CASE REPORT

A Case of Mania with Malignant Catatonia due to Non Para Neoplastic Anti-N-Methyl-D-Aspartate Receptor Encephalitis in a 29 Year Old Female: A Rare Entity

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Abstract:

Anti-N-Methyl-D-Aspartate (NMDA) receptor 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 non-supportive laboratory investigations except the Cerebrospinal Fluid (CSF) analysis delays the diagnosis. We have presented with a case of 29-year-old female with psychiatric symptoms like suspiciousness, decreased sleep and boastfulness. Within a few days, the patient developed neurological symptoms like seizures and disorientation while the patient was on an antipsychotic drug 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-NMDA receptor encephalitis through CSF analysis. Patient recovered completely with the help of immunotherapy and intensive cognitive rehabilitation. This case emphasises 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 Receptor Encephalitis, Cerebrospinal Fluid Analysis, Immuno-therapy, Malignant Catatonia

Introduction:

Anti-N-Methyl-D-Aspartate (NMDA) receptor encephalitis is an autoimmune disorder that has been recognised 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 like ovarian teratoma (94%), teratoma of testis and small cell lung carcinoma or in some infections like mycoplasma, Epstein-Barr Virus (EBV), varicella zoster etc., or maybe it is idiopathic, but the initiating event is yet to be identified [3]. Some authors have described its association with non-para-neoplastic 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 multi-phasic model in five stages–prodromal, neurobehavioral, non-responsive, hyperactive and gradual recovery stage [6]. The nonspecific prodromal phase is suggestive of viral–flu like symptoms in which fever, malaise or diarrhoea may be prominent. The patient presents with neuropsychiatry manifestations within 2 weeks of prodromal phase. This condition is mostly recognised in the psychotic phase in which agitation, mania, psychosis, anxiety,

depression or disorganised behaviour may occur. Following these psychotic symptoms, it may be progress to neurological symptoms like complex seizures, catatonia or stupor, dyskinesias, impaired attention or confusion, memory loss or delirium, ataxia along with autonomic instability (fluctuating blood pressure, hypo ventilation, tachycardia) [7]. However, overlap of these symptoms leads to misdiagnosis and inappropriate treatment. It was observed that anti NMDA receptor encephalitis cases did not follow this phasic progression or all of the symptomatology, thereby complicating the diagnosis [8]. Magnetic Resonance Imagining (MRI) brain and Electroencephalogram (EEG) had been reportedly negative in most of the cases and they were diagnosed on the basis of CSF analysis [9].

In the following case report, we discussed a patient who reported to the Emergency Department with behavioural symptoms and was diagnosed as a case of non-para-neoplastic anti-NMDA receptor encephalitis. Only a few publications have been published on the idiopathic or non-para-neoplastic anti-NMDA receptor encephalitis cases. There has been a growing understanding of the disease process and presentation since its first appearance. So, 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 characterised by agitation, suspiciousness, talking unusually, boastfulness, over religiosity, decreased sleep and appetite from last 4-5 days. She was given intramuscular haloperidol 5mg and lorazepam 4 mg to calm her. Then the patient was admitted to the psychiatry ward. She had fever 10 days prior to 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 and renal function tests with electrolytes, a metabolic panel (blood sugar, thyroid and lipid profiles) 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 5mg, lorazepam 4mg 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, was 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. So, we stopped the treatment and she was kept under observation in psychiatry ward. Without any improvement in the condition of the patient, on the 6thday of admission, the patient started having seizures like activity. Despite being repeatedly injection by lorazepam and institution of antiepileptic (injection phenytoin) in higher doses, patient had multiple episodes in the next 2 days.

On the 8thday, 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 work up. 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/MRA 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 non-specific in nature. Viral markers were non-reactive. So, acyclovir was stopped. Over the course of the ensuing week, the patient continued to exhibit disorganised behaviour and a state of confusion but her seizures subsided. After one 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 (LCT) 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-NMDA receptor encephalitis and lumbar puncture was performed. In view of this illness, a five day course of Intravenous Immunoglobulin (IVIG) 0.4 mg/kg was initiated. On 24th day, 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 (CECT) abdomen and pelvis, which was insignificant. On 25th day, a mild improvement (5-10%) was experienced in neurological symptoms. Then, a five-day course of IV methylprednisolone (1g per day)followed by 60 mg of oral prednisolone once daily, tablet quetiapine 100 mg for behavioural symptoms and disturbed sleep through nasogastric tubewere given. Injection phenytoin was replaced by tablet levetiracetam 1000 mg to control the seizures. Over the course of three weeks, the patient was seizure free and showed improvement in behavioural 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 recognising her family members and stood without any support. Afterwards, intensive psychological treatment like 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 hospitalisation, 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 (1mg). After one month of discharge, at psychiatry outpatient unit, the patient was described as continuing to improve in the terms of cognitive and functional areas. So, 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 medications were successfully withdrawn.

Discussion:

Our case presented initially with psychological symptomatology, seizures, 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-NMDA receptor encephalitis.

This case presented with a prodromal period of 10 days. Dalmau *et al*. [5] also observed that 70% of the patients presented with prodromal period, averaging 5 days but in rare cases could be 2 weeks. NMDA receptors play a central role in synaptic transmission helping in memory, cognition and learning modulation [5]. The antibodies in anti-NMDA encephalitis are directed against an epitope on the NR2A/B subunit of NMDA receptor in hippocampus and fronto-temporal 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 use of antipsychotics was more helpful in treating the psychotic symptoms rather than increasing the vulnerability to the side effects like 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 reveal non-specific 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-NMDA receptor encephalitis. But it was only seen in 7 out of 23 patients in a study done

by Schmitt and colleagues [15-16]. In index patient, EEG showed non-specific focal or lateralising epileptiform discharges. So, 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-NMDA receptor 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 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 tumour. More than 50% patients improved with immunotherapy (either individual or in combination) within one month. Patients had shown improvement with Immunosuppressive drugs like 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, Dalmau *et al*. have also suggested that concurrent use of immunoglobulins and methylprednisolone had better outcomes than plasma exchange [6]. In the present case, quetiapine was preferred to control the unusual behaviour 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% patients achieved full recovery or continue to have only mild deficits and 25% 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]. But 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 one month of initial presentation and treatment (immunotherapy) was instituted without much delay.

Conclusion:

Anti-NMDA receptor 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 two years by using MRI/ultrasound sonography 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 beaware of this under-diagnosed disorder and consider it in their differential diagnosis.

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