A Toddler with Lower Extremity Weakness, Emotional Lability, and Enuresis due to N-Methyl-D-Aspartate Receptor Encephalitis

James Crooks, MD* and Rawan Musaitif, MD
Department of Pediatrics, University of Illinois College of Medicine at Peoria, USA

Abstract

A Toddler with N-Methyl-D-Aspartate (NMDA) Receptor Encephalitis. A previously healthy three-year-old boy presented to the emergency department due to episodes of leg jerking, clumsiness, a brief unresponsive episode, and a single generalized tonic clonic seizure. Parents had also noted behavioral changes and secondary enuresis in the week prior to admission. Initially he was very well appearing and cooperative. He had normal strength in his upper extremities but weakness in his lower extremities with an abnormal gait. Soon after this exam he became inconsolable seemingly without a trigger. He would not cooperate with an exam or instruction during this time. This inconsolability lasted for approximately 20 min and resolved. EEG results were nonspecific. MRI brain and total spine was normal. Spinal fluid studies returned positive for N-Methyl-D-Aspartate (NMDA) receptor antibodies consistent with NMDA encephalitis. NMDA encephalitis was first recognized in 1997 in association with an ovarian teratoma; however, in the pediatric population this is not always the case. Classically, adolescent patients first present with psychiatric symptoms and often proceed to develop neurological symptoms. However, in younger children the opposite often occurs. Typical neurologic symptoms include movement disorders and seizures. Psychological symptoms typically include behavioral changes but can also include psychosis and catatonia. The diagnosis is made after finding NMDA receptor antibodies. Treatment is aimed at the source of the autoantibodies. For this reason, in all ages it is critical to search for a teratoma. First line therapies are often corticosteroids, IVIG, or plasma exchange. Some patients may require immunotherapies such as rituximab or cyclophosphamide.

Case Presentation

A previously healthy three-year-old boy presented to the emergency department due to about two weeks of intermittent right leg jerking, increased clumsiness, and one brief unresponsive episode, and described as “zoning out.” Parents had also noted behavioral changes including increased agitation and emotional outbursts as well as secondary enuresis during the day and night. During further questioning the parents also endorsed an unsteady gait and significant photophobia during this same time period. While in the emergency department, the patient had a witnessed generalized tonic-clonic seizure that lasted three minutes. He received lorazepam which aborted the seizure and he was subsequently admitted for further testing.

On the inpatient unit, an EEG was done which showed background slowing in the right posterior quadrant but did not reveal any electrographic seizures. A brain MRI was done and was normal. Labs drawn included Complete Blood Count (CBC), Comprehensive Metabolic Panel (CMP), and inflammatory markers which were all unremarkable. He was started on levetiracetam,
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which can be severe and require admission to an intensive care unit include hypoventilation, decreased consciousness, and dysautonomia have been reported as well [12]. Other types of neurological complications with NMDA encephalitis develop multiple different movement disorders orofacial dyskinesia and choreoathetosis [3,4]. Frequently, children with NMDA encephalitis develop multiple movement disorders [3,4,7,8,10]. Classically, adult and adolescent patients first present with psychiatric symptoms and later develop neurological findings [3,8,9]. This pattern has also been reported in children under 10 years old [4], but it is not a typical presentation in this age group. Younger children more frequently present with neurological signs or symptoms and subsequently develop psychiatric symptoms [3,6,8,10]. The most common psychiatric symptoms often seen in children are personality or behavioral changes [6,8,10]. Psychosis and catatonia have been reported as well [4,6,11].

The neurological symptoms that occur most often include seizures and movement disorders. Seizures are most commonly generalized tonic clonic and can be the initial symptom, or may present later [8,9]. The vast majority of patients develop movement disorders [3,4,7,9] and these typically continue during times of unresponsiveness [9]. The movement disorders can appear in a variety of ways including abnormal postures, hypertonicity, atactic gait, cranial nerve abnormalities, aphasias, ataxothes, and tremors [3,4,7,8,10]. However, the most commonly observed movement disorders are orofacial dyskinesia and choreoathetosis [3,4]. Frequently, children with NMDA encephalitis develop multiple different movement disorders [4]. Weakness is not a frequent motor finding but this has been reported as well [12]. Other types of neurological complications include hypventilation, decreased consciousness, and dysautonomia which can be severe and require admission to an intensive care unit [1,4,8,10].

Following admission the initial workup typically includes imaging and an EEG. MRI studies are often normal but can reveal some nonspecific signal changes in the gray and white matter [1,6]. EEG results are frequently abnormal but often nonspecific [6]. Staley et al. reported diffuse theta, delta, or anterior predominant slowing as the most common finding. Spinal fluid studies often reveal a pleocytosis with a lymphocytic predominance as well as elevated protein but this is not always present [1,6]. Diagnosis is ultimately made by finding NMDA receptor antibodies in the CSF. Serum testing can be done as well although this does not rule out disease if negative [6].

At this time there are no specific guidelines regarding treatment of NMDA encephalitis but this is often done under the guidance of an experienced neurologist. Frequently initial treatment, sometimes started before diagnosis, is aimed at the acute symptoms such as seizures, psychosis, or catatonia. For this reason anti-epileptic medications or anti-psychotics may be used [6]. Following diagnosis, the first line of treatment is often corticosteroids or Intravenous Immunoglobulin (IVIG), although plasma exchange has been used as well [1,4,6,11]. These initial treatments are intended to address the underlying autoantibody production. It is not uncommon for the initial treatment to fail and for patients to require immunotherapies aimed at suppressing the immune system, such as rituximab or cyclophosphamide [1,6,10,11]. Early treatment has been found to be critical in the recovery process [11] And intensive neuropsychiatric rehabilitation is required throughout the often prolonged recovery process [1,6,10]. Electroconvulsive therapy has also been used in cases of severe catatonia and has shown some benefit although this is not routinely used [11]. In those patients whose disease is found to be secondary to a neoplasm, classically an ovarian teratoma, the recommendation is that the mass be removed [6,9,10]. Patients with paraneoplastic syndrome have a better prognosis after the neoplasm is removed when compared to patients who do not have a mass [1,6,9]. Relapse can also occur and is more common in patients who do not have a neoplasm associated with their encephalitis [6,7,9]; however, neoplasms can occur after the acute phase as well [1,6]. Long term outcomes vary considerably from full recovery with proper treatment to lasting neurological deficits which has been seen in up to 20% of patients [6,8]. Death can also occur if treatment is not begun promptly [4].

Patient Course

The patient was initially treated with three doses of IVIG. He was discharged home and over the course of the following month, continued to have loss of motor coordination, expressive language regression, and seizures. He was evaluated by neurology at a second institution and the decision was made to admit him due to worsening symptoms and subclinical seizure activity seen on EEG.

On admission, he was placed on EEG and found to be in non-convulsive status epilepticus. He was transferred to the intensive care unit and placed on a continuous midazolam infusion which ultimately abated the seizures. He underwent four sessions of Plasma Exchange (PLEX) but during these sessions he experienced refractory status epilepticus. He was switched to rituximab and continued to receive weekly methylprednisolone injections. Ultimately, he became seizure free on clobazam and lacosamide. A CT of his chest, abdomen, and pelvis was done to investigate for a teratoma; however, this was...
unremarkable.

He was discharged to an inpatient rehabilitation facility. The plan was for him to continue receiving weekly methylprednisolone injections for a total of 10 weeks and receive another dose of rituximab in six months.

References


