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Anti-NMDA receptor encephalitis: A neurological disease in psychiatric disguise

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ABSTRACT

Anti-NMDA receptor encephalitis was first described in 2005 when psychiatric features, memory loss and altered consciousness were found in four women with ovarian teratoma. We report a case of anti-NMDA receptor encephalitis in a 16-year-old female who presented with psychiatric features followed by autonomic dysfunction and orofacial dyskinesias that showed drastic improvement to intravenous immunoglobulin. As many patients of anti-NMDAR encephalitis initially present with psychiatric features, it is important for psychiatrists to have high index of suspicion for this disease and thus avoid the delay in diagnosing this treatable condition which may be otherwise fatal.

1. Introduction

Anti-NMDA receptor encephalitis was first described in 2005 when psychiatric features, memory loss and altered consciousness were found in four young women with ovarian teratoma (Titulaer et al., 2013). NMDA receptor antibodies were later identified in these four and eight other women (Maggina et al., 2012). Autonomic dysfunction and central hypoventilation are seen in the majority of patients with anti NMDR encephalitis but the severity is low in children (Jones et al., 2013). We report a case of anti-NMDA receptor encephalitis in a 16-year-old female who presented with psychiatric features followed by autonomic dysfunction and orofacial dyskinesias that showed drastic improvement to intravenous immunoglobulin. We would like to highlight the importance of identifying the psychiatric manifestations followed by autonomic dysfunction and orofacial dyskinesias in a patient of subacute encephalitis as features suggestive of anti-NMDA receptor encephalitis and thus avoid the delay in diagnosing this treatable condition which may be otherwise fatal.

2. Case report

A 16-year-old female presented with a history of fever of 2–3 days duration which was followed by change in behaviour since 15–16 days. Her mother reported that, earlier, the patient was very obedient and well behaved girl, but recently she had become increasingly aggressive. The patient was noted to be agitated all the time and verbally abusive over trivial issues and it was difficult to control her. She reportedly threw her dinner plate over a small argument with her younger brother. The patient felt nervous and anxious to go to school and she was unable to focus her attention during school lectures. Her parents had noticed that she could not sit at one place for long and would frequently get up from her chair and start roaming around. She was unable to sleep at night and would get up before her morning alarm bell. Initially, her parents took her to a psychiatrist who prescribed her antianxiety medication consisting of alprazolam (0.5 mg at night) which improved her insomnia a little but her other clinical features remained the same. Over the next 3 days, the patient had three episodes of generalized tonic clonic seizures for which her psychiatrist referred her to our Department of Neurology. At the time of admission, pulse rate was 110/min, blood pressure 180/110 mmHg, and the patient was drowsy with Glasgow coma score (GCS) of E3V4M5. On examination there was no focal neurological deficit. A provisional diagnosis of subacute encephalitis was made and the patient was advised CSF examination, electroencephalogram (EEG), and contrast enhanced magnetic resonance imaging (MRI). CSF examination revealed mild increase in protein (80 mg%) and 50 cells (lymphocytic predominance). Polymerase chain

Abbreviation: NMDA, N-methyl-D-aspartate.

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reaction (PCR) for Herpes simplex virus and tuberculosis were negative. EEG showed diffuse background slowing with no epileptiform discharges, however, the contrast enhanced MRI was normal. The patient was put on empirical treatment comprising of antibiotics and acyclovir. During the initial ICU stay, it was noted that the patient had labile hypertension with episodic tachycardia for which the patient was put on propranolol (40 mg twice a day). Over the next seven to 8 days, patient showed progressive deterioration in consciousness and developed respiratory dysfunction and required ventilatory support. Subsequently over the next three to 4 days, patient developed orofacial dyskinesia comprising of grimacing of face and lip smacking. Considering autonomic dysfunction with orofacial dyskinesias as delayed features of sub acute encephalitis a possibility of anti-NMDA receptor encephalitis was considered and patient's CSF and serum were sent for NMDA receptor antibody which was reported to be positive. The patient was then started with intravenous (IV) methylprednisolone (1 g for 5 days) but the patient did not show any improvement. Intravenous immunoglobulins (IV Ig) (0.4 g/kg/day) was started and was administered for 5 consecutive days and the patient showed dramatic improvement and became responsive within 2–3 days of initiating IV Ig and was off the ventilator support on the fifth day of treatment. After starting IV Ig, the patient did not experience any seizure and her abnormal involuntary facial movements also subsided. At the time of discharge, the patient was ambulatory with amnesia for the illness and subtle behavioural abnormality which improved completely over the next one month. At the time of follow-up, one month after discharge, the patient had no neurological deficit and had started going to college and led a completely normal life.

3. Discussion

Anti-NMDA receptor encephalitis is characterized by psychiatric features (hyperactivity, anxiety, mania, psychosis, and irritability), neurological features (seizures, movement disorders, and cognitive disorders), and autonomic dysfunction (hypertension, tachycardia, and hypoventilation) (Consoli et al., 2011; Florance-Ryan and Dalmau, 2010; Bayreuther et al., 2009). Clinical features of anti-NMDA receptor encephalitis can be divided into three stages. First is the prodromal stage characterized by fever, headache, and rhinitis (Jones et al., 2013). Second stage (early features) characterized by cognitive dysfunction, psychiatric features and seizures which usually occurs within two weeks of prodromal phase (Irani et al., 2010). Third stage (late features) is characterized by reduced consciousness, involuntary movements, and autonomic dysfunction, and occurs 10–20 days after early features. Our patient presented to us with psychiatric features since 15–16 days followed by autonomic dysfunction and orofacial dyskinesias. Presence of psychiatric features followed by autonomic dysfunction and orofacial dyskinesias were the key features which made us to consider a possibility of Anti-NMDA receptor encephalitis.

Anti-NMDA receptor encephalitis has a strong association with presence of tumour which is most commonly an ovarian teratoma seen in 62% of the population (Jones et al., 2013). However, its association depends on the age and gender as tumours are less commonly found in children and males as compared to adult females (Irani et al., 2010). The patients without an associated tumour have increased chances of relapse as compared to those with a tumour which has been surgically removed. In our case no tumour was found even after extensive workup. Repeat MRI pelvis done at one month follow up was also normal.

MRI is normal in 50% of the patients and those showing abnormalities in MRI mostly have non-specific T2 hyperintensity in hippocampus, frontal and insular cortex (Dalmau et al., 2011). EEG abnormalities can be divided into early and late changes. Early changes are comprised of epileptic activity whereas EEG done later usually show background slowing (Consoli et al., 2011). CSF abnormalities include lymphocytosis which is seen in early stage and oligoclonal bands in later stage (Irani et al., 2010). sensitivity of NMDA receptor antibody in CSF is more as compared to that in serum and the decline in antibody titre shows a good correlation with clinical improvement (Titulaer et al., 2013). Our patient's MRI of the brain was normal, whereas EEG showed background slowing. CSF showed lymphocytosis with increased protein. Test for oligoclonal band in CSF was not advised due to financial constraints of the patient.

The differential diagnosis of anti-NMDR encephalitis is wide and includes infections of the brain (mainly viral), other autoimmune encephalitis, and CNS vasculitis.

The treatment of anti-NMDA receptor encephalitis can be divided into first line therapy and second line therapy. First line therapy includes corticosteroid, IV Ig, and plasmapheresis used alone or in combination. Second line therapy includes rituximab and cyclophosphamide or in combination. Various studies have shown that approximately 50% of the patients show significant improvement within four weeks of first line treatment and tumour removal. Second line therapy can be effective in up to two third of the patients who had failed first line of treatment (Titulaer et al., 2013). Thus, the patients who have received first or second line therapy of recovery of with minimal residual neurological deficit. Our patient received combination of corticosteroid and IV Ig and showed dramatic improvement after starting IV Ig and had no residual neurological deficit at one month of follow-up.

4. Conclusion

This case highlights the importance of early diagnosis and treatment of anti-NMDA receptor encephalitis, as delay in treatment leads to increase morbidity and mortality. As many patients of anti-NMDAR encephalitis initially present with psychiatric features, it is important for psychiatrists to have high index of suspicion for this disease. Anti-NMDA receptor encephalitis should always be considered in patients of encephalitis, later developing autonomic dysfunction or involuntary movements, which should be confirmed by presence of NMDA receptor antibodies in CSF or serum.

Conflicts of interest

The authors declare they have no conflicts of interest.

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