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Case Report

Anti-NMDA Receptor Encephalitis Responding to Gabapentin: A Case Report and Review of the Literature

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Abstract

Anti-N-methyl-D-aspartate (NMDA) receptor encephalitis is a well-characterized immune-mediated encephalitis. It is increasingly recognized as one of the common causes of encephalitis in children but is frequently misdiagnosed, especially in resource-constrained settings. There is ongoing debate regarding optimal treatment strategies. In this case report, we would like to highlight the dramatic response of this clinical neuropsychiatric disorder to gabapentin despite the lack of response to methylprednisolone, probably through its direct effect on NMDA receptors. This disorder should be a differential diagnosis in patients with unexplained behavioral/psychiatric symptoms and progressive encephalopathy with movement disorders. The improvement witnessed with gabapentin should be further investigated in controlled clinical trials.

Keywords: *Encephalitis, Immune-mediated encephalitis, N-methyl-D-aspartate receptors, Gabapentin*

Introduction

Anti-N-methyl-D-aspartate receptor encephalitis (Anti-NMDAR encephalitis) is a novel type of autoimmune encephalitis mediated by anti-N-methyl-D-aspartate receptor (NMDAR) antibodies mainly involving the limbic system.[1–3] Antibodies targeting the NR1 subunit of the NMDAR lead to internalization and decline of NMDAR-associated synaptic functions, resulting in diverse neurological and psychiatric manifestations.[3] Early diagnosis and immunotherapy have a crucial role in the outcome of this disease.[1–4]

Despite infections being a common cause of encephalitis, immune-mediated encephalitis is increasingly recognized as a cause (20-30%).[2,4] Many cases previously labeled as "encephalitis of unknown cause" were later found to be immune-mediated.[4,5]

Here, we report a case of anti-NMDAR encephalitis that failed to respond to methylprednisolone but was successfully treated with gabapentin (GBP) and other antiepileptic drugs (AEDs). Our case report aims to propose alternative therapeutic approaches and emphasize the positive clinical response to GBP in anti-NMDAR encephalitis where financial constraints limit Intravenous Immunoglobulin (IVIG) availability or pulse steroids are ineffective.

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Case Presentation

A 7-year-old developmentally normal girl was transferred to our hospital for neuropsychiatric symptoms, movement disorders, and uncontrolled seizures. History dated back to 7 weeks before transfer when she had a four-day flu-like illness. She was asymptomatic for two days following the illness but then developed abnormal behavior intermittently. Over the next three days, she became increasingly restless, agitated, and anxious and suffered from insomnia for three consecutive nights before being admitted to a local hospital. She experienced hallucinations and delusions with bouts of shouting. There was no inadvertent drug intake, abdominal pain, dark-colored urine, jaundice, dog bite, or stressful life events. From the hospital report from her first hospitalization, she was oriented to place and person but demonstrated inappropriate speech, restlessness, and agitation. The rest of the examination was unremarkable. Liver function tests, serum ammonia, and lactate were within normal limits. Neuroimaging of the brain was unremarkable. Cerebrospinal fluid (CSF) examination, including herpes simplex virus, was normal. Over the next two days, she developed features of catatonia in the form of echolalia, echopraxia, and posturing, followed by gradually decreasing verbal output that progressed to complete mutism by day 8. On day 9, she had multiple episodes of focal and generalized seizures (interictal electroencephalography (EEG) revealed a slow background). Later, she started having abnormal movements in the form of oro-facial dyskinesias (grimacing, chewing, tongue thrusting, lip smacking, and frowning) that progressed to dystonic storm and choreoathetosis of the limbs that were difficult to control. Brain Magnetic Resonance Imaging (MRI) was unremarkable. Before being transferred to our hospital, she was managed as a case of infectious encephalitis and was given acyclovir and ceftriaxone. Different AEDs were trialed (carbamazepine, Levetiracetam (LVT), Valproate, and Clonazepam) but failed to control her seizures. She was then given five days of pulse methylprednisolone empirically, but continued to deteriorate and then was transferred to our hospital by air medical services.

She was transferred to the Specialty Hospital in Amman. She was in a wheelchair, had a nasogastric tube (NGT) due to swallowing difficulties, was irritable, and unaware of her surroundings. She had catatonia, dystonia, abnormal movements, motor deficits, and uncontrolled and recurrent seizures. CSF studies were collected again and were normal. A CSF sample was sent for anti-NMDAR antibodies. EEG performed at admission yielded occasional bursts of slow wave activity with diffuse slowing and no delta brush activity. Shortly after admission, she was started on prednisone 2 mg/kg. IVIG was not administered due to financial constraints and late presentation. Repeat brain MRI was normal. On transfer, she was on LVT (50mg/kg) and valproate (30mg/kg), but her seizures were uncontrolled. We decided to substitute LVT with Lamotrigine (LTG). LTG was added, and LVT was gradually tapered, leading to control of her seizures. We also started her on GBP (20mg/kg) and clobazam (1mg/kg), and her dystonia and involuntary movements significantly improved. NMDAR antibodies returned positive ten days after admission.

Contrast-enhanced computed tomography abdomen was done to look for ovarian teratoma and returned normal. Her stereotypic movements (pelvic thrusting, floating limbs, writhing movements), hyperthermia, and urinary incontinence started to improve. Gradually, her sensorium improved, and abnormal movements resolved. After the second week of therapy, she started to swallow slowly, say a few words and follow simple commands. Repeat EEG after three weeks of hospitalization demonstrated improved background activity and slowing. Seven weeks after symptom onset, she had no abnormal movements or seizure activity, near-normal speech, and improved cognition.

Discussion

Following the first report on pediatric anti-NMDAR encephalitis in 2010, anti-NMDAR encephalitis has become more frequently recognized. It is the second most common etiology for acute demyelinating encephalitis after viral encephalitis.[4,6] It is characterized by psychiatric symptoms, altered consciousness, epilepsy, involuntary movements, dystonia, and autonomic and sleep dysfunctions, with or without associated tumors or teratomas.[7]

In a population-based study done in England, anti-NMDAR encephalitis constituted 4% of all cases of encephalitis.[2] Most cases occur in females (about 80%), and the disorder is more frequent in young teenagers and children.[7] The frequency of tumor association (mostly teratoma) is more common in adult African-American women and less likely in younger patients and men. Tumors other than teratoma are uncommon (2%).[7,8]

Antibodies against the NR1 subunit of NMDAR cause a reversible decrease in NMDAR cluster density in postsynaptic dendrites in a titer-dependent fashion resulting in a characteristic neuropsychiatric syndrome that evolves in several stages of the illness.

The reduction in NMDAR density is reversible upon the removal of the antibodies and exhibits a good response to tumor removal and immunotherapy, even when symptoms are severe.[9] The trigger for the immune response remains unclear, but genetic and racial predisposition has been suggested.

The illness begins with a prodromal phase of low-grade fever and nonspecific features followed by a prominent "psychiatric phase" characterized by anxiety, insomnia, bizarre behavior, delusions, hyper-religiosity, mania, and visual/auditory hallucinations, usually within two weeks. Language problems are common, varying from reduced verbal output and echolalia to complete mutism. Short-term memory loss is frequent. The neurological phase follows the psychiatric phase and is characterized by decreased responsiveness that may alternate with periods of agitation and catatonia. Abnormal movements and autonomic instability predominate in this phase. Orofacial dyskinesia is particularly striking. Other abnormal movements include choreoathetosis, complex and stereotypic movements, dystonic posturing, episodic opisthotonos, and oculogyric crises. Autonomic manifestations include hyperthermia, tachycardia, hypersalivation, bradycardia, hypotension, and hypoventilation. In children, autonomic manifestations are milder.[8] Seizures are common. Recovery usually occurs in reverse order of symptom presentation, and a complete amnesia for the preceding events is expected.[9]

In most patients, CSF shows lymphocytic pleocytosis, mild protein elevation, and oligoclonal bands.[7–9] EEG abnormalities are found in all patients as non-specific slow and disorganized activity, sometimes with electrographic seizures.[7–9] Brain MRI is unremarkable in 50% of the patients and may show non-specific hyperintensities in cortical/subcortical areas and the cerebellum, with contrast enhancement in the affected areas or meninges.[7] Diagnosis is established by demonstrating antibodies against NMDAR in CSF or sera of patients.

Management of NMDAR encephalitis includes immunotherapy and removal of tumors if present. First-line immunotherapy includes IVIG, methylprednisolone, and plasma exchange. The suggested treatment is the concurrent use of IVIG and methylprednisolone followed by rituximab, cyclophosphamide, or both in case of poor response.[7] Additional IVIG/methylprednisolone/plasma exchange courses is suggested if both CSF and serum antibody titers remain high.[10] Our patient received methylprednisolone with deterioration of her neurological status prior to transfer. Upon transfer, financial restraints prevented the administration of IVIG. We put her on 2mg/kg of oral prednisone for two weeks. Because of the involuntary movements, dystonia, and catatonia, we started her on 20 mg/kg/day GBP and 1mg/kg/day clobazam in 2 divided doses. Her sleep, dystonia, and agitation started to improve as early as 2-3 days on therapy. Her seizures were controlled one week after tapering LVT and adding LTG, followed by gradual improvement of psychiatric symptoms, higher functioning, swallowing, and speech. We hypothesize that her rapid recovery may be attributed to the inhibitory effect of GBP on NMDAR. The concurrent use of clobazam has the potential to synergistically mitigate neuropsychiatric symptoms. The response to GBP might parallel previous evidence of its effectiveness on neuropathic pain.[11]

Reported recovery from this disease is slow (months-years), but 75% of patients show substantial recovery.[7–9] The outcome is better with early diagnosis and treatment.[7,10] Our patient's rapid and progressive improvement may support the importance of blocking NMDAR by GBP, as reported in animal studies.[12]

Conclusion

Many questions remain unanswered regarding management of NMDAR encephalitis. The uncertainty prevails regarding the appropriateness of immunotherapy for patients presenting later and whether therapy utilizing GBP, clobazam, AEDs suffices in the presence of seizures. Additionally, if the NMDAR antibody tests are unavailable due to resource constraints, is clinical suspicion and exclusion of other diagnoses adequate for initiating therapy? Furthermore, the optimal duration for maintaining AEDs, GBP, clobazam in children exhibiting a positive response remains unclear.

To conclude, anti-NMDAR encephalitis is a prevalent cause of encephalitis in children. The use of GBP as monotherapy or in combination with clobazam may play a unique and significant role in anti-NMDAR encephalitis management, leading to potentially reversible outcomes. Multicenter-controlled studies are needed to verify this efficacy.

Conflicts of Interest

The authors declare no conflicts of interest.

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