Abstract:
Anti–*N*-methyl-D-aspartate receptor encephalitis should be considered for pediatric patients who present with seizures, dysautonomia, dyskinesias, and psychiatric disturbances. Life-threatening complications from this disorder, including seizures, hypoventilation, bradycardia, and ictal asystole, should be anticipated, and the patient should be closely monitored and supported. Morbidity and mortality can be mitigated with early detection and initiation of immunotherapy and resection of a teratoma, if found. In young patients treated soon after symptom onset, the prognosis is favorable with most patients having no or mild residual neurologic deficit. Early recognition of the protean signs of this disorder in the emergency department is essential to help establish immunomodulation therapy in a timely fashion.

Keywords:
anti-NMDA receptor encephalitis; seizures; dysautonomia; dyskinesias

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Recognition and Treatment of Anti-*N*-Methyl-D-Aspartate Receptor Encephalitis

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In 2005, young women with a syndrome of psychiatric symptoms, seizures, decreased level of consciousness, and hypoventilation in association with an ovarian teratoma were found to have autoantibodies, which reacted with neuronal membranes in the brain.[1] Subsequently, this syndrome of psychiatric symptoms, seizures, dyskinesias, and autonomic dysfunction was shown to be caused by antibodies, which react with NR1/NR2 heteromeric subunits of the *N*-methyl-D-aspartate receptor (NMDAR).[2,3] Anti-NMDAR encephalitis includes, to varying degrees, a prodrome of fever, vomiting, diarrhea, and/or upper respiratory symptoms, followed by combinations of neuropsychiatric symptoms and seizures, movement disorders, dysautonomia, and hypoventilation, and may progress to a state of unresponsiveness, coma, and death. Autoantibody binding leads to decreased expression and resultant hypofunction of NMDAR due to internalization of the receptor at neuronal surfaces, disrupting normal glutamate signaling.[4]

The diversity of initial neuropsychiatric symptoms in these patients, from agitated delirium to movement disorders and seizures, may lead to a missed diagnosis. Although randomized

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clinical trials are lacking, early detection and initiation of immune modulation therapy are important to improve the likelihood of good neurologic outcome.[3] These patients may present to the emergency department with symptoms of a psychiatric disorder, and a high index of suspicion is necessary to begin appropriate diagnostic studies and treatment.

EPIDEMIOLOGY

N-methyl-D-aspartate receptor encephalitis has been reported by the California Encephalitis Project to be a more common cause of encephalitis in those 30 years or younger than individual viral encephalitides, such as those caused by herpes simplex virus (HSV) 1, West Nile Virus, enterovirus, and varicella zoster virus.[5] This finding is limited by selection bias in that diagnostic dilemmas tended to be referred to the California Encephalitis Project. However, a prospective, multicenter observational study in England found NMDAR encephalitis to be the sixth most common cause of encephalitis, behind unknown causes, HSV, *Mycobacterium tuberculosis*, varicella zoster virus, and acute disseminated encephalomyelitis (ADEM).[6]

The patient population affected by NMDAR encephalitis has grown beyond women with teratomas, to include infants as young as 8 months with no identifiable neoplasm.[7] Of the patients with NMDAR encephalitis, 37 to 40% are children,[8,9] and like adults, females are disproportionately represented at 70 to 80%, although this predilection is less robust in young children and infants.[7,9]

CLINICAL PRESENTATION

The clinical history often includes a prodrome of fever, headache, nausea, vomiting, diarrhea, or upper respiratory tract infection symptoms a couple weeks before onset of neurologic or psychiatric changes. The initial presentation in children differs from adults, with a predominantly neurologic phenotype, including seizures (potentially status epilepticus) and movement disorders (choreoathetosis and orofacial dyskinesias),[7,8,10] as opposed to adults, who predominantly have psychiatric complaints such as anxiety, agitation, paranoia, and hallucinations and may be first evaluated by a psychiatrist.[3] Psychiatric signs may be difficult to identify in children, leading to underrecognition of these symptoms. Behavioral changes such as temper tantrums, irritability, insomnia, and alternating periods of somnolence/unresponsiveness with normal mental status have been described early in the course of this syndrome.[9–11] Adolescents often present, like adults, with psychiatric symptoms in addition to seizures and dyskinesias.[9] Uncommon presentations of NMDAR encephalitis in children include isolated Broca aphasia and paroxysmal exercise-induced foot weakness. In both case reports, the patients subsequently had seizures in addition to their initial neurologic complaint. After resolution of their seizures, the isolated neurologic deficit persisted and improved after starting therapy for NMDAR encephalitis.[12,13]

Herpes simplex virus infection is emerging as potential trigger of NMDAR encephalitis in case reports of children who were either undergoing therapy for HSV encephalitis or ocular HSV and developed seizures, dyskinesias, behavioral changes, and/or sleep disturbances.[7,14,15] Although polymerase chain reaction testing of the cerebrospinal fluid (CSF) was negative for HSV, anti-NMDAR antibodies were detected. The children had recently completed a course of intravenous acyclovir therapy at the time of diagnosis, been discharged home and returned to medical attention, or were actively being treated with intravenous acyclovir but had a persistence or evolution of neurologic abnormalities, which led to testing for NMDAR encephalitis.[7,14,15] The association between HSV and NMDAR encephalitis may be more prevalent than is conveyed in the case reports. A retrospective study of CSF and serum samples from patients who had been treated for HSV encephalitis found that 30% of patients had anti-NMDAR antibodies; however, NR1-specific reactivity was detected in only 7% of patients, whereas others had reactivity to NR1/NR2 heteromers.[16] A child who presents with a history of HSV encephalitis and new abnormal neurologic signs may have an antibody-mediated process and not a reactivation of infection.

DIAGNOSIS

Definitive diagnosis is made by identification of antibodies to the NR1 subunit of the NMDAR. Evaluation of the CSF is more sensitive than serum, although serum antibodies may be rarely detected in the absence of CSF antibodies.[16] Evaluating both serum and CSF for anti-NMDAR