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Clinical Observations

Possible Autoimmune Association Between Herpes Simplex Virus Infection and Subsequent Anti–N-Methyl-D-Aspartate Receptor Encephalitis: A Pediatric Patient With Abnormal Movements

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ABSTRACT

AIM: We describe a child with severe generalized choreoathetosis and anti–N-methyl-D-aspartate receptor encephalitis after herpes simplex virus type 1 encephalitis. Recent evidence supports an autoimmune trigger for anti–N-methyl-D-aspartate receptor encephalitis following a viral infection. This is emerging as a common and potentially treatable autoimmune condition in the pediatric population. **PATIENT DESCRIPTION:** A 6-month-old girl presented with fever, diarrhea, and partial seizures and was subsequently treated for proven herpes simplex virus type 1 encephalitis. Shortly thereafter, she developed irritability, insomnia, dysautonomia, orolingual and facial choreodystonic movements, spontaneous vocalizations, and choreoathetoid movements of her trunk and limbs. Cerebrospinal fluid analysis confirmed anti–N-methyl-D-aspartate receptor antibodies. Management of her movements required titrated doses of clobazam, valproate, tetrabenazine, and immunotherapy. At 3 months' follow-up, her abnormal movements had completely resolved. **CONCLUSIONS:** Our patient adds to recent evidence linking a viral trigger for brain autoimmunity. Movement disorders appear early, leading to severe patient and family distress, and pose a serious management dilemma because of a paucity of clinical trials assessing treatments in the pediatric population. Abnormal hyperkinetic movements present early and prominently, requiring a combination of symptomatic and immune-modulating therapies for successful treatment.

Keywords: NMDA, encephalitis, herpes simplex, tetrabenazine, rituximab, dyskinesias

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Introduction

In 2007, Dalmau[1] described anti–N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis as a potentially reversible immune-mediated paraneoplastic disorder in young women with ovarian teratomas. Since then, multiple reports of a variety of autoimmune encephalitides have emerged, highlighting the underrecognized frequency of the disorder. The N-methyl-D-aspartate cell surface receptors are described as ligand-gated, voltage-dependent channels for nonselective cations that are expressed in the hippocampus and forebrain. Antibodies against the N-terminal domain of the NR1 subunit of these receptors have been demonstrated in patients with anti-NMDAR encephalitis. The classic neuropsychiatric syndrome associated with anti-NMDAR encephalitis is well described and follows a predictable pattern. Clinically, patients often present with a subacute encephalopathy, behavioral changes, autonomic dysregulation, seizures, and movement disorders. When untreated, this syndrome may result in death, but early immunotherapy offers the potential for excellent neurological recovery.[1,2]

The pediatric population with anti-NMDAR encephalitis differs from adults in clinical presentation and lack of

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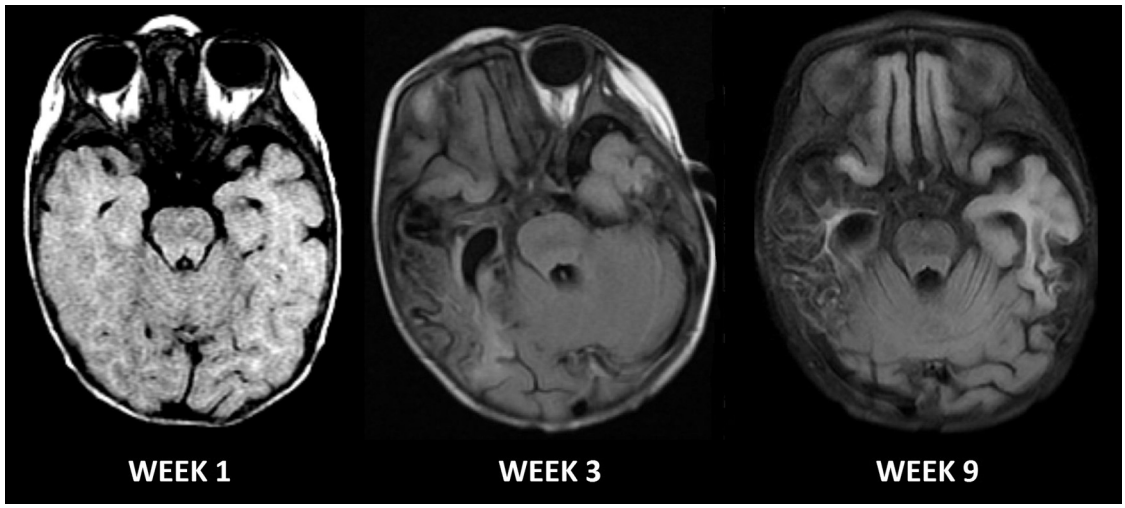

FIGURE.
Sample timeline of cranial magnetic resonance imaging with fluid-attenuated inversion recovery sequences. Week 1 shows early evidence of cytotoxic edema related to herpes simplex virus infection, most notably within the right temporal lobe. Subsequently, necrosis and gliosis led to the encephalomalacic changes seen in weeks 3 and 9. Of note, patient positioning and technical differences between 1.5 Tesla (week 1) and 3 Tesla (weeks 3 and 9) magnetic resonance imaging scanners create the variability in image qualities seen.

association with malignancy.[3,4] From a clinical perspective, hyperkinetic movement disorders appear early in the course of the disease, leading to severe patient and family distress, functional disability, and impaired sleep and nutrition, and pose a serious management dilemma. Here, we present our experience with a 6-month-old girl with herpes simplex encephalitis (HSE) and subsequent anti-NMDAR encephalitis with a special focus on treatment of her abnormal movements.

Patient Description

A previously healthy 6-month-old girl was brought to the emergency department with a fever of 102°F, 2 days of vomiting, and 4 days of profuse watery diarrhea from presumed viral gastroenteritis. The next day, she was noted to have episodes of staring, decreased responsiveness, left eyelid drooping, and right-sided twitching resulting from seizures. Anticonvulsant therapy was immediately initiated with phenobarbital at 3-5 mg/kg/day while waiting for additional testing. Cranial magnetic resonance imaging (MRI) revealed extensive bihemispheric regions of diffusion restriction involving the temporal, parietal, and occipital lobes, which worse in the right hemisphere. Cerebrospinal fluid results were suggestive of a viral meningoencephalitis with positive herpes simplex virus type 1 DNA by polymerase chain reaction. An electroencephalograph showed left frontotemporal slowing superimposed on generalized background slowing. She was medically stabilized and discharged home after 9 inpatient days with plans to continue phenobarbital and complete 21 total days of intravenous acyclovir at 20 mg/kg every 8 hours with visiting nurse services.

One week later, she returned to the emergency department for evaluation of "abnormal movements." A repeat cerebrospinal fluid analysis was unremarkable, including negative herpes simplex virus DNA by polymerase chain reaction. Her parents reported unusual and continuous movements associated with poor sleep, irritability, and restlessness. Her symptoms quickly progressed, with increasing irritability, insomnia, altered level of consciousness, and dysautonomia. The phenomenology of her abnormal, involuntary movements was consistent with fast, generalized, constant, fairly symmetric, large-amplitude choreoathetoid (at times ballistic), and choreodystonic movements prominently affecting her limbs, trunk, and neck. Associated oral, lingual, and jaw choreiform movements were present along with abnormal spontaneous vocalizations indicative of phonic chorea. (See Video S1-S2, supporting material published online.)

A repeat lumbar puncture showed mildly elevated lymphocytic pleocytosis and a repeat cranial MRI did not show any new abnormalities. She was transitioned from phenobarbital to valproic acid (30-60 mg/kg/day) and clonazepam at bedtime, with modest improvement in her movements and sleep cycle—she had long periods without sleep, at times more than 24 hours, and central hypoventilation. She eventually required placement of a gastrostomy tube because the severe and relentless nature of her movements limited oral intake. She was treated with intravenous immunoglobulin and intravenous corticosteroids for 1 week.

In an effort to promote rest and reduce her movements further, several pharmacologic interventions were attempted. In addition to valproic acid, trials of lorazepam, clonidine, gabapentin, dexmedetomidine, and midazolam were attempted with only partial benefit. Unsuccessful therapies were stopped, and tetrabenazine (goal 7-15 mg/kg/day divided into three doses daily) was added to valproic acid with clear amelioration of dyskinesias. Clobazam (up to 2.5 mg in the morning and 12.5 mg in the evening) was added, with discontinuation of benzodiazepines, with additional benefits were seen in her movements and sleep. There was a quick reduction of her abnormal movements with initiation of these combined interventions. Eventually, cerebrospinal fluid anti-NMDAR antibodies were detected and she was started on immunotherapy with Rituxan 375 mg/m^2 weekly for 4 weeks and Cytoxan 500 mg/m^2 monthly for 6 months. A repeat cranial MRI was performed at 9 weeks post-HSE, which showed extensive encephalomalacia (Figure). There were no abnormalities appreciated within the basal ganglia structures. Despite a complicated hospitalization, she was successfully discharged to a rehabilitation facility. At 3 months' follow-up, her abnormal movements were completely resolved and she was seizure-free. At 9 months' follow-up, she has global developmental delay but appears more social and interactive. She is tolerating a slow taper from clobazam and tetrabenazine, and valproate continues to be her primary antiepileptic therapy.

Discussion

The initial pediatric patients with anti-NMDAR encephalitis presented with evolving neuropsychiatric symptoms, typically preceded by a viral-like syndrome with fever, headache, and emesis.[3] Behavioral changes (irritability, restlessness, and psychosis), seizures, and movement

disorders ensued. Subsequently, language, sleep, and autonomic dysfunction followed and may led to central hypoventilation and the need for intensive supportive care. This sequence of predominant early neurological symptoms is seen in 60% of children with anti-NMDAR encephalitis. Importantly, 70% of adults initially present with psychiatric symptoms and may have an association with malignancy.[5,6]

In 2012, Pruss et al.[7] first described the presence of anti-NMDAR antibodies in patients with HSE. This was followed by an observation in another case series in 2013 by Armangue et al[5] in which a single pediatric patient was found to have anti-NMDAR antibodies four weeks after HSE. The authors astutely noted a lack of clinical response to acyclovir but neurological improvement after initiating immunotherapy. They concluded that some patients with post-HSE movement disorders may in fact have anti-NMDAR encephalitis.[5] HSE rarely presents with movement disorders without structural changes on neuroimaging, leading clinicians to assume that either herpes simplex virus reinfection or a postinfectious process is responsible for the movement disorder.[8-10] Following appropriate therapy, our patient also underwent significant reversibility of the abnormal movements because core basal ganglia structures were relatively unaffected.

From a clinical perspective, hyperkinetic movement disorders appear early in the course of the disease, leading to severe patient and family distress, functional disability, and impaired sleep and nutrition, and pose a serious management dilemma. Our patient illustrates the potential association between HSE and anti-NMDAR encephalitis, an association that may be more common than previously thought. Recent work by Armangue et al[11] has demonstrated novel anti-NMDAR antibody synthesis within weeks of diagnosed HSE in those presenting with relapsing or worsening neurological symptoms. They concluded that HSE may trigger brain autoimmunity, including anti-NMDAR encephalitis. The nature of this increasing association between infectious and immune-mediated encephalitis remains unclear, but a possible immunologic trigger is now suspected. In the future, researchers may attempt to prove that this is not merely an epiphenomenon of antibody positivity. A study would have to be designed to obtain cerebrospinal fluid in all patients several weeks after HSE, including those without relapsing or worsening neurological symptoms.

Successful management of this condition requires prompt diagnosis and early initiation of immunotherapy. Symptomatic treatment for persistent or severe generalized choreodystonic movements is challenging, and no prospective clinical trials are available in the pediatric literature. The use of high-dose benzodiazepines, valproic acid, and dopamine-depleting agents should be considered for symptomatic treatment in refractory patients because the combination drastically improved clinical features in our patient. However, in our patient and as in adult patients with anti-NMDAR encephalitis, it was not until the initiation of cytotoxic immunosuppressant and B-cell–depleting therapy that remission was achieved.

Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.pediatrneurol.2014.10.011.

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