CASE REPORT

Steroid unresponsive anti-NMDA receptor encephalitis during pregnancy successfully treated with plasmapheresis

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SUMMARY

Anti-*N*-methyl-D-aspartate (NMDA) receptor encephalitis is an autoimmune disorder resulting in neurological and psychiatric symptoms. It is rare during pregnancy and treatment is extremely challenging as little data exist to guide management. A 26-year-old woman presented at 22 weeks of gestation with intermittent headache and an acute episode of bizarre behaviour and grandiose delusions resulting in hospitalisation. The patient was worked up for encephalitis and was found to have anti-NMDA receptor antibody in cerebrospinal fluid as well as in serum. She was initially treated with high-dose steroids but failed to improve clinically and serologically. She was then treated with plasmapheresis and showed clinical and serological response. She had a successful delivery at 37 weeks and the baby did not show serological evidence of disease. This case adds to the sparse literature of anti-NMDA receptor encephalitis during pregnancy and adds to the differential diagnosis of new onset psychiatric symptoms during pregnancy.

BACKGROUND

Anti-*N*-methyl-D-aspartate receptor (NMDAR) encephalitis is a synaptic autoimmune disorder that is likely mediated by antibodies against the NR1 subunit of the receptor. Results from the California Encephalitis Project show that half the children with idiopathic encephalitis and psychiatric symptoms had antibodies against the NMDAR, and the frequency was four times that of encephalitis caused by herpes simplex, varicella-zoster and West Nile viruses.[1] The growing body of literature suggests that antibodies formed in response to a number of possible stimuli (ie, tumour, infection), cross-react with synaptic proteins, most commonly the NMDAR. In the largest case series to date, anti-NMDAR antibody encephalitis was found to be more frequent in women, with a median age of 23 years at the time of diagnosis.[2] Previous cases of NMDAR encephalitis occurring during pregnancy have been reported in the literature, however, treatment could be extremely challenging and little data exist to guide management.[3–5]

CASE PRESENTATION

A 26-year-old woman of Indian origin presented at 22 weeks of gestation with 2 weeks of intermittent headache followed by an acute (1 day) onset of bizarre behaviour and grandiose delusions resulting in hospitalisation. The family was concerned as the patient persisted in referring to herself as 'Mary' and kept saying that she was going to be giving birth to 'Lord Jesus'. This was her first pregnancy and the family denied any past medical or psychiatric symptoms. There were no concerns for substance use per the family.

Mental status examination was significant for an alert and oriented woman with grandiose delusions, mildly agitated behaviour when interviewed, and poor insight into her symptoms. Vital signs were within normal limits (temperature (T)=37.6 C, pulse (P)=86/min, blood pressure=112/68 mm Hg and respiratory rate (RR)=15/min) and there were no signs of autonomic dysfunction. Neurological examination revealed symmetrical hyper-reflexia (3+) in all major muscle groups with flexor plantar response. Muscle strength and tone were normal in all muscle groups and there were no abnormal movements or signs of extrapyramidal symptoms or catatonia.

INVESTIGATIONS

There were initial concerns for eclampsia in this patient; however, her vital signs, complete blood count and complete metabolic profile were within normal limits. MRI and MR angiography of the brain did not reveal intracranial abnormalities and EEG did not demonstrate seizure-like activity. Urine toxicology screen was negative for recent illicit drug use.

DIFFERENTIAL DIAGNOSIS

Medical conditions such as systemic lupus erythematosus, antiphospholipid syndrome, Sjögren's syndrome, Hashimoto's disease and substance-induced psychotic disorders that could mimic psychosis in a young female patient, were considered. Infectious aetiologies that could mimic psychosis, such as viral encephalitis and neurosyphilis, were also considered. The following serological tests were ordered: HIV, rapid plasma reagin, thyroid-stimulating hormone, antinuclear antibodies, change to rheumatoid factor, Anti-neutrophil cytoplasmic antibodies, antiproteinase 3, antimyeloperoxidase and complement C3/C4; however, they were all within normal limits.

A lumbar puncture was then performed and the cerebrospinal fluid (CSF) analysis showed a lymphocytic pleocytosis (82 cells/μL, 90% lymphocytes) with elevated protein (86 mg/dL), normal glucose levels and absence of oligoclonal bands. CSF work up, which included bacterial culture, herpes simplex virus PCR, cytomegalovirus PCR, varicella-zoster virus PCR, human herpes virus-6 PCR, Epstein-Barr virus PCR and John Cunningham virus PCR,

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and cryptococcal antigen test and Venereal Disease Research Laboratory test, were negative.

NMDAR encephalitis was considered in our differential, and anti-NMDAR (NR1) IgG antibodies using immunofluorescence assay (IFA) were detected both in the CSF (1:640) and serum (1:80).

TREATMENT

The patient was initially treated with high-dose steroids (1 g of intravenous methylprednisolone) for 5 days followed by oral prednisone 60 mg for 9 days and then tapered over the next 6 days (40 mg for 2 days, 20 mg for 2 days, 10 mg for 2 days and then discontinued). The patient failed to improve clinically with the above steroid therapy. At this time (after 3 weeks of hospitalisation), the CSF and serum anti-NMDAR (NR1) IgG antibodies were repeated, and remained unchanged. Other options such as intravenous immunoglobulin, rituximab and cyclophosphamide were considered for the patient; however, the use was deferred secondary to lack of safety data in pregnant patients. After much discussion with the family, and from our institutional experience and evidence gleaned in the literature,[3 4] we decided to treat the patient with plasmapheresis after approximately 1 month of hospitalisation. The patient received a total of seven plasma exchange treatments, given every 2 days over 14 days with one plasma volume exchange per treatment. The patient tolerated the procedure well and showed clinical and serological response (serum NR1 IgG IFA<1:10) after completion of therapy.

OUTCOME AND FOLLOW-UP

The patient had a successful normal vaginal delivery at 37 weeks and the baby did not show any serological marker for the disease. Considering the high association of anti-NMDAR encephalitis with malignancy, especially ovarian teratoma, the patient was screened in her postpartum period with a transabdominal and transvaginal ultrasound, and did not show any evidence of ovarian teratoma. Ovarian teratomas have a characteristic ultrasound appearance, which allows reasonably accurate non-invasive diagnosis with reported specificity of 98–100%.[6 7] The patient has been followed in an outpatient clinic without any relapse of her symptoms, 18 months after her initial episode.

DISCUSSION

The author reports a unique case of anti-NMDAR encephalitis during pregnancy, which was steroid unresponsive, however, it was treated successfully with plasmapheresis and the patient had a positive outcome.

As in a number of other autoimmune diseases, anti-NMDAR encephalitis and other variants in the autoimmune synaptic protein encephalopathy syndromes spectrum exhibit a female predominance (female-to-male ratio 4:1), primarily targeting women of childbearing age.[8] One reason for the female bias in anti-NMDAR encephalitis may relate to the frequent association with ovarian teratomas. The reasons for the female predilection and pregnancy effects of anti-NMDAR encephalitis have not yet been explored. If the same mechanisms apply as in other autoimmune conditions, the effect of sex hormones on autoreactive T and B cells may provide insight.[9]

Oestrogen has the general effect of stimulating B cell survival and antibody production, whereas it can suppress T cell expansion when present at high levels (as seen in pregnancy). Such observations explain why autoantibody disorders may flare with pregnancy.[10] IgG transport from mother to fetus begins at 13 weeks; however, the largest amount of IgG transport occurs in the third trimester. Studies have shown that NR1 antibodies of subtype IgG1 and IgG3 decrease NMDAR clusters in vitro, and that these antibody subtypes are known to cause other autoimmune newborn diseases.[5]

Schmitt *et al* have demonstrated 'extreme delta brush' as a novel EEG finding seen in some patients with anti-NMDAR encephalitis. Though this pattern was not observed in our patient, its presence has been associated with a more prolonged illness. Although the specificity of this pattern is unclear, its presence should prompt consideration of anti-NMDAR encephalitis.[11]

Currently, there are no established guidelines; however, the previous cases of anti-NMDAR encephalitis occurring during pregnancy have been generally steroid unresponsive. Clinicians have used pulsed intravenous methylprednisolone followed by high-dose oral prednisolone, with addition of plasma exchange and/or intravenous immunoglobulins in the four previously reported cases of anti-NMDAR encephalitis occurring during pregnancy.[3–5]

To conclude, this is a unique case of anti-NMDAR encephalitis during pregnancy, which was steroid unresponsive, however, it was treated successfully with plasmapheresis and the patient had a positive outcome. This case adds to the sparse literature of anti-NMDAR encephalitis during pregnancy, and adds to the differential diagnosis of new onset psychiatric symptoms during pregnancy.

Learning points

- Anti-*N*-methyl-D-aspartate receptor (NMDAR) encephalitis is a synaptic autoimmune disorder that is likely mediated by antibodies against the NR1 subunit of the receptor.
- In the California Encephalitis Project, half the children with idiopathic encephalitis and psychiatric symptoms had antibodies against the NMDAR, and the frequency was four times that of encephalitis caused by herpes simplex, varicella-zoster and West Nile viruses.
- Clinicians have used pulsed intravenous methylprednisolone followed by high-dose oral prednisolone, with addition of plasma exchange and/or intravenous immunoglobulins in the previously reported cases of anti-NMDAR encephalitis occurring during pregnancy.
- Delay in diagnosis and treatment of this condition can result in need of more aggressive and prolonged therapy, and patients are more likely to have permanent cognitive impairment. Therefore, prompt diagnosis and treatment is paramount, and treatment should be initiated when suspicion of anti-NMDAR encephalitis is high, while waiting for serological confirmation.

Competing interests None declared.

Patient consent Obtained.

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