Ictal Asystole and Anti–*N*-Methyl-D-aspartate Receptor Antibody Encephalitis

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ABBREVIATIONS
NMDAR—*N*-methyl-D-aspartate receptor
V-EEG—video electroencephalogram

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abstract

Anti–*N*-methyl-D-aspartate receptor (NMDAR) antibody encephalitis is a recently identified autoimmune disorder that is increasingly recognized in children. Most cases occur in girls and women and may be paraneoplastic with an associated ovarian teratoma. Characteristic clinical features include neuropsychiatric symptoms, dyskinesias, decreased consciousness, and autonomic instability. We report the first case of asystole associated with temporal lobe seizures in this disorder and highlight the need for careful monitoring for this potentially fatal complication. A 15-year-old previously healthy girl presented with focal seizures and personality changes that progressed to periods of agitation and confusion alternating with catatonia. Anti-NMDAR antibodies were detected in the cerebrospinal fluid and serum. Twenty-six days after initial presentation, new seizures developed characterized by bradycardia and oxygen desaturation. Continuous video-electroencephalogram monitoring captured 3 seizures with left-temporal onset and associated asystole. An ovarian teratoma was diagnosed by pelvic ultrasound and computed tomography, and surgical resection was followed by gradual improvement in her neuropsychiatric symptoms. Treatment with phenobarbital beginning on day 26 lead to the cessation of seizures. However, asymptomatic bradycardia and pauses of 3 seconds continued. After insertion of a demand pacemaker on day 46, there were no further cardiac events. The patient was also treated with 2 courses of intravenous immunoglobulin. Outpatient follow-up at 4 months revealed near-complete neurologic recovery and no cardiac events. To our knowledge, ictal asystole has not previously been described as a complication of anti-NMDAR encephalitis; it is a preventable cause of death in this emerging pediatric disorder, which presents with protean symptoms and is easily misdiagnosed. *Pediatrics* 2011;127:e781–e786

Anti–*N*-methyl-D-aspartate receptor (NMDAR) antibody encephalitis is a recently described immune-mediated disorder that has been reported most commonly in young women and girls.[1–3] Presentation usually includes a viral-like prodrome, followed by prominent changes in mood and personality that often lead to initial misdiagnosis of a primary psychiatric disorder. Symptoms progress over days or weeks to alternating periods of catatonia with agitation. Typical clinical features include dyskinesias, seizures, and autonomic instability.[2,3] This disorder is increasingly common among children, who comprise up to 40% of all cases.[2,3]

Ictal asystole is rare and usually associated with focal seizures that arise from the temporal lobes.[4,5] Cardiac rhythm abnormalities seen with anti-NMDAR antibody encephalitis have been attributed to autonomic instability, but to our knowledge, ictal asystole has not been previously reported with this disorder. In the initial case series of 100 patients with a mean age of 23 years (range: 5–76 years), 37 had cardiac dysrhythmia. Sixteen patients had tachycardia, 7 had bradycardia, and 14 had both. Four patients required cardiac pacemaker placement.[2] A better understanding of ictal asystole is important in the prevention of SUDEP (sudden unexplained death in epilepsy).[5–8] The following case is reported to show the association of ictal asystole and anti-NMDAR antibody encephalitis.

CASE REPORT

A 15-year-old, previously healthy, right-handed girl presented with sudden onset of personality changes and seizures. During seizures, she sat up with her eyes open, was confused, stared, and raised both arms (right slightly more than left) for 30 to 45 seconds with recurring events every 30 to 45 minutes. Occasional longer seizures of up to 1 minute progressed to bilateral tonic extension of arms and legs. The patient reported a poorly characterized generalized cutaneous sensory aura. Initial video-electroencephalogram (V-EEG) monitoring revealed a normal background and poorly characterized ictal pattern during the longer seizures. At the onset, a midline and bilateral frontal-central low-voltage sinusoidal 10- to 12-Hz rhythm evolved to rhythmic-theta and then rhythmic-delta frequencies. As the clinical seizure continued, the amplitude of the ictal pattern gradually increased and discharges became generalized. Intravenous fosphenytoin initially controlled the seizures completely.

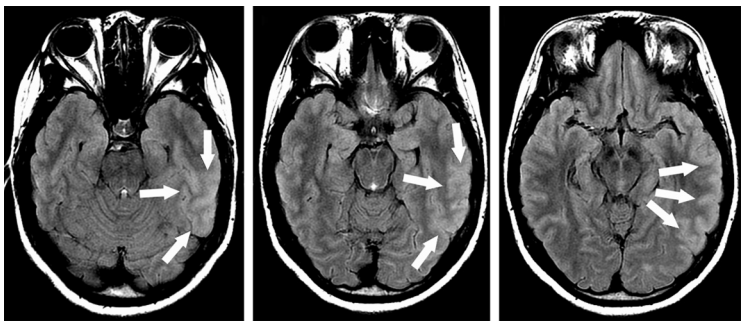

FIGURE 1
Sequential MRI axial fluid-attenuated inversion recovery (FLAIR) images of the brain performed 2 weeks after initial presentation. Subtle increased FLAIR signal in the left posterior temporal lobe cortex (arrows), with associated subtle gyral thickening, can be seen. The mild increased FLAIR signal in the medial temporal lobes was also noted.

The patient had a prodrome of mild upper respiratory infection symptoms and diarrhea that had resolved 1 week before onset of the seizures. There was no family history or other risk factors for epilepsy. After treatment for seizures with fosphenytoin, findings from the neurologic examination were normal. Initial screening serum study results were remarkable for a leukocytosis (white blood cell count: 21×10^9/L; normal range: 4.5–13.5 $\times 10^9$/L). Cerebrospinal fluid revealed a red blood cell count of $<1 \times 10^6$/L (normal range: 0–10 $\times 10^6$/L), a white blood cell count of 17×10^6/L (normal range: 0–5 $\times 10^6$/L), lymphocytes at 84% (normal range: 63%–99%), a protein level of 18 g/L (normal range: 20–80 g/L), and a glucose level of 3.8 mmol/L (normal range: 2.1–3.6 mmol/L). Empiric intravenous acyclovir was given until the results of herpes simplex virus polymerase chain reaction from the cerebrospinal fluid returned negative. MRI of the brain with contrast was significant for cortical increased signal in the fluid-attenuated inversion recovery sequence located in the left posterior temporal lobe (Fig 1).

By day 5 after presentation, her mental status regressed to periods of aggression and disinhibition alternating with catatonia. Risperidone was added for the treatment of aggressive behavior and delirium. On day 13, intravenous methylprednisolone, 1 g/day for 7 days, was started and led to slightly less agitation. An elevated serum creatine kinase level on day 20 (2896 IU/L; normal range: 29–165 IU/L) resolved with hydration. Hypertension was treated with amlodipine and atenolol. Intermittent hyperthermia occurred without an identified infectious source. Clinical suspicion of an infectious-, metabolic-, or immune-mediated encephalitic process was high, and extensive cerebrospinal fluid and serum studies, including a test for anti-NMDAR antibodies, were sent. On day 21, intravenous immunoglobulin (2 g/kg) also led to partial subjective im-

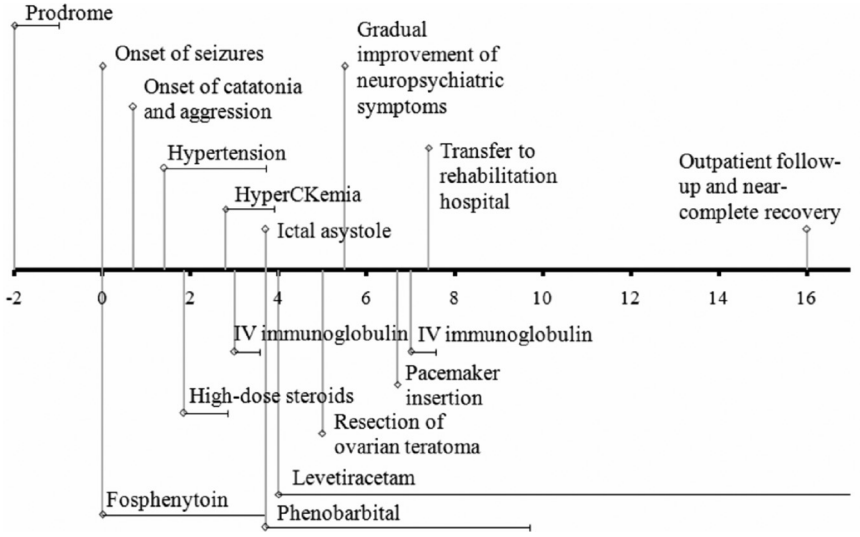

FIGURE 2
Time line (in weeks) of symptoms and treatment of anti-NMDAR encephalitis. HyperCKemia indicates elevation of serum creatine kinase concentration.

provement (Fig 2). Despite the mild improvement, the patient had a persistent poor sleep-wake cycle, abnormal movements of her face and arms, and periods of agitation.

On day 26, the patient had new episodes of bradycardia and oxygen desaturation. V-EEG monitoring performed to evaluate for subclinical seizures captured 3 focal seizures with left-temporal onset and secondary generalization, all associated with cardiac asystole (Fig 3). At the end of the seizure (during asystole), the patient exhibited bilateral limb extension and stiffening followed by a few myoclonic jerks. The V-EEG showed a well-organized, but slowed, background with a 7- to 8-Hz posterior dominant rhythm and no interictal epileptiform discharges, asymmetries, or focal abnormalities. All of the seizures lasted ~3 minutes and resolved without intervention. Cardiac asystole lasted an average of 22 seconds (range: 13–32 seconds) and occurred an average of 73 seconds (range: 65–80 seconds) after onset of the seizure. Two separate asystolic events occurred during 2 of the seizures, and a single asystole occurred during 1 seizure. The patient was transferred to the ICU, and results of cardiac rhythm monitoring, an electrocardiogram, and an echocardiogram were normal. In response to the arrhythmia, phenobarbital replaced fosphenytoin (serum phenytoin level: 12.6 mg/L; therapeutic range: 10–20 mg/L), and the risperidone and antihypertensive medications were discontinued. The absence of further seizures was confirmed by V-EEG monitoring, and the record also revealed the persistent lack of normal sleep-wake patterns. Cerebrospinal fluid and serum specimens, collected before intravenous immunoglobulin administration and sent to a university research laboratory after informed consent was obtained,[1–3] contained antibodies to NMDAR. All other test results were negative. Pelvic ultrasound and computed tomography revealed an ovarian mass that measured ~2 cm^2. The patient underwent laparoscopic partial resection of the ovary, and pathology revealed a mature cystic teratoma.

After removal of the teratoma, the patient's neuropsychiatric symptoms gradually improved. Follow-up screening V-EEG monitoring showed improvement of the posterior dominant rhythm to 9 Hz. Cardiac rhythm monitoring showed occasional asymptomatic bradycardic events and pauses up to 3 seconds. The patient received a transvenous single-chamber rate-responsive pacemaker. Intravenous immunoglobulin continued monthly for 2 months, and the patient was transferred to inpatient rehabilitation on day 52. At follow-up 4 months after initial presentation, the patient had no recollection of the hospitalization, is seizure-free on levetiracetam monotherapy, and has normal sleep patterns and no abnormal movements. There were no significant cardiac events, and the pacemaker activated for a heart rate of <60 beats per minute only 4% of the time since insertion. Results of a neurologic examination were normal except for subtle short-term memory deficits.

DISCUSSION

Encephalitis associated with the NR1/NR2 heteromers of the NMDAR is a recently identified autoimmune disorder. Although originally described in women with ovarian teratoma,[1] subsequent case series included men, women, and children with and without tumor.[2,3] As in adults, pediatric anti-NMDAR encephalitis is usually preceded by a viral-like illness. Within weeks, changes in mood and personality appear and progress over days or weeks. Prominent features include dyskinesias, seizures, and autonomic instability.[2,3] In case reports, two-thirds of adult[2] and only 23% of pediatric[3] patients had severe central hypoventilation. Other autonomic features such as hypertension, tachycardia, or hyperthermia have been reported to occur in both adults and children.[3] Severe cardiac dysautonomia, including asystole,[9] necessitates pacemaker insertion in up to 4% of adults in reported series. In contrast, there have been no pediatric cases of severe cardiac dysrhythmia.[2,3]

FIGURE 3

EEG showing seizure-associated asystole (sensitivity: 10 μV/mm; bars = 1 second). A, Near-onset of seizure in left anterior-midtemporal region with rhythmic-theta-alpha pattern that spread to the frontal area and then the entire left hemisphere. B, An EEG of the same seizure 80 seconds after onset showed generalized epileptiform discharges with asystole (arrow) that lasted 28 seconds.

Ictal tachycardia is common (occurs in 80% of seizures), whereas ictal bradycardia is rare with a prevalence closer to 5%.[5,8,10–12] Ictal asystole is usually associated with focal seizures and has a reported prevalence of 0.3% to 0.4% of patients with epilepsy.[4,8,13] Asystole does not occur with every seizure, so prevalence may be artificially low because of limited sampling. Clinical signs of ictal asystole include a sudden loss of tone or unexplained falls.[14] Asystole that persists beyond 10 seconds or more may present with atonia with or without generalized tonic posture followed by myoclonic jerks.[4] Cardiac events associated with seizures are important because of their potential link to the phenomenon of SUDEP (sudden unexplained death in epilepsy).[5,7]

Activation of the autonomic centers in the temporal lobes is the leading mechanism associating ictal activity with asystole.[4,5,8] Results of animal studies have shown that persistent stimulation of the left posterior insular cortex results in bradyarrhythmia, complete heart block, and asystolic death.[15] In some human studies, intraoperative stimulation of the left posterior insula caused bradycardia, and stimulation of the right anterior insula caused tachycardia.[16,17] Another study found no lateralization and reported onset of bradycardia after generalization of the seizure.[8]

Pharmacologic management of ictal asystole focuses on complete seizure control.[18] After the diagnosis of ictal asystole in this case, phenytoin was empirically replaced by phenobarbital as a precaution. Even after a negative evaluation for cardiac structural and electrical abnormalities, it seems prudent to use anticonvulsants that do not have potential cardiac rhythm effects. Data on the indications for the use of pacemaker therapy for patients with severe ictal bradycardia or asystole have been limited to case reports or series.[14,18–21] In a study of 6 patients with intractable epilepsy and pacemakers for ictal asystole, none had recurrence of asystole or bradycardia leading to pacemaker activation after 5 years.[19] In the present case, the decision was based on the duration of the asystole and the uncertainty of potentially fatal recurrence despite anticonvulsant therapy.[14]

On the basis of case reports and series, treatment of anti-NMDAR encephalitis includes resection of an identified tumor and immunotherapy.[1–3,9,22] Initial immunotherapy consists of methylprednisolone, intravenous immunoglobulin, or plasma exchange. Refractory cases without an identified tumor may benefit from rituximab or cyclophosphamide.[2,3,22,23] Approximately 75% of the patients will have full or near-complete recovery with effective treatment, but 25% may relapse.[3] Full recovery occurs more frequently in patients with an identified and resected teratoma.[1,3]

CONCLUSIONS

This case illustrates the novel association of ictal asystole and anti-NMDAR antibody encephalitis. Although ictal asystole is rare, a high index of suspicion and evaluation with continuous V-EEG with cardiac rhythm monitoring may help identify a potentially fatal complication of this emerging pediatric autoimmune disorder.

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