Case Report

Mania with Malignant Catatonia due to Nonparaneoplstic Anti-N-Methyl-D-Aspartate Receptors Encephalitis in a 29-Year-Old Female: A Rare Entity

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Abstract

Anti-N-methyl-D-aspartate receptors (NMDARs) encephalitis is a rare neurological autoimmune encephalitis. Its symptoms may mimic psychosis as this disease is a neurological disorder in psychiatry costume. Disparity in clinical symptoms and nonsupportive laboratory investigations except the cerebrospinal fluid (CSF) analysis delays the diagnosis. We are presented with a case of 29-year-old female with psychiatric symptoms such as suspiciousness, decreased sleep, and boastfulness. Within a few days, the patient developed neurological symptoms such as seizures and disorientation, while the patient was on an antipsychotic along with benzodiazepines. Her symptoms worsened with autonomic instability, and the patient entered into catatonic phase of the illness. We reached a positive diagnosis of anti-NMDAR encephalitis through CSF analysis. The patient recovered completely with the help of immunotherapy and intensive cognitive rehabilitation. This case emphasizes the need of a multidisciplinary approach in the management, early detection, and adequate treatment of this challenging illness for better results for patients.

Keywords: Anti-N-methyl-D-aspartate encephalitis, cerebrospinal fluid analysis, Immunotherapy, Malignant catatonia

Introduction

Anti-N-methyl-D-aspartate receptors (NMDAR) encephalitis is an autoimmune disorder that has been recognized in 2005 and can be mistaken for schizophrenia, acute psychosis, catatonia, or substance-induced psychosis.[1] It was first defined in 2007 by Dalmau *et al*., in a woman with ovarian teratoma.[2] Anti-NMDA antibody formation has been associated with the presence of malignancies such as ovarian teratoma (94%), teratoma of testis, and small-cell lung carcinoma or in some infections such as mycoplasma, EBV, and varicella zoster or may be it is idiopathic, but the initiating event has yet to be identified.[3] Some authors have described its association with nonparaneoplastic syndromes.[4] Most of the cases are found in children and adolescents and mainly occur in females. Exact incidence is unknown as it is a rare diagnosis, with just a few hundred cases reported in the literature.[5]

The clinical presentation of encephalitis has been described through a multiphasic model in five stages – prodromal, neurobehavioral, nonresponsive, hyperactive, and gradual recovery stage.[6] The nonspecific prodromal phase is suggestive of viral –flu-like symptoms in which fever, malaise, or diarrhea may be prominent. The patient presents with neuropsychiatry manifestations within 2 weeks of prodromal phase. This condition is mostly recognized in the psychotic phase, in which agitation, mania, psychosis, anxiety, depression, or disorganized behavior may occur. Following these psychotic symptoms, it may be progress to neurological symptoms such as complex seizures, catatonia or stupor, dyskinesias, impaired attention or confusion, memory loss or delirium, ataxia along with autonomic instability (fluctuating blood pressure, hypoventilation, and tachycardia).[7] However, overlap of these symptoms leads to misdiagnosis and inappropriate treatment. It was observed that anti-NMDAR encephalitis cases did not

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follow this phasic progression or all of the symptomatology, thereby complicating the diagnosis.[8] Magnetic resonance imaging (MRI) brain and electroencephalography (EEG) had been reportedly negative in most of the cases and they were diagnosed on the basis of cerebrospinal fluid (CSF) analysis.[9]

In the following case report, we discussed a patient who reported to the emergency department with behavioral symptoms and was diagnosed as a case of nonparaneoplastic anti-NMDAR encephalitis. Only a few publications have been published on the idiopathic or non-paraneoplastic anti-NMDAR encephalitis cases. There has been a growing understanding of the disease process and presentation since its first appearance. Hence, we planned to report this case study.

Case Report

A 29-year-old married female belonging to urban joint family of middle socioeconomic status without significant past personal or family history of psychiatric illness and surgical history, reported to emergency department with symptoms of acute onset characterized by agitation, suspiciousness, talking unusually, boastfulness, over religiosity, decreased sleep, and appetite from last 4 to 5 days. She was given intramuscular haloperidol 5 mg and lorazepam 4 mg to calm her. Then, the patient was admitted to the psychiatry ward. She had a fever 10 days before the development of these symptoms which was relieved with some antibiotics and paracetamol at home in 2 days. Initially, laboratory studies which included complete blood count, liver function test, renal function test with electrolytes, a metabolic panel (blood sugar, thyroid profile, and lipid profile), and viral markers (HIV, anti-HBsAG, and anti-HCV) were unremarkable. Her provisional diagnosis was kept as Mania with psychotic symptoms and treated accordingly. Thus, the patient was put on tablet olanzapine 5 mg, lorazepam 4 mg, and sodium valproate 1000 mg. On her 4th day of admission, the family members reported worsening of the symptoms in the form of being forgetfulness were not making any sense, and she was not acting like herself. The patient was so confused in the morning that she was not able to feed her 1-year-old baby. On further examination, it was found that the patient was disoriented. Hence, we stopped the treatment, and she was kept under observation in psychiatry ward. Without any improvement in the condition of the patient, on the 6th day of admission, the patient started having seizures such as activity. Despite being repeatedly injection by lorazepam and institution of antiepileptic (injection phenytoin) in higher doses, the patient had multiple episodes in the next 2 days. On the 8th day, her mental status rapidly worsened and immediately medicine consultation was sought. Then, the patient was shifted to intensive care unit (ICU) for close neurological monitoring and further workup. Having concern for viral encephalitis, acyclovir was started empirically along with high doses of antiepileptics. Her vital signs were within normal limits. Neurological examination was performed and found insignificant. Laboratory studies and urine toxicology screening were unrevealing of any profound metabolic or toxic disturbances. Imaging like MRI/magnetic resonance angiography of the brain revealed no intracranial or neurovascular lesions. A lumbar puncture was performed for CSF examination which revealed no abnormality. EEG showed some focal epileptiform discharges which were nonspecific in nature. Viral markers were nonreactive. Hence, acyclovir was stopped. Over the course of the ensuing week, the patient continued to exhibit disorganized behavior and a state of confusion but her seizures subsided. After 1 week in ICU, i.e. on the 14th day, her condition deteriorated further. Within 2–3 days, she became immobile, verbally mute, started staring, and refused to eat or drink orally along with some autonomic disturbances (increased blood pressure, heart rate, respiratory rate, and sweating). On 18th day, psychiatric consultation was solicited. On examination, the patient was found to have posturing, rigidity, waxy flexibility, and negativism. A trial of lorazepam challenge test was done, and the patient showed mild improvement in her symptomatology, which confirmed the malignant catatonia. A nasogastric tube was placed, and parenteral nutrition was started because of poor oral intake. A medical cause of the symptoms was contemplated, most likely due to the persistence of psychotic and neurological symptoms along with autonomic disturbances. At this juncture, the possibility of autoimmune phenomenon was considered. On 19th day, we agreed with presumptive anti-NMDR encephalitis and lumbar puncture was performed. In view of this illness, a 5-day course of intravenous immunoglobulin 0.4 mg/kg was initiated. On 24th day, the presence of oligoclonal bands and anti-NMDA antibody in CSF confirmed the diagnosis. Meanwhile, a complete oncological screening was done including the X-ray chest and contrast-enhanced computed tomography abdomen and pelvis, which was insignificant. On 25th day, a mild improvement (5%–10%) was experienced in neurological symptoms. Then, a 5-day course of intravenous methylprednisolone (1 g/day) followed by 60 mg of oral prednisolone once daily, tablet quetiapine 100 mg for behavioral symptoms, and disturbed sleep through nasogastric tube were given. Injection phenytoin was replaced by tablet levetiracetam 1000 mg to control the seizures. Over the course 3 weeks, the patient was seizure free and showed improvement in behavioral and catatonic symptoms, but she was confused and not following commands. She attempted simple motor reactions, was able to sit with support, and started accepting the meals orally. On the 45th day, the first verbal and emotional reaction was noted in the patient. Then, the patient was shifted to psychiatric ward from the ICU. On the 60th day, she started recognizing her family members and stood without any support. Afterward, intensive psychological treatment such as rehabilitation and psychotherapy were started. Consecutively, the patient showed much improvement over a gradual course of 2–3 Weeks, and the dose of methylprednisolone was tapered slowly. Then, on the 80th day, we performed CSF examination, MRI brain, and EEG which were within normal limits and without any anti-NMDA antibodies. After 84 days of hospitalization, the patient was discharged in good condition

with residual memory deficit. We followed up the patient with tablet quetiapine (100 mg), levetiracetam (1000 mg), methyl-prednisolone (30 mg), and lorazepam (1 mg). After 1 month of discharge, at psychiatry outpatient unit, the patient was described as continuing to improve in terms of cognitive and functional areas. Hence, we again decreased the doses of prescribed medications. At her latest follow-up, 8 months after her discharge, the patient presented with normal neurological and psychological profile. She was also able to take care of her children and doing household work, and all medication s were successfully withdrawn.

Discussion

Our case presented initially with psychological symptomatology, seizures, and fluctuations in mental status; then, it was complicated by malignant catatonia with autonomic instability which are idiopathic in nature. Herken and Pruss described that "yellow flag" and "red flag" symptoms were particularly indicative of autoimmune processes.[8] Index case fulfilled these criteria and was diagnosed as anti-NMDAR encephalitis.

This case presented with a prodromal period of 10 days. Kayser and Dalmau[5] also observed that 70% of the patients presented with prodromal period, averaging 5 days, but in rare cases could be 2 weeks. NMDARs play a central role in synaptic transmission helping in memory, cognition, and learning modulation.[5] The antibodies in Anti NMDAR encephalitis are directed against an epitope on the NR2A/B subunit of NMDA receptor in hippocampus and frontotemporal regions. Blockade of NMDA glutamate receptor removed the GABAergic inhibition followed by the release of acetylcholine and glutamate, responsible for the neurotoxicity and psychosis in the patients. It also results in the development of seizures and deficits in memory and learning.[10]

It was presumed that the use of antipsychotics was more helpful in treating the psychotic symptoms rather than increasing the vulnerability to the side effects such as Neuroleptic Malignant Syndrome (NMS).[11] In case of autoimmune encephalitis, it was very difficult to distinguish that whether the symptomatology was a part of natural disease or due to the NMS. In addition, worsening of disease occurred with antipsychotics before the use of immunomodulatory agents may be the potential feature of the disease process.[12,13] These findings were consistent with presentation of the index case, where antipsychotics worsened the symptomatology and the patient started having confusion and seizures. Due to which the antipsychotic (olanzapine) was stopped. Few studies suggested that the use of benzodiazepines mainly lorazepam helped in treating the aggression and agitation with or without catatonic features.[13,14] Unfortunately, it was also observed that, in the presence of autonomic instability, benzodiazepines may cause or worsen the delirium and excessive sedation.[14]

EEG generally reveals nonspecific abnormalities such as diffuse slowing in 90% of the patients. EEG may reveal extreme versions of "delta brush pattern" which are transient and appears to be unique to anti-NMDAR encephalitis. However, it was only seen in 7 out of 23 patients in a study done by Schmitt *et al*.[15,16] In index patient, EEG showed nonspecific focal or lateralizing epileptiform discharges. Hence, EEG was not a diagnostic entity in index case like other cases reported in the literature.[13,17] Brain MRI has been reportedly negative in 50%–70% of the cases. Brain MRI studies are normal or show transient fluid-attenuated inversion recovery or contrast-enhancing abnormalities.[17] In present case, MRI findings were normal and consistent with other studies.[13,17] Serum anti-NMDAR antibodies assays were not as sensitive as CSF assays (sensitivity 98.8% vs. 85.6%). CSF studies showed lymphocytic pleocytosis, increased protein, and oligoclonal bands in 60% of the patients.[18] Consistent with findings of other cases,[13,17] the present case was also diagnosed on the basis of the presence of oligoclonal bands and anti-NMDA antibodies on CSF analysis.

Titulaer *et al*. revealed that full recovery was rather slow (1–18 months) and challenging in idiopathic cases.[19] Immunotherapy (immunoglobulins, methylprednisolone, and plasma exchange) is the first-line therapy with or without the tumor. More than 50% of patients improved with immunotherapy (either individual or in combination) within 1 month. Patients had shown improvement with immunosuppressive drugs such as rituximab, cyclophosphamide, or azathioprine if they showed no or minimal response with first-line therapy. These therapies also helped in preventing the hippocampal damage.[20] Similar to the present case, Rosenfeld *et al*. also suggested that the concurrent use of immunoglobulins and methylprednisolone had better outcomes than plasma exchange.[6] In the present case, quetiapine was preferred to control the unusual behavior and sleep because of lesser side effect profile like NMS or other extrapyramidal symptoms. Electroconvulsive therapy (ECT) has been found to be very effective in treating the malignant catatonia and autonomic instability in patients who failed to response with aggressive immunotherapy or benzodiazepines in idiopathic cases. The combination of other forms of treatment with ECT may resolve the life-threatening condition.[21] In index case, ECT was discussed but postponed due to the predominant signs of acute encephalitis.

Approximately 75% of patients achieved full recovery or continue to have only mild deficits and 25% of patients have severe disability with 4%–7% mortality rate. Barry *et al*. suggested that there is a 12%–24% chance of relapse mainly in idiopathic cases or in the cases where immunotherapies were not used.[20] A study by Titulaer *et al*. found that 97% of the patients had better results within 24 months.[19] However, our patient showed a full recovery within 8 months of the initial presentation. Despite the aggressive symptomatology and admission to ICU care, our patient had a better result within a short period as she was diagnosed within 1 month of initial presentation and treatment (immunotherapy) was instituted without much delay.

Conclusions

Anti-NMDAR encephalitis is a serious and potentially lethal syndrome of psychological and neurological dysfunctions. Gradually, its diagnosis or recognition is increasing as psychiatrists and physicians are becoming aware of the condition and its presentation. The antipsychotics should be used with caution. The recommendation is to do the screening for ovarian teratoma for the next 2 years using MRI/USG of abdomen and pelvis, even after the full recovery of patient. The present case demonstrated the appropriate need of psychiatrists, neurologists, and other emergency physicians to manage the condition, to be aware of this underdiagnosed disorder and consider it in their differential diagnosis.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given her consent for her images and other clinical information to be reported in the journal. The patient understands that name and initial will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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