7% (10/144) of children <5 years of age who received 2011 TIV (Solvay) had fever reported, and only 1 child had a temperature >39.5°C. No convulsions were reported, and none of the children who had adverse events required assistance from a healthcare professional.[14] It is also similar to a recent report of Sanofi Pasteur seasonal vaccine experience in Canada in 2008.[15]

Reduced TIV vaccine uptake in children is likely to result in increased influenza-related hospitalization, morbidity, and mortality.[14,16,17] It remains important that both providers and the public have confidence in the safety of TIV in children. Pharmaceutical regulatory agencies may require that reactogenicity/fever studies be conducted in children by vaccine manufacturers each year before widespread use in the community, as was done in Australia in 2011 with CSL trivalent influenza vaccine; however, this was limited to children aged more than 9 years. Vaccine safety and adverse events after TIV receipt should continue to be monitored each year by immunization surveillance systems following adverse events, and experiences in the southern hemisphere can be used to inform the use of TIV in northern hemisphere countries and vice versa.

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ANTI-*N*-METHYL D-ASPARTATE RECEPTOR ENCEPHALITIS MIMICS VIRAL ENCEPHALITIS

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Abstract: We describe the clinical courses of 3 children with a psychochoreiform encephalitis associated with anti-N-methyl D-aspartate receptor autoantibodies. These cases, including the most severely medically complicated survivor to date, illustrate the challenges of diagnosis, supportive care, and immune-modulating therapy. Clinical and laboratory features are similar to those of viral encephalitis, and the condition is often reversible with appropriate diagnosis and treatment.

Key Words: anti-NMDA, *N*-methyl D-aspartate receptor, encephalitis, autoimmune, movement disorder, choreoathetosis

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Viral encephalitis is challenging to manage because of the severity of illness, extensive potential etiologies, and overlap with noninfectious encephalitis. Among the latter, physicians should be aware of an emerging group of disorders associated with antibodies to synaptic proteins.[1] The most frequent and best

studied of these disorders is anti-N-methyl D-aspartate receptor (NMDAR) encephalitis, which was initially described in young adult females with teratomas.[2] Recent studies show that this entity also occurs without tumors in adults and children of either sex.[3,4]

We report 3 patients with anti-NMDAR encephalitis seen in a single institution during a 12-month period. Diagnostic and management differences with viral encephalitis are underscored in all 3 cases, including one of the most severe, yet reversible, clinical courses of this disorder reported to date.

CASE 1

A 15-year-old girl presented to an emergency department with a week-long history of agitation and new-onset auditory and visual hallucinations, and she was transferred to a psychiatric facility. Other than a temperature of 38°C, there was no preceding illness. Evaluation of subsequent hypertension included normal cranial computed tomography (CT) and electroencephalography (EEG) demonstrating unilateral temporal epileptiform activity. Erythrocyte sedimentation rate (ESR) was 54 mm/h, and C-reactive protein (CRP) level was 4.7 mg/dL. Cerebrospinal fluid (CSF) showed 100 white blood cells/mm^3, with 96% lymphocytes and normal protein and glucose levels. After receiving anticonvulsants and ceftriaxone, the patient was transferred to our pediatric intensive care unit (PICU).

On hospital day (HD)1, the patient was afebrile and obtunded. Given concern for viral encephalitis, acyclovir was added to the therapy. Because acute disseminated encephalomyelitis was suspected, a 3-day course of high-dose methylprednisolone was administered. Loss of airway protective reflexes prompted intubation on HD3. She developed rhythmic movements of the mouth, choreoathetosis, and temporal seizures. Brain magnetic resonance imaging (MRI) results were normal. Repeat CSF examination on HD3 revealed oligoclonal bands, but the results were otherwise normal; test results were negative for enterovirus, herpes simplex virus (HSV)-1 and 2, human herpesvirus 6, and varicella.

On HD6, she developed fever of 38.9°C, followed the next day by multiorgan dysfunction, disseminated intravascular coagulation, worsening lung disease, and renal failure requiring continuous venovenous hemodiafiltration. Acyclovir was discontinued. Abdominal/pelvic ultrasound and CT suggested calcification in the right ovary.

CSF analysis revealed anti-NMDAR antibodies. She was restarted on methylprednisolone, together with intravenous immunoglobulin (IVIG). On HD13, abdominal MRI revealed an ovarian teratoma. Both serum carcinoembryonic antigen (CEA) and cancer antigen 125 (CA-125) were elevated at 25.1 ng/mL and 265 U/mL, respectively.

Plasmapheresis was initiated on HD13, and the ovarian teratoma was resected on HD14. With worsening acute respiratory distress syndrome, on HD17, a 4-day course of extracorporeal membrane oxygenation was started, followed by prolonged high-frequency oscillatory ventilation. By HD28, CEA levels were normal (2.6 ng/mL), and CA-125 levels were decreasing (75 U/mL). Methylprednisolone and IVIG treatment was repeated. By HD49, ongoing multiorgan dysfunction, lack of neurologic improvement, and increasing CEA (8.2 ng/mL) and CA-125 (124 U/mL) levels suggested an occult contralateral ovarian teratoma. Two days after a dose of cyclophosphamide, she underwent contralateral oophorectomy, notable for incidental bowel obstruction, requiring hemicolectomy and temporary ileostomy. Ovarian histology, however, was normal. In the following week, she became more alert, with increasingly purposeful movements.

She underwent tracheotomy for chronic ventilation on HD78, and after 3 months in the PICU, was transferred to the rehabilitation service. She was discharged on HD167, decannulated and ambulating independently, with neurologic status near baseline. One year later, she was at age-appropriate grade, with no appreciable deficits.

CASE 2

An 11-year-old previously healthy girl developed headache and vomiting without fever or other signs of illness. Two days later, she inexplicably began to scream and cry. The following day, she was seen at an emergency department for facial twitching. She was afebrile and awake but was admitted for abnormal behavior. She developed rhythmic arm movements persisting in sleep, with intermittent agitation and nonsensical statements alternating with periods of lucidity. On transfer to our PICU, CSF examination findings were normal. Treatment with anticonvulsant and acyclovir was started. EEG demonstrated temporal slowing. ESR was 28 mm/h, and the CRP level was normal. With decreasing purposeful movements and episodic apnea, she was intubated. Brain MRI revealed mild right parietal cortical edema suggesting encephalitis. She developed intermittent low-grade fever (38.2°C). Polymerase chain reaction results were negative for enterovirus and HSV-1 and 2. IVIG therapy was ineffective. Abdominal/pelvic ultrasound and CT results were obtained on HD12, suggesting a calcified complex ovarian mass. Archived CSF from HD5 revealed oligoclonal bands and tested positive for NMDAR antibodies.

Laparoscopic oopherectomy on HD13 revealed a teratoma. Subsequently, she was started on a 5-day course of methylprednisolone. By HD23, she showed voluntary movements and was mouthing words. She was discharged on HD55. Neurologic examination findings 3 months later were normal except for short-term memory deficit.

CASE 3

A previously healthy, 9-year-old identical twin girl presented with new-onset generalized tonic-clonic seizure without fever. MRI results were normal, and EEG showed left hemispheric slowing. She was discharged home on valproate. One week later, she developed recurrent seizures, followed by ataxia, confusion, agitation, hallucinations, roving eye movements, facial dyskinesias, and chorea. ESR was 15 mm/h, with normal CRP levels. Repeat brain MRI and CT results were normal. CSF examination showed 24 white blood cells/mm^3 (94% lymphocytes), with normal protein and glucose levels; she received ceftriaxone and acyclovir, until culture results and HSV-1 and 2 and enterovirus polymerase chain reaction results were negative. She had fever from HD4 to 7. Screening was positive for CSF anti-NMDAR antibodies. Extensive work up for teratoma, including serum tumor markers, pelvic ultrasound, and CT and MRI of the chest, abdomen, and pelvis were negative.

Symptoms did not respond to a 5-day course of IVIG and methylprednisolone, followed by 10 cycles of plasmapheresis. On HD25, she received cyclophosphamide, which resulted in substantial improvement of the abnormal movements and agitation. However, she continued to have difficulty with communication, eating, and sleep-wake cycles. She was discharged on HD69. Monthly cyclophosphamide therapy continued for 6 months, and prednisone was tapered slowly. One year later, abdominal/pelvic MRI results were normal; CSF analysis revealed oligoclonal bands. Nearly 20 months after discharge, she had moderate expressive and receptive language deficits, and an otherwise nonfocal neurologic examination.

DISCUSSION

Recognition of anti-NMDAR encephalitis is important because it is a potentially reversible condition that can be confused

with viral encephalitis. Although HSV is considered and treated empirically in many cases of encephalitis, including our series, anti-NMDAR encephalitis may be at least as common in the preadolescent/adolescent population. Our 3 patients presented to a single tertiary pediatric center (with ~1700 PICU admissions/y) during a 12-month period. Our institution annually tests approximately 100 CSF samples for HSV; in the last 4 years, we have identified only 2 positive cases outside the neonatal period. A prospective study of encephalitis in Europe showed that 4% of patients had anti-NMDAR encephalitis, which, among immune-mediated causes, was second only to acute disseminated encephalomyelitis.[5]

Anti-NMDAR encephalitis usually presents with prodromal headache, fever, or fatigue, followed by psychiatric symptoms or memory problems, and abnormal movements, including choreoathetosis, dyskinesia, or dystonia. Additionally, many patients have seizures, autonomic instability, decreasing level of consciousness, and hypoventilation.[2,3,6] In children and adolescents, behavioral and speech problems and seizures are relatively common at presentation.[3] Our patients presented with neuropsychiatric symptoms and subsequently developed mild fever. In comparison with encephalitides caused by HSV, enterovirus, and rabies, anti-NMDAR encephalitis has an increased frequency of psychiatric symptoms and lower frequency of abnormal MRI findings.[7] In both viral and anti-NMDAR encephalitis, the CSF often shows mononuclear pleocytosis.

Initial treatment is directed toward removal of teratoma, if present. However, detection of teratoma can be challenging. In case 1, ultrasound and CT were inconclusive, whereas MRI was diagnostic. When teratoma resection and first-line immunotherapies (corticosteroids, IVIG, plasma exchange) fail, second-line immunotherapy including rituximab and cyclophosphamide is usually effective.[1,6] In children, rituximab has been preferred over cyclophosphamide, but the latter is equally efficacious.[8] The frequent necessity of aggressive immunotherapy is likely because of the production of antibodies intrathecally and in the central nervous system by infiltrating plasma cells.[9] Bilateral ovarian teratomas may occur, and radiographically occult teratoma in the contralateral ovary should be considered in refractory or relapsing cases.[2] The role of tumor markers in establishing risk for occult tumor is undetermined. Some patients with nonresected tumors have recovered spontaneously[10]; however, the duration and severity of symptoms may be increased.[11]

Although 2 of our cases had teratomas identified, this is less common in pediatric anti-NMDAR encephalitis. In a recent large series, of girls <18 years and <14 years of age, the frequency of teratoma was 31% and 9%, respectively.[3] No tumor was identified in case 3, whose recovery was slowest and least complete.

The severity of this disease is illustrated, in our series, by the need for ICU admission and extended hospitalization. The extremely complicated clinical course of case 1 underscores the utility of intensive care for eventual complete recovery. This is the first case necessitating extracorporeal membrane oxygenation, continuous veno-venous hemodiafiltration, and high-frequency oscillatory ventilation.

In summary, anti-NMDAR encephalitis is relatively frequent, and it should be considered in the differential of viral encephalitis, especially in the older female child. Clinicians should have a high index of suspicion when characteristic psychochoreiform features are present, even when fever is absent. Management of such patients is based on a thorough search for teratoma (and prompt removal, if found) as well as aggressive immunotherapy and supportive care.

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DISSEMINATED CRYPTOCOCCAL INFECTION IN PATIENT WITH NOVEL JAK3 MUTATION SEVERE COMBINED IMMUNODEFICIENCY, WITH RESOLUTION AFTER STEM CELL TRANSPLANTATION

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Abstract: Disseminated cryptococcal infection is the second most common cause of death after tuberculosis in acquired immune deficiency syndrome patients. Surprisingly, it has been reported only in few patients with primary immunodeficiency diseases. Herein, we report the clinical presentation and outcome of a 23-month-old boy with novel JAK3 mutation severe combined immunodeficiency disease complicated by severe disseminated cryptococcal infection.

Key Words: cryptococcosis, SCID, hematopoietic stem cell transplantation

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