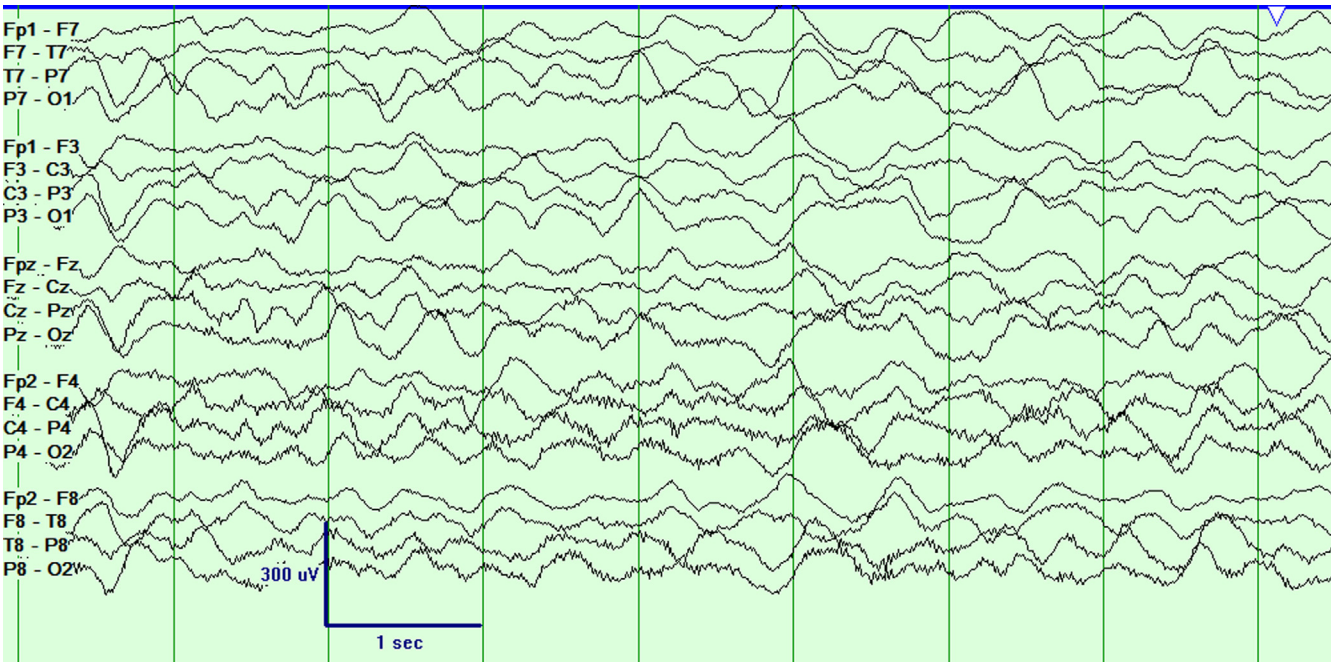

Figure 1 EEG at 1 month from clinical presentation during comatose phase. Extreme delta brush is seen as generalized diffuse delta activity with superimposed beta activity (LFF 1 Hz, HFF 70 Hz, notch 60 Hz, and sensitivity 15 uV/mm). (Color version of figure is available online.)

weeks from presentation, was interpreted as potentially demonstrating subtle volume loss involving the left cerebral hemisphere, raising concern for possible Rasmussen syndrome. At 7 weeks after clinical presentation, intravenous (IV) immunoglobulin (IVIG) treatment was started (5 doses of 0.4 g/kg/d) and improvement was noted in interictal epileptiform discharges on continuous EEG monitoring. Sedation was then discontinued; however, extubation was not successful, and he was transferred to our institution for further evaluation and treatment. Before transfer, serum and CSF samples were submitted for analysis of autoantibodies.

On general examination after transfer, he was found intubated and sedated without dysmorphic features or neurocutaneous stigmata. Near-continuous orofacial dyskinesia with repetitive chewing or grimacing motions were noted around the eyes and jaw as well as hyperkinetic movements of his upper and lower limbs. Continuous video EEG monitoring showed no EEG correlates for his orofacial or appendicular movements. There was persistent diffuse generalized delta slowing with superimposed beta fast activities (Fig. 1). Re-review of serial MRI images showed no cortical asymmetry but demonstrated a few scattered ill-defined areas of subcortical T2 hyperintensity. CSF anti-N-methyl-D-aspartate -receptor (NMDAR) autoantibody returned at markedly elevated titer of 1:64, confirming diagnosis of anti-NMDAR encephalitis.

Computed tomography scans of the chest, abdomen, and pelvis and testicular ultrasound for occult neoplasm were unrevealing. A second 5-day course of 0.4 g/kg/d of IVIG and 5 days of 30 mg/kg/d IV methylprednisolone rendered limited improvement. Rituximab therapy (375 mg/m^2), with pulse IV methylprednisolone (30 mg/kg) every 3 days, also had limited clinical response. Multiple extubation attempts failed due to inadequate ventilation, despite non-invasive BiPAP support, suggestive of central hypoventilation. Tracheostomy was performed at 7.5 weeks after presentation.

After several plasma exchanges, the patient demonstrated an improved level of alertness and was weaned off sedation. Weekly administration of IV methylprednisolone continued for 10 weeks followed by once every 3 weeks over the subsequent 3 months. Over the next month, the patient demonstrated gradual clinical improvement: increased sleep duration, reduction in abnormal movements, and purposefully fixated and followed people across his visual field. At 6 months from his initial presentation, and 4 months from his IVIG, plasma exchange, and rituximab treatments, he was able to use several words to express wants but was not yet using 2-word sentences, he was able to manipulate toys with either hand with a resolved right-sided paresis, he was able to ambulate independently, and he no longer demonstrated any abnormal dyskinetic movements. EEG at that time demonstrated mild generalized slowing, reduced amplitude over the left hemisphere, without epileptiform abnormalities (Fig. 2).

Discussion

Description

The constellation of subacute onset of neuropsychiatric symptoms, labile affect and sleep difficulty, seizures, and distinct orofacial dyskinesia, with negative metabolic, infectious, and genetic evaluations is concerning for a primary or paraneoplastic autoimmune process. Although it was first