Annals of Clinical Case Reports

Case Report
Published: 06 May, 2020

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

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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.

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Received Date: *09 Apr 2020*
Accepted Date: *24 Apr 2020*
Published Date: *06 May 2020*

Citation:
Crooks J, Musaitif R. A Toddler with Lower Extremity Weakness, Emotional Lability, and Enuresis due to N-Methyl-D-Aspartate Receptor Encephalitis. Ann Clin Case Rep. 2020; 5: 1834.
ISSN: 2474-1655

Introduction

N-Methyl-D-Aspartate (NMDA) encephalitis is a type of autoimmune encephalitis first described in 1997 in association with an ovarian teratoma; however, it was only recognized to be associated with NMDA antibodies in the mid-2000s [1,2]. Classically, this condition occurs in women and is associated with an ovarian teratoma, but this is less typical in the pediatric population. It is now known that NMDA encephalitis can occur in the absence of an autoantibody producing neoplasm, which is more commonly the case in younger children and males [1,3-5]. In this case we report on a young pediatric patient who developed a series of vague signs and symptoms early in the course of NMDA encephalitis.

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,

monitored for two days without any further seizure-like activity, and was discharged home. Within one week, he followed up with pediatric neurology and was noted in clinic to have worsening lower extremity weakness, lower extremity pain especially the left side, and two episodes of bilateral lower extremity jerking. The patient had worsening secondary enuresis and parents also reported the patient had decreased spontaneous speech. The patient was readmitted to the inpatient unit. On initial examination during this admission, he appeared very agitated and was very resistant to exam. Approximately 20 min later, his behavior was significantly changed and he was much more cooperative. Parents noted similar emotional lability at home. His vitals were within normal limits. Labs including CBC, CMP, and inflammatory markers were drawn and unremarkable. MRI of the C-spine, L-spine and T-spine were done and were normal. Additionally, a lumbar puncture was performed which ultimately revealed the diagnosis.

Initial spinal fluid tests were unremarkable including glucose, protein, and cell counts. However, spinal fluid NMDA Receptor antibodies returned positive with a titer of 1:2. This finding and the patient's symptoms were consistent with a diagnosis of NMDA encephalitis.

Discussion

This case helps to paint a broader image of the signs and symptoms of NMDA encephalitis in a younger pediatric population. The California Encephalitis Project was a study performed from 1998 to 2005 which sought to investigate etiologies of encephalitis in patients. The project found that NMDA encephalitis was more common than any one type of viral encephalitis [3,6,7]. Although it is important to mention this study was not limited to the pediatric population and was likely influenced by the region in which it was performed. Also, NMDA encephalitis has been found to be the second most common cause of autoimmune encephalitis after Acute Disseminated Encephalomyelitis (ADEM) [3,6].

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, ataxic gait, cranial nerve abnormalities, aphasias, athetosis, 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 hypoventilation, 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.

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