Case Report

An anti-n-methyl-d-aspartate receptor antibody syndrome-like presentation and negative result of testing for autoantibodies in a Saudi boy

Abstract

Autoimmune encephalitis is a diverse group of neuropsychiatric disorders recognized recently. It gained attention because of its favorable response to immunotherapy. Based on epidemiological studies, anti-N-methyl-D-aspartate (NMDA) receptor encephalitis is the most common cause of autoimmune encephalitis, ranking immediately after acute demyelinating encephalomyelitis (ADEM).

It is associated with anti-NMDA (IgG) receptor antibodies, which bind to extracellular epitopes in the NR1 and NR2 heteromers of the NMDA receptor. Its pathogenesis remains unknown; however, evidence of antibody-mediated encephalitis is supported by the disappearance of antibodies during remission and the favorable response to immunotherapy. It was established by Josep Dalmau and colleagues in 2007. It has been identified mostly in females with first-onset psychiatric symptoms, in association with paraneoplastic syndrome secondary to ovarian teratomas, but it can also be found in the absence of any evident tumor. It is becoming increasingly recognized in children and affects both sexes, and 30–50% of affected children exhibit associated neoplasms.

Its clinical presentation is characterized by four main stages: nonspecific prodrome initially, followed by psychiatric symptoms with rapid progression to the last neurological stage, before the recovery stage started in Table 1. It is confirmed by detection of NMDA receptor antibodies in serum and/or cerebrospinal fluid. Patients benefit from combined immunotherapy and early tumor resection in paraneoplastic form. Recovery is usually slow and can take years, and the outcome is usually favorable, but neuropsychological sequelae and relapses have been reported.

This report describes a 6-year-old male patient with a typical clinical presentation suggestive of anti-N-methyl-D-aspartate receptor encephalitis. He did not manifest the antibody, although he responded to combined immunotherapy.

Introduction

Autoimmune encephalitis is a diverse group of neuropsychiatric disorders recognized recently. It gained attention because of its favorable response to immunotherapy. Based on epidemiological studies, anti-N-methyl-D-aspartate (NMDA) receptor encephalitis is the most common cause of autoimmune encephalitis, ranking immediately after acute demyelinating encephalomyelitis (ADEM).

Case report

A previously healthy 6-year-old boy presented with two days’ history of sudden onset of unprovoked generalized tonic-clonic seizures, occurring 3 times a day and lasting less than 10 minutes. At home he was noted to have extreme fatigability, anorexia, excessive sleepiness, slowness in thinking and inappropriate affect. His previous development was normal, and his immunizations were up to date. Five days before presentation, he had viral-like illness with fever and gastroenteritis-like picture, with vomiting and diarrhea. His history was free of any psychiatric disorders like anxiety or social phobia. No family history of any neurologic or movement disorder was reported.

On examination, he was not oriented with regard to time, but was oriented in regard to place and person. He was withdrawn and lethargic because of his apraxia. Other cerebellar, sensory, motor, and gait examinations produced normal results.

He was admitted to intensive care unit to control his frequent left-sided partial seizures with secondary generalization. Intravenous midazolam and multiple antiepileptic drugs, including phenytoin, phenobarbitone, topiramate and carbamezapine were tried. His condition worsened, he became completely withdrawn, and he would not read, write or follow commands. He manifested confusion, impaired memory, bouts of agitation, bizarre behavior, visual hallucination, and movement disorders in the form of orofacial grimacing and dyskinesia. He had a blank stare, with tongue thrust, frequent daily episodes of extension posturing of the right upper extremity and twisting of the right leg, each lasting for several minutes and causing frequent fall, episodic physical outburst, incoherent speech and insomnia.

Keywords: Anti-NMDA encephalitis, autoimmune encephalitis, immunotherapy
There were bouts of central hypoventilation with tachycardia and daytime incontinence. He remained afebrile and normotensive throughout the hospitalization. His complete blood count showed white blood count (WBC) 4.7, hemoglobin 13.6 g, platelets 153, erythrocyte sedimentation rate 10 mm/hr, liver, renal, and bone profiles were normal. CSF analysis revealed a lymphocytic pleocytosis with WBC 8, RBC 500/cumm, as well as negative gram stain and culture. Protein and glucose were normal. CSF also produces negative results for polymerase chain reaction for viral multiplex DNA, including Epstein-Barr, herpes simplex type I, human herpes-6, adenovirus and enterovirus. Given the concern about viral encephalitis, acyclovir was started empirically.

Owing to the stepwise progression of the neuropsychiatric symptoms, a second CSF done 5 days later on showed no cells, and persistently negative gram stain and culture. Protein and glucose remained normal. Oligoclonal band was negative and lactate level was normal. N-methyl-D-aspartate receptor antibody, anti-glial nuclear antibody type 1, amphiphysin antibody produced negative results in serum and cerebrospinal fluid. Serum anti-voltage-gated potassium channel antibody produced a negative result. Work-ups for autoimmune vasculitis, metabolic disorders, Hashimoto’s thyroiditis, and PANDAS were negative; serology tests for mycoplasma pneumonia and common viruses were also negative.

Electroencephalogram (EEG) showed diffuse delta slowing with no epileptiform discharges. Brain MRI and MRA were normal. Due to the stepwise worsening of his symptoms noted by the end of the first week of hospitalization, he received combined immunotherapy for presumed autoimmune encephalitis in the form of pulse methylprednisolone (25mg/kg/day) for three consecutive days, and intravenous immunoglobulin 1g/kg/day for two consecutive days, which resulted in moderate improvement of his symptoms. CT scan of chest, abdomen and pelvis did not reveal any tumors.

His psychiatric symptoms were controlled with risperidone. His movement disorder improved and eventually resolved on carbamazepine. His seizures achieved control on triple medications of phenobarbitone, carbamazepine and topiramate. He was discharged home after 45 days of hospitalization. Follow-up visit at one and 3 months after the discharge revealed a second CSF done 5 days later on showed no cells, and persistently negative gram stain and culture. Protein and glucose remained normal. Oligoclonal band was negative and lactate level was normal. N-methyl-D-aspartate receptor antibody, anti-glial nuclear antibody type 1, amphiphysin antibody produced negative results in serum and cerebrospinal fluid. Serum anti-voltage-gated potassium channel antibody produced a negative result. Work-ups for autoimmune vasculitis, metabolic disorders, Hashimoto’s thyroiditis, and PANDAS were negative; serology tests for mycoplasma pneumonia and common viruses were also negative.

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<table>
<thead>
<tr>
<th>Stages</th>
<th>Clinical manifestations</th>
<th>Duration</th>
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<tbody>
<tr>
<td>I - Initial</td>
<td>Viral prodrome</td>
<td>Lasts up to 1-2 wks</td>
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<td></td>
<td>Fever, headache, flu-like symptoms or nausea, vomiting, and diarrhea</td>
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<td>II - Intermediate</td>
<td>Psychiatric symptoms, i.e. cognitive, memory, behavioral changes, delusions, confusion, hallucinations, anxiety, emotional disturbances, mania, agitation, sexual disinhibition, unresponsive/ catatonic state, disorganization, and acute primary psychosis-like schizophrenia.</td>
<td>Lasts up to 1-3 wks</td>
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<td>III - Prominent</td>
<td>Neurological symptoms, i.e. movement abnormalities as orofacial - limb dyskinesia's, dystonic posturing and choreic-like movements of limbs seizures, speech changes, impaired consciousness, dystautonimia as hyperthermia, tachycardia, hyper-salivation, hypertension, bradycardia, hypotension urinary incontinence, and central hypoventilation.</td>
<td>Lasts from wks to months</td>
</tr>
<tr>
<td>IV - End</td>
<td>Gradual Recovery</td>
<td>Expected within months, full recovery over 3 or more years</td>
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Table 1 The clinical presentation of anti-NMDA receptors encephalitis

Discussion

Anti-NMDA receptor encephalitis is a recently described paraneoplastic syndrome often associated with teratoma or idiopathic autoimmune encephalitis.15 The paraneoplastic type has been reported in association with ovarian tumors, small cell carcinoma, testicular cancer,16 or Hodgkin’s lymphoma,17 while the idiopathic type has been found to be provoked by a viral infection. Herpes simplex virus (HSV) has recently been recognized as a trigger of anti-NMDA encephalitis, and several cases were reported in association with HSV, whereas other reported cases manifested as clinical relapses of HSV owing to anti-NMDA encephalitis.18

Most children present with seizures or movement disorders rather than psychiatric symptoms such as anxiety, agitation, paranoia, and visual or auditory hallucinations, which are more predominant in adults with anti-NMDAAR encephalitis.14 Due to the presence of refractory partial seizures, the possibility of immune-mediated epilepsies was entertained, including Anti-NMDA receptor encephalitis, limbic encephalitis, refractory seizures associated with GABA receptors antibodies, Rasmussen’s encephalitis, and Febrile infection-related epilepsy syndrome (FIRES). The probability for anti-NMDA receptor encephalitis was high owing to the stepwise progression of symptoms, especially the sudden behavioral changes, neurological manifestations and dysautonomia,19 consistent with the several cases of anti-NMDA receptors encephalitis that have been reported in the literature (Table 1).14 In this syndrome, seizures occur in up to 72% of young children, and focal seizures account for 42%, with a median onset of 15 days before other encephalitis symptoms appear.16
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Typically, an MRI of the brain is either normal or shows nonspecific changes, focal enhancement or medial temporal lobe abnormalities; EEG often reveals diffuse delta slowing without paroxysmal discharges despite frequent bouts of seizures, while CSF shows features of inflammation with pleocytosis, increased protein and oligoclonal bands. The patient in this report had mild CSF and EEG changes consistent with anti-NMDA encephalitis. Since early diagnosis and effective treatment in patients with anti-NMDAR encephalitis have a relatively good prognosis and can achieve baseline recovery and complete resolution at follow-up examination, another CSF analysis was carried out on the 5th day of illness. Serum was taken for auto-antibodies against NMDA, GABA b, AMPA 1 and 2, LG1, and GAD receptors, and he was given combined immunotherapy (Pulse corticosteroid, and IVIG).

Typically, treatment for this syndrome includes first-line immunotherapy with corticosteroids, intravenous immunoglobulin (IVIG), or plasmapheresis, and it is effective in only half of patients. Rituximab or cyclophosphamide is usually recommended for the treatment of clinical symptoms if there is no response to the first-line therapy and for prevention of relapse. Patient, serum titers were negative as were CSF antibody titers, which is atypical, but given his characteristic neuropsychiatric dysfunction with rapid resolution of symptoms after immunotherapy, he was given a presumptive diagnosis of idiopathic autoimmune encephalitis with presentation like anti-NMDA encephalitis syndrome. A follow-up CSF and serum autoantibodies screen, as well as tumor surveillance, remained negative at 3 and 12 months from the onset.

Shah Rikin et al. reported two cases with a clinical picture suggestive of anti-NMDA encephalitis and negative antibodies. One case was a 13.5 years old boy with negative tumor surveillance. The other case was an 8-year-old boy with a benign thymic hyperplasia on surveillance for tumors. Both showed improvement on combined immunotherapy in the form of pulse methylprednisolone therapy and intravenous immunoglobulin, in addition to plasmapheresis in the second case. Their outcome was variable as the first one continued to have psychiatric manifestation and needed monthly immunoglobulin for stabilization, while the other one continued to have motor disability with intermittent dystonia. The patient here responded well with almost complete recovery one year after the event, except for controlled seizures.

The current diagnosis is based upon finding anti-NMDAAR antibodies in the CSF or serum. The CSF antibody has been found to be more sensitive and generally appears to correlate with disease activity. A possible explanation for a false negative result includes smaller quantities of antibodies produced, antigen denaturation during tissue-based immunofixation and variability between human and mouse epitopes used in analysis.

Conclusion

This case highlights the importance of early recognition of anti-NMDA encephalitis-like presentation in patients presenting with seizures, and stepwise progression of neuropsychiatric symptoms, and the importance of prompt immunotherapy treatment even in the absence of antibodies as early therapy improves the long-term neurological outcome of those patients.

Acknowledgments

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Conflicts of interest

The author declares no conflict of interest.

References