EIA is a recurring section of Hospital Pediatrics where expert pediatric hospitalists give their interpretation of the recent evidence in reference to common clinical questions encountered in their daily practice.

How should I manage a patient with presumed encephalitis and neuropsychiatric symptoms?

A previously healthy 12-year-old girl is admitted to your service with new-onset seizures, disorientation, and visual hallucinations. The illness began 10 days before admission with fever, malaise, vomiting, and headache. Despite a supple neck, lumbar puncture in the emergency department revealed cerebrospinal fluid (CSF) pleocytosis with normal glucose and protein levels, a negative Gram stain, and a negative enteroviral polymerase chain reaction (PCR) result. Supportive therapy and acyclovir are initiated. Are any other treatments indicated?

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Although this question will depend on further diagnostic evaluation for entities such as acute disseminated encephalomyelitis, ingestions, and even brain tumors, many practitioners will place encephalitis, likely infectious, at the top of their differential diagnoses on the basis of fever, encephalopathy, and CSF pleocytosis. How many practitioners would consider autoimmune encephalitis secondary to anti–*N*-Methyl-D-aspartate receptor (NMDAR) antibodies in this patient with a febrile viral prodrome and neuropsychiatric symptoms?

Anti-NMDAR encephalitis results from an antibody-mediated immune response against the NR1 subunit of the NMDA receptor. Psychiatric and behavioral symptoms are prominent, as are seizures (usually generalized tonic-clonic), dyskinesias, language dysfunction (more frequent in children), and autonomic instability (less frequent in children). Patients with the fulminant form often require prolonged hospitalization with cardiorespiratory support. Conversely, variations in presentation and the protracted course of symptom development can lead to delays in treatment and misdiagnosis. Originally described in 2007 as a paraneoplastic syndrome (especially in young women with ovarian teratomas), current evidence suggests it should be classified as a neuroautoimmune syndrome, in which antibodies are formed in response to both tumors and infection.[1] The condition predominately affects women and younger individuals, with children comprising ~40% of cases in 2 large series.[2,3]

In the April issue of *Clinical Infectious Diseases*, Gable et al[4] report on the frequency of anti-NMDAR encephalitis versus infectious etiologies on the basis of data from the California Encephalitis Project (CEP), a program established in 1998 to study the epidemiology and identify the etiologies of encephalitis. Physicians of patients with suspected encephalitis submit specimens to the CEP for diagnostic testing. The CEP case definition is: immunocompetent, ≥6 months of age, and under hospitalization for encephalopathy (altered mental status) with at least 1 clinical or diagnostic finding of fever, seizure, focal neurologic finding, CSF pleocytosis, EEG alteration, or neuroimaging abnormality. A standardized case history

is submitted by the referring physician. Serum, CSF, and respiratory specimens are also submitted and tested for 15 potential agents, including herpesviruses, arboviruses, respiratory viruses, and *Mycoplasma pneumoniae.* Since 2007, if signs and symptoms are suggestive of anti-NMDAR encephalitis (eg, movement disorders, autonomic instability, psychosis), CEP contacts the referring physician to obtain consent for additional testing. Although serum testing for anti-NMDAR antibodies can be done, CSF testing is much more sensitive.

The authors studied cases of patients who presented to the CEP between September 2007 and February 2011 if they met the CEP case definition and were ≤30 years of age.[4] By using appropriate statistical techniques, the authors compared demographic characteristics, frequency, and clinical data of patients who tested positive for anti-NMDAR antibodies versus those with identified infectious etiologies: enteroviruses, herpes simplex virus 1 (HSV-1), varicella-zoster virus (VZV), and West Nile virus (WNV).

In the 761 cases studied, an infectious etiology was identified in 47 patients (enterovirus in 30 patients, HSV-1 in 7, and VZV and WNV in 5 each).[4] Another 47 patients were suspected of having anti-NMDAR encephalitis and were tested; 32 tested positive. Among the 79 encephalitis cases with a known etiology, anti-NMDAR encephalitis was significantly more common than HSV-1 (41% vs 9%; $P < .01$), VZV (41% vs 6%; $P < .01$), and WNV (41% vs 6%; $P < .01$). Most (65%) anti-NMDA encephalitis cases occurred in patients aged ≤18 years. Females were affected significantly more often than males, at ~3 times the rate ($P < .01$), whereas other causes had no gender predilection. The article goes on to delineate differences in physical signs and symptoms, as well as laboratory, EEG, and imaging findings between anti-NMDAR encephalitis and the infectious encephalitides. Financial data presented suggest that early testing in appropriate patients may be cost-effective as well as life-saving.

Clearly the major limitation of this study[4] is referral bias. Referrals are voluntary and most likely reflect more severe cases in which an etiology has not been determined after testing performed at other laboratories. Enteroviral and HSV PCRs are widely available, and (especially if positive) physicians may not pursue further testing or be unaware of the CEP. Despite this limitation, the authors add to the growing literature about the importance of this newly described condition, which has crucial diagnostic and treatment implications. Although there are other autoimmune mediators of encephalitis that are known and for which testing is possible, anti-NMDAR encephalitis seems to be the 1 more commonly reported in pediatric patients.

Treatments include potent immunosuppressant agents such as high-dose intravenous corticosteroids, intravenous immunoglobulin, anti-inflammatory agents, plasmapheresis, and monoclonal antibodies. Patients often require intensive care and may be hospitalized for 2 to 14 months. Recovery, which may be incomplete, can take ≥3 years and relapse may occur in 20% to 25% of patients.[1]

If the patient in the vignette tests positively, in addition to supportive care, she should be treated with immunosuppressive therapy and worked up for malignancy.

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