Anti-NMDAR encephalitis in a paediatric patient: A case report

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ABSTRACT

A rare autoimmune disease called anti-NMDAR encephalitis usually affects young people and frequently manifests as cognitive deterioration, seizures, and psychiatric symptoms. The diagnostic challenge and the importance in recognizing the clinical features and employing appropriate laboratory and imaging techniques for accurate and timely diagnosis will be discussed. We describe the example of an 8-year-old girl who suddenly began exhibiting strange behavioral and speech problems. Anti-NMDAR encephalitis was diagnosed after further investigation. This casee illustrates how different clinical presentations can lead to a delay in the disorder's diagnosis. Healthcare practitioners continue to have difficulties in diagnosing heterogeneous clinical manifestations of anti-NMDAR encephalitis, particularly in the juvenile age range.

Keywords

anti-NMDAR encephalitis

INTRODUCTION

Autoantibodies against synaptic NMDA receptors cause anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis, a rare inflammatory disease of the brain parenchyma. It was initially identified in 2007 and is the most common autoimmune encephalitis in children[1]. Male preponderance and post-viral infection in children under 10 years old are the most common causes of acute disseminated encephalomyelitis (ADEM), an inflammatory illness that affects the central nervous system and causes acute demyelinating disease[2]. In contrast to ADEM, the prevalence of anti-NMDAR encephalitis occurs primarily in women (70 percent), between the ages of 8 and 18. The first case of anti-NMDAR encephalitis was reported in a young woman who subsequently had an ovarian tumor discovered; however, further investigations revealed that both genders can be affected, with or without tumour[3]. The incidence of anti-NMDAR encephalitis is unknown, however a study carried out in Malaysia between 2010 and 2011 identified ten cases overall[4].

CASE REPORT

An 8-year-old girl was brought in by her parents to a primary care clinic for a sudden onset of abnormal behavior for 4 days. The mother described it as her daughter having a sudden onset of crying while watching a cartoon show. This was followed by incoherent speech whereby the girl spoke in babbling sound and was unable to understand commands. She appeared weak and was unable to hold things with her right hand. She also started walking with an abnormal gait on the right side of her body during the 4 days of

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illness. There was no history of fever, upper respiratory tract symptoms, vomiting or fitting episodes or history of falls before the onset of symptoms. The mother described her daughter as an active child with excellent school performance before. On physical examination, she was alert, conscious and orientated with GCS of E4V2M5. Her temperature was 37 °C, blood pressure was 100/62 and pulse rate was 80 beats per minute. She was well-hydrated and had no rashes or neck stiffness. The cardiovascular and respiratory examinations were unremarkable. On neurological examination, there was a decrease in muscle power over the right upper and lower limb with a power of 3/5. There was no clonus and other neurological examinations were unremarkable. She was able to walk, however, with a high-stepping gait over the right side of body.

She was subsequently admitted to the ward for further assessment. She was treated for meningoencephalitis and was started on Intravenous (IV) Ceftriaxone and Intravenous (IV) Acyclovir. Urgent CT Brain done during admission noted the presence of a bilateral parietal hypodense lesion (Figure 1). An MRI Brain was subsequently performed on the second day of admission, with findings of a bilateral parietal lesion likely to represent a previous old insult with no MRI evidence of acute disseminated encephalomyelitis (ADEM). Electroencephalogram (EEG) showed an asymmetrical background with focal slowing over the left hemisphere, occasional sharp waves over the right frontal and occasional delta brushes over the left frontal.

There was no improvement after two days of treatment. Furthermore, she had episodes of disorganized and aggressive behavior which required restraint, sedation, and antipsychotic medication. A lumbar puncture was finally done on day three of admission after the parents consented.

Laboratory testing demonstrated no abnormalities, with normal white cell count, and C-reactive protein. Screening for autoimmune autoantibodies was done, with anti-nuclear antibodies (ANA) being positive with titer 1:320, however anti-double stranded DNA was not significant. Lumbar puncture revealed clear cerebrospinal fluid (CSF) with normal glucose and protein levels. Full and microscopic examination (FEME) of the CSF were normal with no acid-fast bacilli (AFB) noted and no cryptococcus. Polymerase chain reactions (PCR) for herpes zoster and herpes simplex were normal. Blood and CSF culture and sensitivity (C&S) were negative. However, serum and CSF NMDAR antibody were found to be positive.

She was subsequently referred to a Pediatric neurologist for further assessment and management. A 5-day course of intravenous (IV) methylprednisolone 30 mg/kg daily was started followed by oral prednisolone 2mg/kg daily. The patient showed slight improvement after methylprednisolone as she started to communicate, was able to read and write, and had no more aggressive behavior. The treatment was followed by an intravenous immunoglobulin (IVIG) 0.5 mg/kg daily for a total of 4 days in view of persistent mild neurological impairment. She also received one cycle of Intravenous (IV) Cyclophosphamide as there were remaining clinical symptoms. Her clinical condition gradually improved, and she was allowed for discharge with oral prednisolone in a tapering dose after 44 days of hospitalization. When evaluated one month after her discharge, she had good clinical improvement in that she could resume her studies and had normal speech, despite a minor cognitive and memory impairment. Unfortunately, she had 2 episodes of relapse since diagnosis, in which requiring a cycle of Intravenous Tocilizumab and Intravenous Cyclophosphamide.

DISCUSSION

Anti-NMDAR encephalitis is a rare inflammatory disease of brain parenchyma and not commonly found especially in primary care settings. It is challenging to correctly diagnose anti-NMDAR encephalitis due to its diverse range of clinical manifestations, which include behavioral abnormalities, psychosis, seizures, memory and cognitive impairments, dyskinesia, and autonomic dysfunction. Pediatric patients frequently appeared with convulsions, aberrant movement, and localized neurological impairments, which is different from how adults would present clinically[5].

Psychosis (82.7%) and seizures, together with mobility disorders—which are more common in younger patients than in adults—were the most frequently reported

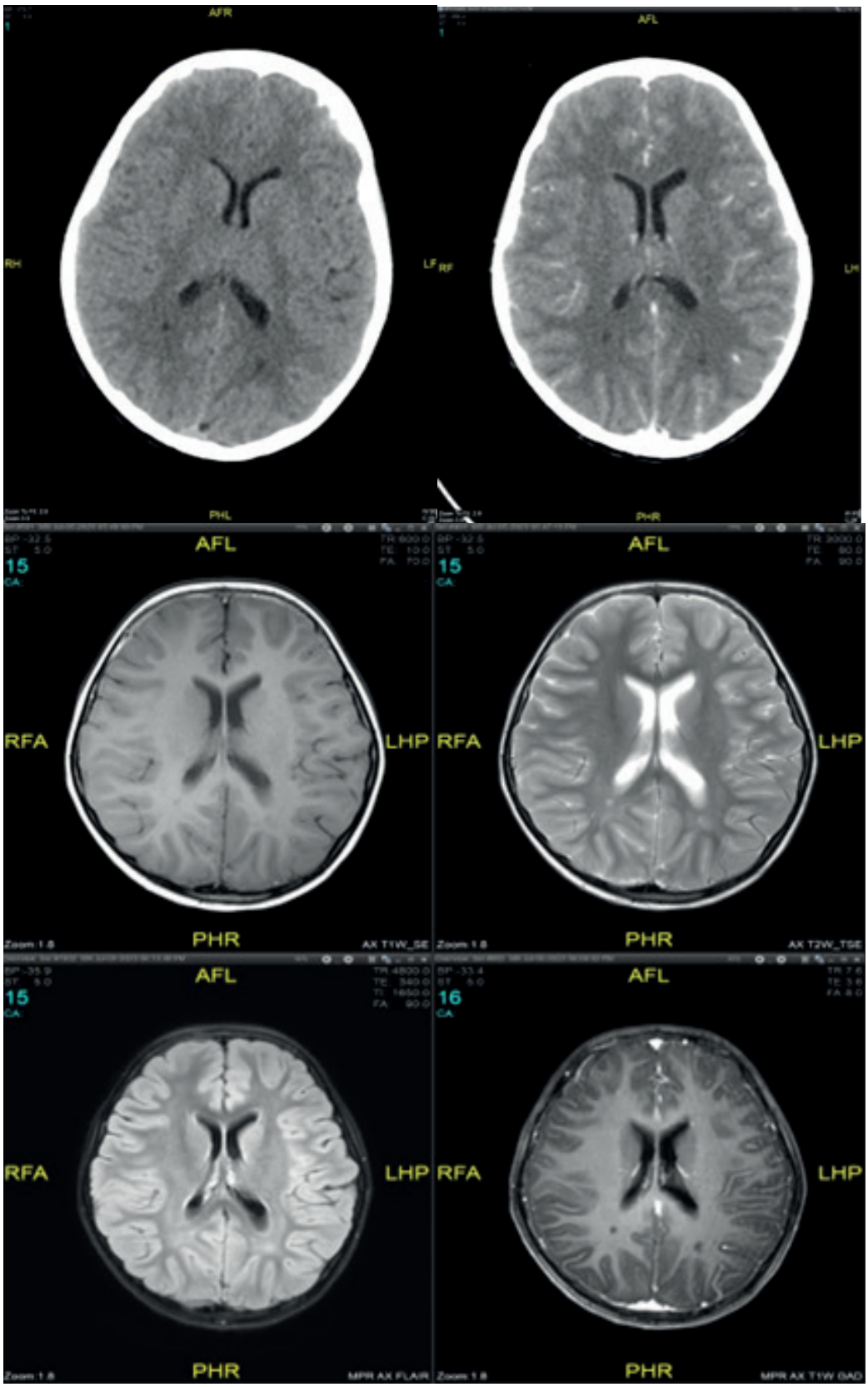

Figure 1: CT and MRI brain showed bilateral hypodense lesion over the parietal area.

clinical manifestations. Children with anti-NMDAR encephalitis have been known to exhibit tantrums, behavioral changes, agitation, hostility, and increasing speech degradation as early symptoms[6]. Nevertheless, these behaviors may go unnoticed at first. As seen in our case, she first displayed an abrupt start of aberrant conduct together with speech difficulties in the absence of any prodromal symptoms.

In 2016, Graus stated that three conditions had to be met for a probable diagnosis of anti-NMDAR encephalitis: 1) at least four of the six major groups of symptoms—such as abnormal behavior/cognitive dysfunction, speech dysfunction, seizures, movement disorder, decreased consciousness level, and autonomic dysfunction—had to manifest quickly. 2) An irregularity in at least one of the test results, such as the presence of CSF pleocytosis or oligoclonal bands, or an aberrant EEG (exhibiting focal or diffuse sluggish or disordered activity, epileptic activity, or severe delta brush). A positive result for antibodies against the NMDA receptor in the serum or CSF is necessary for the diagnosis of NMDAR encephalitis to be confirmed. Immunoglobulin G (IgG) anti-GluN1 antibodies are required for a definitive diagnosis to be made when there are at least one of the six main categories of symptoms, which include abnormal behavior/cognitive dysfunction, speech dysfunction, seizures, movement disorder, reduced consciousness, and autonomic dysfunction. About 80% of cases have been reported to exhibit CSF abnormalities, such as moderate lymphocytic pleocytosis, slightly elevated protein content, and CSF-specific oligoclonal bands[7].

Seventy percent of brain MRIs have been described as normal; the other few may exhibit contrast-enhancing anomalies or transient fluid-attenuated inversion recovery (FLAIR) in cortical or subcortical regions like the hippocampus, basal ganglia, and white matter[8]. When determining the difference between encephalitis and main psychiatric disorders, electroencephalograms (EEGs) are useful. In the case of anti-NMDA receptor encephalitis, most patients exhibit non-specific slowing at some point during their illness[9].

In our case, preliminary blood tests revealed no abnormalities; nonetheless, serum and CSF testing revealed the presence of NMDAR antibodies. There were no signs of any anomalies in the cortex or subcortical regions of her brain according to the MRI. Nevertheless, the preliminary electroencephalogram (EEG) in our case revealed an uneven background featuring focal slowing over the left hemisphere, sporadic sharp waves over the right frontal, and sporadic delta brushes over the left frontal, providing further evidence towards the diagnosis of NMDAR encephalitis.

Long-term rehabilitation and a multidisciplinary approach are necessary for the treatment of anti-NMDAR encephalitis. Dalmau's case series indicates that approximately 75% of patients either recover or experience modest sequelae, whereas the remaining 25% either experience severe deficits or pass away[3]. Immunotherapy, which involves methylprednisolone, IVIG, or plasma exchange, as well as the excision of any identifiable teratomas if present, is recommended as the first line of treatment[9]. According to a survey, 53% of patients who receive first-line medication see improvement in the first four weeks of treatment, and 97% of patients exhibit positive results at 24 months. In patients who did not respond to first-line therapy, rituximab and cyclophosphamide are used as second-line therapy. In our situation, IV cyclophosphamide was given due to residual neurological impairment, and IV methylprednisolone was started upon diagnosis. As part of a rehabilitation programme, she was also referred to a physiotherapy and occupational therapy facility.

Relapses are common in about 20 percent of children with anti-NMDAR encephalitis; they can occur at any moment and are often milder than the initial episode. Relapses do not, however, appear to be correlated with the severity of the acute phase or the prognosis at follow-up. Aggressive immunotherapy in the early stages may reduce the likelihood of relapse[10]. According to the study, 15.9% of patients experienced one or more relapses, with 82% of those patients going through their first relapse within 24 months after their diagnosis[11]. Female sex and treatment delays were risk variables associated with relapses, and 76.7% of patients who experienced relapses did so at a lower severity than when they first presented[11]. Unfortunately, within a month of being diagnosed, our patient experienced two episodes of relapse, necessitating IV tocilizumab as second line

therapy and an additional round of cyclophosphamide.

CONCLUSION

In conclusion, anti-NMDAR encephalitis is a potentially treatable condition if it is diagnosed early. Early detection, diagnosis, and treatment can help patients achieve better results. One of the challenges in treating anti-NMDAR encephalitis is its recurrence. To enable early referral and diagnosis, it is crucial that frontline healthcare practitioners, such as emergency departments and primary care physicians, have early suspicions about children who come with distinct clinical syndromes from those typical of bacterial or viral meningitis.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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