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Commentary

Psychotic symptoms in anti-*N*-methyl-D-aspartate (NMDA) receptor encephalitis: A case report and challenges

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ABSTRACT

Anti-*N*-methyl-D-aspartate (NMDA) receptor encephalitis, only recently first described, is an increasingly well-recognized inflammatory encephalitis that is seen in children and adults. An 11-year old girl admitted to the psychiatry ward with a presentation of acute psychosis was diagnosed with NMDA receptor encephalitis following neurology referral and was treated accordingly. This case highlights psychiatric manifestations in encephalitis and the need for the psychiatrist to have high index of suspicion when atypical symptoms (e.g., dyskinesia, seizure, fever etc.) present in acutely psychotic patients.

1. Introduction

Anti-*N*-methyl-D-aspartate (NMDA) receptor encephalitis is a severe form of autoimmune encephalitis associated with antibodies against NR1 and NR2 subunits of the NMDA receptor (Chapman and Vause, 2011). It was conceptualized as a condition primarily affecting adult women with ovarian tumors; however, it has been increasingly recognized among adult males, children, and those with the absence of tumors as well (Barry et al., 2011). A stereotypical clinical course in phases characterized by non-specific flu-like prodrome (low grade fever, headache, and fatigue) is usually followed by a psychotic stage (bizarre behavior, paranoid thoughts, and visual or auditory hallucinations) and cognitive impairment (disorientation and confusion) is noted in the patients with Anti-NMDAR encephalitis. Acute onset of typical psychosis is usually considered initially and the patients are often admitted to psychiatric services (Tsutsui et al., 2012). Organic brain involvement is suspected only after the patients develop seizures, autonomic instability, dyskinesia, or decreased level of consciousness (Iizuka, 2008). We report a case of anti-NMDA receptor encephalitis in 11-year-old girl associated with an incidental precipating factor which made it look like a case of acute transient psychotic disorder. We would like to highlight the importance of identifying extrapyramidal manifestation like oromotor dyskinesia and subtle hand dystonia in the index case at psychiatric setting which would trigger suspicion for NMDAR encephalitis, thus avoiding delay in diagnosing this treatable condition which may otherwise be fatal.

2. Case report

An 11-year-old girl presented in the Psychiatry Outpatient Department (OPD), referred from the District Hospital, had a history of an abrupt change in behaviour, deteriorating over a duration of three weeks. This condition was precipitated by the sight of the post-accident amputated right hand of her father. Although she had not witnessed the accident, she saw the bleeding, bandaged stump. She initially had crying spells, saying that her left hand was not working and dragging her left foot while walking. After 2–3 days she reported of the nihilistic ideas that her hands were cut and they were useless. There were episodes when she would try to run out of the room. She would also bite her fingers and mucosa of the cheeks. She often seemed restless throughout the day. After around a week of the onset of symptoms, she became fearful and reported that a ghost was coming after her and was trying to harm her. Her sleep and appetite decreased and her self-care became impaired. She also had catatonic symptoms in form of staring, mutism, withdrawal, impulsivity, and perseveration. Apart from this, she also had dyskinetic movement of the left

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hand and of the orofacial region. Due to these symptoms, she was taken to the hospital where Magnetic Resonance Imaging (MRI) of the brain and electroencephalogram (EEG) were done. MR imaging showed normal study for the brain parenchyma and no abnormality was detected in EEG. She was prescribed Alprazolam 0.5 mg which slightly improved her anxiety. She was then referred to our center (All India Institute of Medical Sciences, New Delhi). She was seen in OPD and was advised admission. At the time of admission, her pulse rate was 110/min, blood pressure 110/65 mmHg, and she was irritable with a Glasgow coma score (GCS) of Eye Response 4, Verbal Response 5, and Motor Response 6 (EE4V5M6). On examination there was no focal neurological deficit. However, in the Mental Status Examination of uncooperative patients, there was abnormal spontaneous movement of fingers, negativity, biting of the lips, staring, rigidity, indifference to what was said, production of incomprehensible sounds at times, and repeating sentences. A provisional diagnosis of acute transient psychotic disorder (ATPD) was made. She was prescribed Risperidone 2 mg/day and Lorazepam 1 mg/day. Considering the atypical symptoms and age of the patient, a pediatric neurology referral was made. The advice for reviewing MRI and EEG was given and tests for detection of anti NMDA receptor antibody in blood and cerebrospinal fluid (CSF) was suggested. Indirect Immunofluorescence (IIF) showed serum anti NMDA antibody to be positive (1:10). Considering the positive serum anti NMDA antibody, she was transferred to the pediatric neurology ward. Lumbar puncture was done and CSF examination showed 5 cells/mm^3 (100% lymphocytes), protein 20 mg/dl, sugar 68 mg/dl, and CSF culture and sensitivity was sterile. CSF NMDA antibody was sent and came back positive in IIF (1:10). She was started on intravenous methyl prednisolone and intravenous immunoglobulin (IVIg) 2 gm/kg for five days. After that, her sensorium and abnormal posturing and catatonia started to improve. The IV steroids were then replaced by oral prednisolone (40 mg/day). The child was also screened for tumours; USG abdomen and CECT chest and abdomen were done and came back normal. She also continued with tab Risperidone 2 mg/day. After approximately 3 days of taking oral steroids, her behaviour changed in the form of decreased need of sleep, irritability, over-demanding, over-grooming, increased appetite, and expansive mood as evident by singing and dancing in the ward. The Young's Mania Rating Scale (YMRS) score at that time was 14. The oral steroids were stopped at the 4th day and the symptoms gradually improved over a week with a YMRS score of 3. At the time of discharge, the patient was ambulatory and had subtle behavioural abnormality which improved completely over the next one month. At the time of follow-up, 4 months after discharge, the patient had no neurological deficits and had started going to school and leading a completely normal life. She is currently maintaining well on 1 mg/day of Risperidone, which was planned to discontinue after one month following the writing of this paper.

3. Discussion

Initially discovered in 2007 (Dalmau et al., 2007), anti-NMDAR encephalitis and its clinical manifestations have changed the approach to patients presenting with acute psychosis, altered behavior, and catatonia. Most patients with anti-NMDAR encephalitis are evaluated initially by a psychiatrist before neurology or medical teams become involved. It is usually the development of seizures or dyskinesia that alerts treating physicians to the possibility of neurological pathology (Dalmau et al., 2008). Anti-NMDAR antibody has also been found to be associated with various psychotic symptoms without any noticeable clinical signs of encephalitis in the period of disease episodes (Tsutsui et al., 2012). Around 4% of the cases present with isolated psychiatric episodes without neurological involvement (Kayser et al., 2013). Anti-NMDA receptor encephalitis has a strong association with the presence of tumour(s), which is most commonly an ovarian teratoma seen in 62% of the population. This association depends on the age and gender as tumors are less commonly found in children (Irani et al., 2010). In the present case, no tumour was found, even after an extensive workup. MRI results are normal in 50% of the patients and those showing abnormalities in the MRI mostly have non-specific T2 hyperintensity in the hippocampus, and frontal and insular cortex. Early EEG changes mainly comprise of epileptic activity whereas EEG done after a few days usually show background slowing. CSF abnormalities include lymphocytosis which is seen in early stages and oligoclonal bands in later stages (Dalmau et al., 2011). The MRI of the brain, EEG and CSF analysis (except IIF) was normal in case of our patient.

Individuals with schizophrenia or schizoaffective, bipolar, or major depressive disorders are collectively about three times more likely to have elevated NMDAR antibody titers compared with healthy controls (Pearlman and Najjar, 2014). The seropositivity in psychiatric groups have various combinations of IgG, IgM, and IgA class antibodies against NR1, NR1/NR2B, and NR2A/NR2 B subunits (Pearlman and Najjar, 2014). The glutamatergic theories of schizophrenia are also based on the ability of *N*-methyl-D-aspartate receptor (NMDAR) antagonists to induce schizophrenia-like symptoms. Apart from this, there is emergent literature documenting disturbances of NMDAR-related gene expression and metabolic pathways in schizophrenia (Moghaddam and Javitt, 2012). The early presentation of psychosis in anti-NMDAR encephalitis might be evidence of this. There are increasing numbers of recognized autoantibodies against receptors other than anti-NMDA that are seen in psychosis (Endres et al., 2015). Similarly, studies show there is a significantly higher rate of positivity of NMDAR antibodies in child and adolescent psychosis than in adult-onset psychosis (Pathmanandavel et al., 2015). On one hand, these findings lend credence to the hypothesis of autoimmune pathology as an etiologic factor for the causation of psychosis; on the other hand, it might create confusion in clinicians as to when to advise for the antibody test. Similarly, question might arise as to when to label the core psychiatric illness as autoimmune encephalitis. Also, this might lower the sensitivity and specificity of diagnosis on the basis of the detection of the antibodies and may create confusion in the modality of treatment i.e. either to start standard treatment of anti NMDA receptor encephalitis (steroid pulse and IV Ig) or to continue with the conventional treatment of psychosis.

The differential diagnosis of anti-NMDR encephalitis is wide and includes infections of the brain (mainly viral), other autoimmune encephalitis, and CNS vasculitis. The acute transient psychotic disorder is a close differential, mainly in the earlier part of illness. Unlike other cases in literature, one interesting aspect of our case was the presence of the psychological stressor at the onset of the illness and the incorporation of the stressor in the psychopathology in the form of nihilistic ideas. This was regarded as a pointer towards ATPD. However, the appearance of extrapyramidal manifestations in psychiatry ward initially thought to be catatonic symptoms in hinted us to go for relevant investigation that made the diagnosis clear.

To conclude, this case highlights there should be suspicion towards the anti-NMDA receptor encephalitis when the psychiatric symptoms are accompanied by extrapyramidal symptoms, autonomic dysfunction and neurological decompensation. More research and dissemination of knowledge are required to improve clinicians' ability to make the diagnosis of anti NMDA receptor encephalitis and exclude important disease mimics based on clinical and radiological evidence. However, the patient can be labeled as anti-NMDA receptor encephalitis only when the autoantibodies are seen in the serum or CSF. One strength of this case

report is that this particular patient was found to have slightly atypical psychiatric symptomatology, including a stressful event, the content of which was incorporated in the psychopathology. On further investigation her serum and CSF had positive NMDA receptor auto-antibodies, and after immune treatment there was resolution of symptoms, highlighting the need of suspicion and the challenges clinicians face diagnosing anti-NMDA receptor encephalitis

Conflict of interest

None

Ethical standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committee on human experimentation with the Helsinki Declaration of 1975, as revised in 2008. The authors assert that ethical approval for publication of this audit was not required by their local Ethical Committee.

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