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Nine-Year-Old Girl With Altered Mental Status

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Case Report

A 9-year-old girl with no significant past medical history was brought to the emergency department by emergency medical service due to hysteria and altered mental status. According to both family and school reports, her presentation was the culmination of a 2-month history of progressive personality and behavioral changes. During this time, the child went from being a "bubbly" and outgoing honor student to being withdrawn, depressed, and failing all her classes.

Approximately 1 month prior to this presentation, the patient was found unconscious by her family at the bottom of a staircase after a presumed unwitnessed fall. She was evaluated in the local emergency department and discharged home in good condition. A few hours after discharge, however, she had a witnessed seizure-like episode lasting approximately 5 minutes. Head computed tomography (CT), electroencephalography (EEG), and electrolytes were all negative. She was observed overnight and discharged with a diagnosis of posttraumatic seizure.

Family denied any further seizure episodes, recent illnesses, known ingestions or missing medications, fevers, sore throat, headaches, vomiting, diarrhea, rashes, joint swelling, or pain. The patient did have decreased oral intake associated with weight loss of approximately 5 pounds. Review of systems was otherwise negative. She lived at home with married parents and 3 younger siblings. There were no recent changes or stressors in patient's home or school life. Family history was unremarkable; specifically there were no relatives with mental illness, seizures, childhood cancers, or autoimmune disorders.

On admission, vital signs, general physical exam, as well as were neurologic exam, including cranial nerves, fundoscopic exam, sensation, strength, tone, deep tendon reflexes, coordination, and gait were all normal. Mental status exam was significant for emotional liability, easy distractibility, dysphasia, anomia, thought blocking, and confusion. The patient was oriented to self, but not to location, time, or situation. She did not recognize her parents and was able to follow simple commands only intermittently. Head CT, comprehensive metabolic panel, drug screen, and complete blood cell count with differential were all unremarkable. The patient was admitted to the inpatient pediatric service for further evaluation and care. Neurology and psychiatry services were consulted shortly after admission.

Hospital Course

At the time of admission, numerous potential causes of altered mental status were considered. Partial seizures and postictal states were thought to be likely given the recent seizure-like episode. Viral encephalitis was also felt to be possible despite lack of reported fevers, headaches, nausea, or emesis. Pediatric autoimmune neuropsychiatric disorder associated with Streptococcal infection was also considered despite no reported history of proceeding pharyngitis. Psychiatric causes, including major depressive disorder, posttraumatic stress disorder, conversion disorder, and malingering were thought possible despite patient's young age, lack of family history of mental illness, and lack of known precipitating events or stressors. Postconcussive syndrome was felt to be possible given patient's history of head trauma; however, this would not explain the onset of symptoms prior to the fall. Rare causes of altered mental status such as thyroid disorders, Wilson's disease, and paraneoplastic syndromes were also considered, but thought to be unlikely given no suggestive associated symptoms, physical exam, or laboratory findings.

Although herpes simplex virus encephalitis was thought to be extremely unlikely, given the potential devastating consequences of a missed diagnosis intravenous acyclovir while further testing was pursued. Brain magnetic resonance imaging was normal. EEG showed diffuse

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nonspecific slowing in the left frontal lobe. Antiepileptic treatment with Lamotrigine was initiated, but did not alter her symptoms. Cerebrospinal fluid (CSF) analysis was remarkable for 16 white blood cells with lymphocytic predominance in the setting of normal red blood cell count, protein, and glucose. Infectious studies of CSF and serum, including herpes simplex virus, Epstein–Barr virus, enterovirus, cytomegalovirus, and mycoplasma were negative as were antistreptolysin O titers and thyroid studies.

Symptoms of emotional liability and confusion persisted. In addition, the patient developed abnormal hand movements and became increasingly agitated and at times violent toward self and others. Risperidone initiation led to a decreased frequency of violent outbursts. She also experienced periods of bowel and bladder incontinence. On hospital day 6, the child experienced multiple brief transient episodes of bradycardia with heart rates in the 40s associated with bradypnea as well as brief oxygen desaturations to the 70s.

Final Diagnosis

On hospital day 7, serum studies returned positive for anti-*N*-methyl-D-aspartate receptor (NMDAR) antibodies, confirming the diagnosis of anti-NMDAR encephalitis. Given the association of the diagnosis with ovarian teratoma, a pelvic CT was performed and was normal. Immunoglobulin therapy and a 5-day intravenous steroid burst followed by a 6-week oral steroid taper were started. Because of significant limitations in activities of daily living, the child was evaluated and followed by physical, occupational, and speech therapies, an education specialist, as well as by the physical medicine and rehabilitation service. On the second day of therapy, she was able to recognize her parents. Although the patient had no further episodes of autonomic instability or abnormal movements and was overall significantly improving during the hospitalization, she continued to have emotional liability despite increase in risperidone and addition of citalopram. Following a 2-week stay on the medical service, the patient was transferred to inpatient rehabilitation. She was discharged home on hospital day 26 with close follow-up with physical, occupational, and speech therapies, as well as behavioral health, neurology, and rehabilitation.

Discussion

Anti-NMDAR encephalitis is a neuropsychiatric disorder first noted in adult women with ovarian teratoma, but now increasingly recognized in pediatric patients, men, and those without evidence of cancer.[1-7] In 2007, Dalmau et al[4] described a characteristic constellation of symptoms in the presence of positive anti-NMDAR antibodies. Pediatric anti-NMDAR encephalitis was then further characterized by Florance et al[5] in 2009. Characteristic features of this disorder include psychiatric symptoms such as insomnia, anxiety, delusions, paranoia, and social withdrawal followed in days to weeks by speech disintegration, movement abnormalities, seizures, hypoventilation, and autonomic instability.[1-6]

Diagnosis of anti-NMDAR encephalitis can be particularly challenging and consequently delayed in children as early psychiatric symptoms might easily be attributed to developmentally appropriate behaviors such as temper tantrums, anxiety, or hyperactivity.[2,3,5,6] Behavioral changes in our patient, for instance, were initially attributed by her family to normal "moodiness" of approaching adolescence. Although more than three quarters of adolescent and adult patients are first evaluated by a psychiatrist, younger children tend to first present because of nonpsychiatric symptoms associated with this disorder.[1-3,5]

CSF antibody testing is the gold standard of diagnosis and is suggested for all patients in whom anti-NMDAR encephalitis is suspected.[3,6] Positive serum testing is adequate, however, as there have been no known cases in which antibody has been detected in the serum but not in the CSF. However, if serum studies are negative, CSF studies should be completed, as patients can be positive in CSF alone.[5,8] Brain magnetic resonance imaging changes are seen in only about 50% of cases.[2] Nonspecific EEG changes as well as CSF lymphocytic pleocytosis with oligoclonal bands are seen in the majority of patients, especially during later stages of the disease.[2,3,5,6]

Pelvic or testicular imaging is recommended for all patients diagnosed with anti-NMDAR encephalitis as underlying tumors, most commonly teratomas, were present in 58% of patients described in the initial case series.[2] Tumors are less frequent in children, seen in 31% of patients younger than 18 years and in 9% of those younger than 14 years.[5] Continued surveillance is recommended as cancer can present years following the initial encephalitis diagnosis.[3,6]

In addition to identification and management of any associated tumors, first-line treatment also includes steroids and immunoglobulin therapy.[3,6,8] If these are unsuccessful, additional treatment options include cyclophosphamide, rituximab, and/or plasmaphoresis. Behavioral health as well as physical, occupational, and speech therapy and potentially inpatient rehabilitation can be greatly beneficial for these patients and should be used

when available.[1,3] Despite the often severe and devastating symptoms, anti-NMDAR encephalitis responds well to treatment with about 75% of patients showing substantial improvement or complete recovery.[2,3]

Conclusion

Anti-NMDAR encephalitis is a severe, but potentially treatable disorder that should be considered in any child or adolescent presenting with acute or subacute altered mental status changes, especially if accompanied by other characteristic features such as abnormal movements, speech disintegration, insomnia, seizures, or autonomic instability. As patients with mental status and behavioral changes are evaluated in many health care settings, it is important for providers, including primary care and emergency physicians, hospitalists, neurologists, psychiatrists, and psychologists to be aware of this diagnosis.

Declaration of Conflicting Interests

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