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SHORT COMMUNICATION

Anti-NMDA receptor encephalitis presenting as postpartum psychosis—a clinical description and review

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Abstract

Anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis is increasingly being recognised to be associated with protean neuropsychiatric manifestations. Anti-NMDAR encephalitis is considered to be the most common amongst the autoimmune-mediated encephalitic disorders. It is caused by the autoantibodies against GluN1 subunits of N-methyl-D-aspartate (NMDA) receptor and manifests with prominent psychiatric symptoms, especially during the initial phase of illness. Literature anti-NMDAR encephalitis presenting with postpartum psychosis is scant. In this report, we present a 28-year-old lady with postpartum psychosis as presenting manifestation of anti-NMDAR encephalitis and discuss the neuropsychiatric manifestations of this emerging entity.

Keywords NMDA receptor · NMDAR · Autoimmune encephalitis · Psychosis · Postpartum

Introduction

Anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis is a recently discovered autoimmune encephalitis with antibodies directed against the NMDA-type glutamate receptors located at the neuronal synapses (Lee and Lee 2016). It presents with a characteristic spectrum of neurological, cognitive and psychiatric symptoms. This clinical condition often progresses through distinct phases. It starts with a *prodromal phase* characterised by headache, fever, nausea, lethargy, vomiting, diarrhoea and flu-like symptoms. This is followed by 1 to 3 weeks of predominant *psychiatric symptoms* followed by *neurological* involvement with dyskinesia, seizures, autonomic instability progressing to hypoventilation, and severe fluctuations in level of consciousness (Kayser and Dalmau 2011; Dalmau et al. 2008). Presentation with profound psychiatric manifestations alone is less common.

Anti-NMDAR encephalitis can occur as a part of paraneoplastic syndrome or manifest as an independent non-paraneoplastic disorder. Among the paraneoplastic cases, the commonly found tumour is teratoma, especially among females in the age group of 12 and 45 years (Dalmau et al.

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2011; Titulaer et al. 2013; Kayser et al. 2013). It is reported that persons of Asian and African origin may be more vulnerable for paraneoplastic anti-NMDAR encephalitis (Titulaer et al. 2013).

Psychiatric manifestations associated with anti-NMDAR encephalitis include anxiety/ fear, agitation, paranoid ideation, mood lability, bizarre and disinhibited behaviour, delusions, auditory and visual hallucinations (Dalmau et al. 2008). These symptoms can be mistaken as manifestation of an underlying primary psychiatric disorder leading to a delay in definitive diagnosis and treatment of anti-NMDAR encephalitis. It is essential to note that nearly 77% of patients with anti-NMDAR encephalitis are likely to be seen first by the psychiatrists and such patients often receive a diagnosis of primary schizophrenia or bipolar disorder (Mann et al. 2014).

The literature on anti-NMDAR encephalitis during the postpartum period is sparse. We could identify only six reported cases of postpartum onset of anti-NMDAR encephalitis. All the reported cases were initially suspected to have primary postpartum psychosis and were later detected to have anti-NMDAR encephalitis.

In this report, we have described the clinical presentation and treatment details of anti-NMDAR encephalitis presenting as psychosis in the postpartum period along with a discussion on the relevant literature.

Case history

Ms. S, a 28-year-old married lady presented to the emergency services during the fourth month of postpartum period, following the delivery of her fourth child. She presented with 2 weeks history of behavioural changes and two episodes of generalised tonic clonic seizures (GTCS). On examination, she was conscious and vital signs were within normal limits. There were no focal neurological deficits; other systemic examinations were normal. Computed tomography (CT) scan of the brain did not show any abnormality. She was advised Tab. Levetiracetam (500 mg twice a day) at the neurology services and was referred to psychiatry services for evaluation of psychosis.

On exploration, she had developed an acute onset behavioural change in the beginning of the fourth month following delivery, characterised initially by fearfulness, seeing false images of people in clear consciousness, and sleep disturbances. A week later, she developed two episodes of GTCS as described earlier, following which there was a worsening of her condition in the form of poor memory, reduced concentration, and altered speech.

There was no past or family history of psychiatric or neurological disorder. Her previous pregnancies and postpartum periods were uneventful. On psychiatric evaluation, she was found to be conscious and oriented but poorly kempt and restless. There was reduced speech output and vacant staring along with inappropriate smiling and muttering. She acknowledged experiencing auditory hallucinations, fleeting visual hallucinations and fearfulness about some harm being caused to her. Family members reported that she did not care for the baby and also refused to breastfeed. The score on Hindi Mental Status Examination (HMSE) was 20 out of 31, which was below the cut-off score of 23 (Ganguli et al. 1995). The score on Addenbroke's cognitive examination (ACE) was 36 out of 100, much below the cut-off score of 88 (Mathuranath et al. 2000). The deficits were predominantly in the domains of attention, memory and language. In view of the clinical presentation, especially on account of visual hallucinations and cognitive deficits, a diagnosis of postpartum psychosis with a possible organic aetiology was considered. Patient was investigated in detail for possible organic causes (Table 1) including cerebrospinal fluid (CSF) analysis. Scalp electroencephalogram (EEG) revealed spikes arising from bilateral occipital regions. The findings on magnetic resonance imaging (MRI) scan of brain are shown in Fig. 1. Meanwhile, patient was advised Risperidone 2 mg per day which was gradually increased to 6 mg per day to manage the psychotic symptoms. Tab. Lorazepam 2 mg TID was given for the catatonic symptoms that were observed during the clinical course. Even after 3 weeks of this treatment, the clinical response was minimal with an increase in fearfulness and hallucinations. Tablet Risperidone and Lorazepam were stopped and Tab. Haloperidol 5 mg per day was prescribed following which there was an emergence of severe extra pyramidal symptoms and Haloperidol was discontinued. Serum and CSF were tested for anti-NMDAR antibodies tested using a sensitive commercially available cell based immunofluorescence assay (Euroimmun, Germany). The CSF was strongly positive for anti-NMDAR antibodies while serum was negative and a diagnosis of anti-NMDAR encephalitis was considered.

Steroid therapy was initiated with seven cycles of plasmapheresis but there was very minimal improvement in her clinical condition. Patient continued to be mute and cognitive deficits persisted as described above. Screening for ovarian teratoma by ultrasonography (USG) was negative. Family members obtained discharge against medical advice after nearly 2 months of intensive psychiatric and neurological care.

Discussion

Our report highlights the unusual presentation of anti-NMDAR encephalitis with psychosis in the postpartum period. Postpartum onset anti-NMDAR encephalitis has a variable period of onset ranging from 1 week to 3 months following delivery (Doden et al. 2017). Normal vaginal delivery as in the present case has been observed in all the previously reported cases of

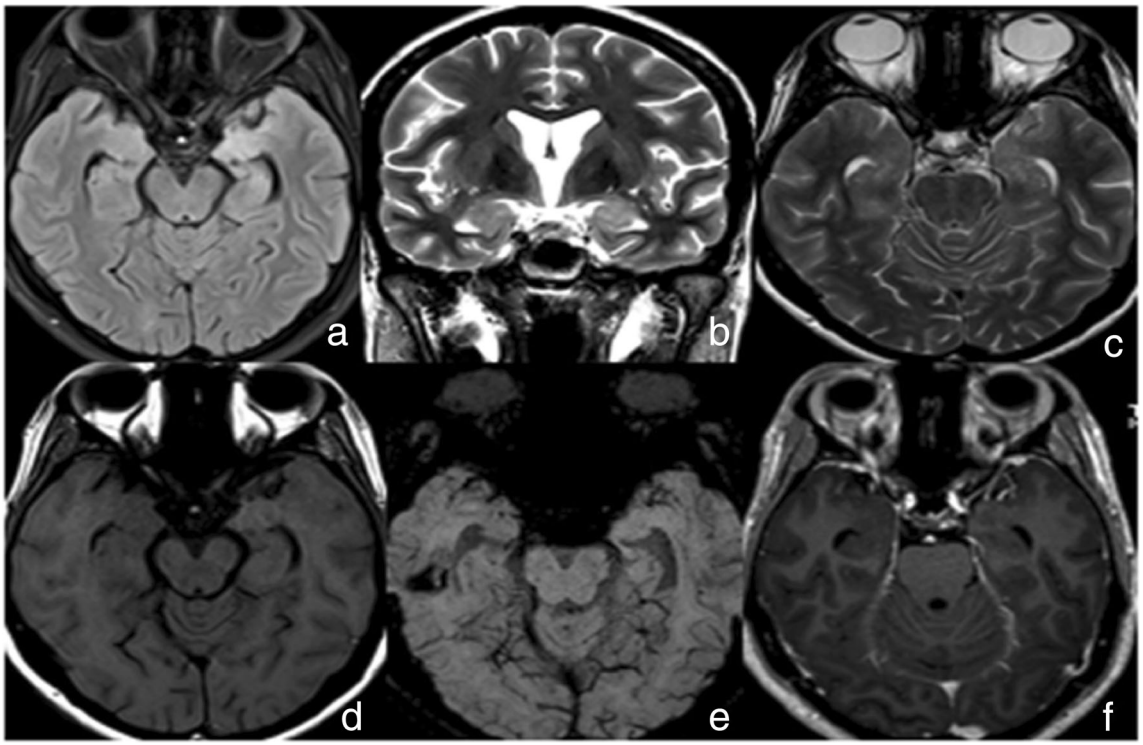

Fig. 1 **a**, **b**, **c**, **d**, **e**, **f** represent FLAIR, T2WI, T1WI, SWI, and post-contrast MPRAGE images. They show hyperintense signal changes on T2WI and FLAIR images and isointense on T1WI involving the left antero-medial temporal lobe structures, i.e., amygdala and hippocampus and parahippocampal gyri. No microbleeds or post-contrast enhancement is seen

postpartum anti-NMDAR encephalitis (Doden et al. 2017). In our patient, the onset of illness complicated the course of her fourth delivery. Multiparity, however, is unlikely to be a risk factor, as onset of anti-NMDAR encephalitis has been observed across any of the birth orders (Doden et al. 2017).

Psychotic symptoms with a polymorphic clinical picture seems to be the most common clinical presentation of anti-

Table 1 Laboratory test results

Investigation	Result (Reference range)
Haemogram	Within the normal limits
Thyroid profile	
T3	117.03 (87–178 ng/dl)
T4	10.32 (6.09-12.3 ug/dL)
TSH	0.62 (0.34–5.60 uIU/ml)
ESR	42 (0–12 mm/h)
Renal function test	Within the normal limits
Liver function test	Within the normal limits
Vitamin B12	375.00 (180–914 pg/ml)
Serum ANA	Negative
Serum Anti-VGKC, Anti-AMPA, Anti-GABA antibodies	Negative
CSF Anti-NMDAR antibodies	Positive
Serum anti-thyro-peroxidase (TPO) antibodies	7.5 IU/ml(up to 34 IU/ml)
Ultrasound abdomen	Mild splenomegaly (Both Ovaries appear normal)
CSF analysis-	
Cells	6 (Lymphocytes)
Protein	31 (15–45 mg/dl)
Glucose	68 (40–70 mg/dl)
Chloride	122 (118–132 mmol/l)

NMDAR encephalitis during postpartum period (Doden et al. 2017). The commonly reported psychiatric symptoms include anxiety, delusions, agitation, irritability, hallucinations, psychomotor excitement, confusion, catatonic features, depression and insomnia (Kayser et al. 2013). Among the reported cases, patients were initially suspected of having a primary postpartum psychosis before arriving at a definitive diagnosis of autoimmune encephalitis. Visual hallucinations, presence of seizures, memory deficits and findings on MRI brain scan are pointers towards a neurological illness in the present case. As a paraneoplastic manifestation, there have been reports of ovarian teratoma being associated with postpartum onset anti-NMDAR encephalitis (Yu and Moore 2011; Koksal et al. 2015; Doden et al. 2017). As in the present case, two earlier reports did not report of an association with the ovarian teratoma (Shaaban et al. 2012; Bergink et al. 2015).

It is important to note that in the present case, testing for serum anti-NMDAR antibodies was negative whereas the CSF anti-NMDAR test was positive. Nearly 15% of patients who test negative for serum anti-NMDAR antibodies are likely to test positive for CSF anti-NMDAR antibodies (Titulaer et al. 2013). Hence, it is important to test CSF even if serum anti-NMDAR antibodies are negative in cases with high clinical suspicion of autoimmune encephalitis.

There are no characteristic neuroradiological changes in patients with anti-NMDAR encephalitis. Hyper-intensities on MRI-brain in the hippocampi, cerebellar cortex, frontobasal and insular regions, basal ganglia, and brain stem regions have been observed (Shaaban et al. 2012). In our patient, hyperintensities on MRI brain were observed in the bilateral medial temporal lobe areas. Abnormal EEGs have been found in most patients with anti-NMDAR encephalitis; non-specific generalised slowing is a commonly observed finding (Tonomura et al. 2007; Kayser et al. 2013). In one third of patients, a unique EEG pattern characterised by extreme delta brush, consisting of 1–3-Hz rhythmic activity with superimposed 20–30-Hz rhythmic activity has been reported (Yu and Moore 2011; Schmitt et al. 2012). Contrastingly, spikes in the bilateral occipital areas were noticed in the present case.

Treatment response and pathogenetic mechanism

Patients with anti-NMDAR encephalitis show variable responses to treatment. Nearly 80% improvement in psychiatric manifestations have been noted in patients of anti-NMDAR encephalitis who were treated with either tumour removal or immunotherapy (Doden et al. 2017; Koksal et al. 2015; Kayser et al. 2013; Shaaban et al. 2012; Yu and Moore 2011). The two cases of anti-NMDAR encephalitis without ovarian teratoma showed a significant improvement in behavioural symptoms following treatment with psychotropic drugs such as haloperidol, olanzapine, lithium and lorazepam (Bergink et al. 2015). Contrastingly, the response to psychotropics and also to steroid therapy and plasmapheresis was poor in our patient. An earlier report too suggests of poor improvement in higher brain functions despite intensive interventions (Doden et al. 2017).

The pathomechanism for evolution of psychiatric symptoms in this condition is due to rapid and reversible loss of surface NMDAR by antibody-mediated capping and internalisation, and emergence of a state of NMDAR hypofunction (Höftberger 2015). This is analogous to phencyclidine or ketamine blocking the NMDAR and leading to psychosis (Javitt and Zukin 1991). The exact aetiology underlying the onset of anti-NMDAR encephalitis during postpartum period is unclear and could be due to a generalised immune activation that is seen after delivery (Yu and Moore 2011; Koksal et al. 2015). Also, hormones such as prolactin and oestrogen are associated with differential modulation of B-lymphocytes and generation of autoreactive B-cells (Yu and Moore 2011). The dramatic hormonal changes and rebound immunity during immediate postpartum period could be involved in the pathogenesis of anti-NMDAR encephalitis.

Our report illustrates the need for high index of clinical suspicion of anti-NMDAR encephalitis if postpartum psychosis is accompanied with cognitive impairments, neurological signs and seizures either at the time of presentation or during the course of illness. There is a need for further research in the area of postpartum anti-NMDAR mediated psychosis.

Recommendations

In patients with postpartum psychosis, a thorough examination should be performed for neurological signs and cognitive deficits and in the presence of such findings, the patient should undergo MRI brain scan and CSF studies for anti-NMDAR antibodies. Patients with positive anti-NMDAR encephalitis should be considered for therapy with steroids, plasma exchange or rituximab. In addition, association with tumours such as teratoma should be excluded.

Conclusion

Anti-NMDAR encephalitis is a neuropsychiatric condition which is potentially treatable. A psychiatrist should have a high index of suspicion in cases with atypical psychiatric manifestations during pregnancy and post-partum period.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

This report is not presented anywhere in any form.

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