

Anti-N-methyl-D-aspartate Receptor Encephalitis: Case Series of Psychiatric Presentations

Arpit Koolwal, Supriya Agrawal¹, Ghanshyam Das Koolwal, Kaveri Saxena¹, Ankit Daral¹

Department of Psychiatry, Dr. S. N. Medical College, Jodhpur, Rajasthan, ¹Department of Psychiatry, Subharti Medical College, Meerut, Uttar Pradesh, India

Abstract

Anti-NMDAR encephalitis is an autoimmune encephalitis with a typical clinical progression. Patients can often present to psychiatric outpatient departments (OPDs) mimicking psychiatric illnesses. In this case series, we have described two cases of adolescent age group that were eventually diagnosed with anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis. They had presented to psychiatry OPD and were admitted to the psychiatry ward. Both cases had predominantly, although varied, psychiatric symptoms with a variable course, response to treatment and prognosis. We have tried to speculate if initial presentation in anti-NMDAR encephalitis can be suggestive or can predict response to treatment and prognosis in a patient. We advocate a high degree of suspicion for psychiatrists toward patients presenting acutely in the first episode of mania or psychosis, particularly in adolescent age group.

Keywords: Anti-N-methyl-D-aspartate receptor encephalitis, mania, psychiatric, psychosis

INTRODUCTION

Anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis is an autoimmune encephalitis with a stereotypical clinical progression starting with a viral prodrome, followed by psychiatric, cognitive and behavioral manifestation and subsequently developing, dysautonomia, seizures, and refractory dyskinesia.^[1] In this case series, we have reported two cases of anti-NMDAR encephalitis initially presenting with psychiatric symptoms that later developed varied clinical presentations, course, and prognosis.

CASE REPORTS

Case 1

A 15-year-old boy was brought to the psychiatry outpatient unit with complaints of abrupt onset persistent elevated mood, excessive and big talks, restlessness, aggressiveness, decreased food intake, and sleep disturbance for 4 days. There was no history of fever, vomiting, headache, seizures, altered sensorium, or loss of consciousness. His general physical and neurological examination initially was within normal limits. On mental status examination, increased psychomotor activity, euphoria, pressured speech, and grandiose delusions were recorded. Investigations including complete blood count (CBC), liver and renal function tests, electrocardiogram, and computerized tomography scan head were normal. This was his first episode. There was no significant history of medical, surgical, psychiatric illness, or psychoactive substance use in the patient or family.

His Young Mania Rating Scale (YMRS) score was 40 and diagnosis as per ICD-10 was manic episode without psychotic symptoms (F31.1). The patient was started on sodium valproate (600 mg/day in divided doses which was gradually increased to 1500 mg/day), risperidone (started with 3 mg/

day and gradually increased to 8 mg/day), and clonazepam for 7 days with no improvement in YMRS scores. Along with pediatric neurologist's opinion, panel of investigations for medical differential diagnosis was done including tests for malaria, dengue, herpes simplex which all turned out to be negative. Specific investigations including cerebrospinal fluid (CSF) analysis, CSF cytology, serum anti-NMDA receptor antibodies, and CSF anti-NMDA receptor antibodies were also done.

The presence of anti-NMDA receptor, antibodies in patient's serum and CSF (serum – 2.38 ng/ml and CSF – 18 ng/ml) were in support of the diagnosis of anti-NMDA receptor encephalitis. Following confirmation of diagnosis, in collaboration of pediatric team, mood stabilizers, and antipsychotics were stopped. The patient was started on Methylprednisolone 900 mg in 300 cc normal saline intravenously daily for 5 days and Phenobarbitone 160 mg (dilute as 1:4 solution in Normal saline) intravenously twice a day. The patient showed improvement with YMRS scores reducing to 6 on 8th day of the treatment. The patient was discharged on prednisolone 20 mg and lorazepam 1.5 mg thrice a day and also phenobarbitone

Address for correspondence: Dr. Arpit Koolwal,
27A/51, Light Industrial Area, Adarsh Society, Shastri Nagar, Jodhpur,
Rajasthan, India.
E-mail: arpitkoolwal1989@gmail.com

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75 mg twice a day. Patient on the 15th day of follow-up was completely asymptomatic.

Case 2

A 16-year-old girl presented to the psychiatry outpatient department with abrupt onset of psychotic symptoms including agitation, fearfulness, fleeting auditory hallucinations, and ideas of persecution. The total duration of symptoms was 2 days during which there was a rapid progression in agitation. At the time of presentation, there was no history of any fever, nausea, vomiting, headache, seizure, altered sensorium, or loss of consciousness. There was no significant past or family history of any medical, surgical, psychiatric illness or substance use. The routine investigations including CBC, renal function tests, blood sugar, thyroid, and urine examination were normal. The patient was diagnosed with acute and transient psychotic disorder (F23) as per ICD-10. On the day of admission, the patient developed 99° Fahrenheit fever and tachycardia. Pediatric reference was done for the patient after which panel of investigations for fever including malarial antigen, widal and dengue tests were done. The patient was started on oral haloperidol 3 mg divided doses on which she developed extrapyramidal side effects. Haloperidol was stopped and patient was shifted to oral olanzapine 5 mg. Patient's symptoms rapidly progressed over the course of 2 days with onset of catatonia. On the 3rd day of admission, the patient developed fever 100° Fahrenheit with episodes of vomiting. Increase in perplexity and disorientation with intermittent spike of fever on 4th day aroused suspicions of encephalitis. After neurological opinion, specific investigations including electroencephalogram, cerebrospinal fluid examination, and NMDA receptors serum antibody were done for the patient. Repeat blood counts, urine examination, serum electrolytes, creatine phosphokinase-MB, and magnetic resonance imaging brain were within normal limits. Electroencephalography reported diffuse slowing with delta waves, and mildly elevated protein and lymphocyte count in CSF. Test for NMDA receptor serum antibody was positive (1:10). Methylprednisolone 20 mg in 100 ml of normal saline for 3 days along with nonsteroidal anti-inflammatory drugs were started on 4th day itself on the basis of suspicions. All the antipsychotics were stopped in the patient. After the confirmed diagnosis, the patient was shifted to Intensive Care Unit (ICU) and was started on intravenous (IV) immunoglobulins, with 400 mg/kg body weight for 14 days with no improvement. Abdominal ultrasound was done, revealing a cystic lesion in the right ovary. Patient was subsequently started on Rituximab 500 mg weekly for 1 month, following which the patient improved. After a month, patient-reported acute onset abdominal pain which when evaluated was found to be due to torsion of cystic lesion. The patient was operated where her ovary was removed, and pathological examination showed benign serous cystadenoma.

DISCUSSION

At the time of its first characterization, anti-NMDA receptor encephalitis was believed to be an exclusively paraneoplastic disorder, particularly in association with ovarian teratoma.^[2]

However, since then, it has been shown to be primarily an autoimmune disease, relatively common, with a retrospective study finding approximately 1% of all ICU admissions to between the ages of 18–35 years.^[3]

The autoimmune pathogenesis is mediated by IgG1 and IgG3 antibodies, detected in serum and CSF that mainly target the NR1 subunit of the NMDA receptor on the cell surface of neurons.^[4]

Here, we simultaneously discuss and compare two cases of NMDA encephalitis in two adolescents - a boy and a girl, both developed initial psychiatric symptoms yet with, glaringly, different course and prognosis. One aspect of this case discussion emphasizes on the fact that earlier suspicion and recognition of NMDA encephalitis is necessary for psychiatrists as many such cases are likely to present to a psychiatrists rather than neurologists due to the initial symptoms of mania or psychosis. We also speculate here, that in cases of NMDA encephalitis is it possible to predict the response to treatment on the basis of presenting psychopathology, rapidity of onset of illness and early presence of physical or neurological sign in the patients. It has been said that NMDA encephalitis can have a wide spectrum of clinical presentation and response to treatment with 25% showing poor response.^[4]

Both the cases discussed here were adolescents with abrupt onset of symptoms with no significant medical, surgical, past or family history. However, they differed in terms of psychiatric symptoms with the first case being provisionally diagnosed as manic episode and the second, acute transient psychotic disorder. There have been case reports of both types of clinical presentations being reported previously. One case, of a 16-year-old girl, presenting with predominantly manic symptoms has been reported.^[5] One study showed 6.5% cases of first episode psychosis to be suffering from the disease, with some cases fulfilling the criteria for schizophrenia initially.^[6]

Psychiatrists treating cases of psychosis of abrupt or acute onset especially in children and adolescent, in the absence of significant past psychiatric illness or family history, lack of any precipitating stressful event or showing poor response to treatment should consider autoimmune encephalitis as a differential even in the absence of classical symptoms of fever, vomiting, headache, altered sensorium, and seizure. It is reported that a group of patients with psychosis have anti-NMDA receptor antibody positive even though it remains yet to be established as to how they differ from antibody negative patients.^[7]

Opposed to the first case, the second case developed signs suggestive of medical condition like disorientation and fever earlier in the course of the illness. This was probably also responsible for the relatively earlier diagnosis of the condition in the second case. Furthermore, rapidity of progression of the symptoms was more pronounced in second case. Moreover, the second case showed sensitivity to neuroleptic medication.

Apart from the signs and the symptoms, response to treatment differed in both cases. Case 1 who was treated with steroids and antiepileptic showed good response and showed significant improvement within a week of initiation of therapy. Case 2 was treated initially with steroids for 3 days and later with IV immunoglobulins showed poor response to treatment and had a downward course in spite of the rigorous treatment regime. Literature also recommends corticosteroids and IV immunoglobulin G along with plasma exchange as first-line management and immunotherapy using cyclophosphamide or rituximab as second line which may be required in some patients.^[8]

Several indicators have been identified to favor good prognosis including lower severity of symptoms, not requiring ICU admission, prompt initiation of immunotherapy, and tumor removal where present.^[8] Better outcome has been reported with earlier treatment in children.^[9] The relatively poor response in the second case can be explained by the severity of symptoms and the requirement for ICU admission. As observed in our two cases, first case had indicators favoring good prognosis, such as lesser severity of illness, as seen by predominantly psychiatric features and lack of features suggestive of organic illness on examination, and not requiring ICU management, as compared to second case which had indicators suggestive of poor prognosis including increased severity of symptoms and requiring ICU admission. Additional indicators that need to be considered regarding prognosis, as observed in our case, are possibly gender, rapidity of progression, neurological signs, altered sensorium, sensitivity to neuroleptics, and poor initial response to first-line therapy.

Another interesting aspect to be noted in the second case is that this patient had a benign serous cystadenoma. Anti-NMDAR antibodies have been reported to express only in teratomas and cystadenocarcinomas,^[10] and this is the first case of a benign serous cystadenoma expressing these antibodies.

CONCLUSION

Anti-NMDA receptor encephalitis is still a relatively new entity and though many hundred cases have been reported, clinicians, especially psychiatrists, may be still unaware about this important differential diagnosis and its various presentations. Such cases with primary organic pathology tend to present to psychiatrists and may lead to unsuccessful treatment with antipsychotics and other psychotropics for prolonged periods with the delay causing further worsening of prognosis. It is still very important because it is a potentially treatable cause for the psychiatric symptoms. Although both our cases are adolescents, and anti-NMDA receptor encephalitis is more commonly seen in this age group and young adults, this

condition can be seen in all age groups and predominantly psychiatric presentations reported to be more common in later ages.^[7]

Every case of the first episode psychosis having no past and family history of psychiatric disorder should be investigated thoroughly to rule out the underlying organic pathology warranting vigilance on the part of the psychiatrists and also better collaboration with neurologists.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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