Anti–NMDAR encephalitis complicating pregnancy

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ABSTRACT

Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis was first reported in 2005 in four patients with ovarian teratomas; there have been many further cases reported since the antigen for the NMDAR antibody was confirmed in 2007. Patients characteristically have a well-defined set of features, characterised by psychiatric disturbance, seizures and cognitive disturbance, followed by movement disorders, disorders of consciousness and dysautonomia. To date, 14 cases of NMDAR encephalitis have been described in the context of pregnancy. We report a case of NMDAR encephalitis in a 34-year-old woman at 8 weeks' gestation. She had a turbulent clinical course and was initially admitted to a psychiatric unit. She was successfully treated with first-line immunomodulatory therapies and surgical resection of an ovarian teratoma. Following discharge she delivered a healthy baby and made a complete clinical recovery.

CASE

A 34-year-old woman, previously well, presented to the emergency department with behavioural disturbance characterised by marked aggression. She was pregnant with a gestation of 8 weeks. Her husband reported a 2-day history of disturbed short-term memory followed by visual hallucinations, persecutory delusions and insomnia. Before this she had been well, progressing with a normal pregnancy. She had received the influenza vaccine 2 days before the symptoms had started.

Aside from acute psychosis, neurological and systemic examinations were normal, as were routine blood tests and a CT scan of the head. She was subsequently sectioned under the Mental Health Act, admitted to a psychiatry inpatient unit and treated for an acute psychotic episode with haloperidol and risperidone.

A week later, having made limited clinical progress, she had a 5 min generalised tonic-clonic seizure. She was returned to the hospital and started on ceftriaxone, acyclovir and phenytoin. Once again, a CT scan of the head was normal. She subsequently developed acute respiratory distress, precipitated by aspiration pneumonia. She was promptly sedated, intubated and ventilated, and transferred to the intensive care unit.

Neurological examination at this stage showed a Glasgow Coma Scale score of 6 (eyes-3, motor-3, voice-tube), normal conjugate eye movements and no meningism. She had brisk deep tendon reflexes in both the upper and lower limbs.

MR scan of the brain showed signal hyperintensity in the amygdala bilaterally, more marked on the right (figure 1). Lumbar puncture opening pressure was 21 cmH_2O (10–25), with cerebrospinal fluid having a white cell count of 21 x 10^9/L (≤5) (80% lymphocytes), protein of 0.35 g/L (0.15–0.45), and negative bacterial culture and cytology. A PCR viral panel for herpes simplex, varicella zoster and adenovirus was negative. Electroencephalogram showed non-specific diffuse cortical dysfunction with no epileptiform activity. A fetal ultrasound scan showed appropriate fetal development with a normal fetal heart rate.

Within the first 7 days of her intensive care admission, she developed increasing autonomic instability, manifesting as labile blood pressure, cardiac arrhythmias and fluctuating fever. She then suffered a cardiac arrest secondary to a bradyarrhythmia and was promptly resuscitated. She also developed repetitive oromasticatory movements.

At this stage, she was empirically treated with pulsed methylprednisolone for presumed autoimmune limbic encephalitis, followed by 60 mg of oral prednisolone. Given the high index of suspicion

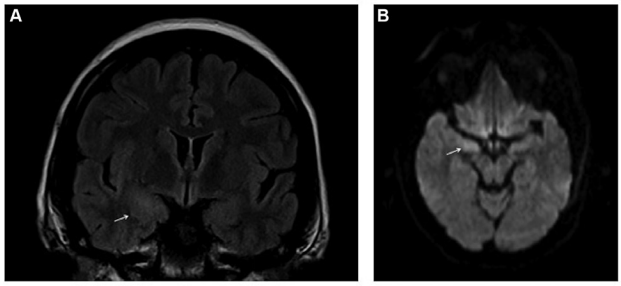

Figure 1 (A) MR scan of the brain, axial T2-weighted image showing subtle hyperintense signal in the right amygdala region with mild gyral expansion (arrow). (B) Axial diffusion weighted image revealing associated restricted diffusion in the right amygdala (arrow).

for limbic encephalitis, she had an ultrasound scan of the pelvis, which showed no significant ovarian mass. However, a subsequent MR scan of the pelvis showed a 4 cm left-sided ovarian lesion. Serum anti-N-methyl-D-aspartate receptor (NMDAR) IgG antibody was positive at a titre of 1:1000.

We gave a 5-day course of intravenous immunoglobulin and surgically removed her ovarian lesion; the histology confirmed an ovarian teratoma. Surgery was quickly followed by a 5-day course of plasma exchange and a further 5-day course of intravenous immunoglobulin. Following this, her serum anti-NMDAR antibody was undetectable (gestation 13 weeks) and has remained so. From this point on, she steadily improved. She was discharged to a neurological rehabilitation unit 8 weeks later, at which stage she had very little motor neurological deficit but more significant cognitive disability, particularly short-term memory and attention. However, this too has gradually improved. She was monitored closely as an outpatient, and the prednisolone was continued at a dose of 60 mg until delivery of the pregnancy.

She spontaneously delivered a healthy baby at 36 weeks' gestation, by which time she had returned to her cognitive baseline. On most recent review at 9 months, the baby continues to develop normally and the patient remains NMDAR antibody-negative.

DISCUSSION

Anti-NMDAR encephalitis refers to an autoimmune disorder with IgG antibodies against the NR1 subunit of the NMDAR. First described in 2007, it is now recognised as one of the most common forms of autoimmune encephalitis and is characterised by psychiatric symptoms, movement disorders and seizures, often evolving into a severe encephalopathy.[1]

Among the 14 previously described cases of anti-NMDAR encephalitis complicating pregnancy (table 1),[2–13] nine healthy infants were delivered with no neurological sequelae. Two fetuses were miscarried and one fetus was aborted. Two infants had neurodevelopmental issues.[6 8] Maternal hypoventilation (a sequelae of autonomic dysfunction secondary to anti-NMDAR encephalitis) may predict a poor fetal outcome. Maternal recovery was generally good, with six making a complete neurological recovery. One mother died from superimposed sepsis in intensive care and seven patients had some residual neurological deficit, with cognitive dysfunction being the most common sequel.[2–13]

The NMDAR has a major role in brain development, and thus there is significant concern for fetal health in patients with anti-NMDAR encephalitis. The literature suggests that transplacental transfer of IgG1 and IgG3 antibody can occur from 13 weeks onwards. Additionally, both in vitro and animal models have highlighted that the presence of antibodies against the NR1 subunit of the NMDAR can decrease NMDA clusters.[5 6 14 15]

Our case also highlights the importance of choice of imaging modality when searching for a paraneoplastic source of the limbic encephalitis. The comorbid presentation of anti-NMDAR encephalitis with teratomas is well documented, and in women typically occurs in the ovaries. Prompt identification and treatment of the teratoma is critical, being linked to better neurological outcomes and lower relapse rates; moreover, tumour resection may be curative.[16] Transabdominal or transvaginal ultrasound scanning is the preferred initial test to look for an ovarian teratoma due to its cost-effectiveness.[17] Transabdominal ultrasonography in our patient did not show an ovarian mass, which was later identified on pelvic MRI. Transabdominal and transvaginal ultrasonography together have a combined sensitivity of approximately 85%, but when used in isolation may miss around 30% of teratomas owing to technical factors and interuser variability.[18] MRI also has very high diagnostic accuracy (approximately 93%) for ovarian masses and is the logical next step in screening for a paraneoplastic source in both pregnant women and those of reproductive age when ultrasonography is negative and in whom CT scanning presents a risk from ionising radiation.[19] The presence of bilateral ovarian teratomas is more common than previously thought. In a series of 174 patients with ovarian teratoma-associated anti-NMDA receptor encephalitis, 20 patients had bilateral teratomas.[20] Ovarian teratomas that are bilateral appear to have a higher risk of recurrence and be associated with treatment-refractory anti-NMDA receptor encephalitis.[21]

There are no current guidelines on managing anti-NMDA receptor encephalitis. The mainstay of treatment is based on removing the offending antibody and preventing further antibody synthesis.[22] Where a tumour is identified, early surgical excision along with immunotherapy is key to rapid recovery and good prognosis. First-line immunotherapy includes high-dose corticosteroids, intravenous immunoglobulin and plasma exchange, the use of which is generally considered safe in pregnancy. In cases refractory to first-line

Table 1 Previously reported cases of NMDAR encephalitis presenting during pregnancy.

Case report/year of publication	Age	Gestation (weeks)	Presenting symptoms	Teratoma	Neonatal antibodies	Treatment	Outcome: mother	Outcome: baby
Kim *et al*[2] 2015	28	7	Abnormal behavior, hypoventilation, dyskineasia and epileptic seizure	Right ovary	Not tested	IV-Methylprednisolone IVIg Oral corticosteroids Plasmapharesis Resection of teratoma Rituximab	Slight cognitive function deficits	Miscarriage
Mathis Stephanie *et al*[3] 2015	21	10	Abnormal behaviour	No	Not tested	IV-Methylpredinisolone IVIg x 2 courses	Slight memory impairment	Normal vaginal delivery at 40 weeks gestation
Chan *et al*[4] 2015	23	1st trimester	Fever, hallucinations, disinhibited behaviour, confusion	Right ovary	Not tested	IV-Methylprednisolone Plasmapharesis Rituximab Rescetion of teratoma	Normal	Miscarried
Lamale-Smith *et al*[5] 2015	24	20	Catatonia, disoriented, confused	Nil	Yes	IV Methylprednisolone IVIg	Disinhibition. Memory impairment	C-section at 28 weeks. Normal
Jagota *et al*[6] 2014	18	9	Orolingual movements, eye deviation, fever	Nil	Yes	Azathioprine IVIg	Patient died due to infection. Baby survived, delivered at 34 weeks (NVD) Baby-Delayed in global development, seizures	Global developmental delay. Seizure
Lu *et al*[7] 2015	36	2	Hallucination, psychosis	Nil	Not tested	Oral steroids IV methylprednisolone	Both mother and baby survived. Baby delivered	Normal
Magley *et al*[8] 2012	24	Diagnosed pre pregnancy (9 weeks before)	Choreoathetosis, bradykinesia, weakness, depression, obsessive thoughts	N/A	Not tested	IVIg	Spasticity right hand. Dystonia Dysphonia	Torticollis, strabismus
Kumar *et al*[9] 2010	19	14	Headache and malaise followed by bizarre behavior and paranoid delusions	Left ovary	Not tested	IVIg IV Methylprednisolone Left oophorectomy	Both mother and baby survived- C-section delivery at 38 weeks gestation	Normal
Kumar *et al*[9] 2010	20	8	Abnormal behaviour	Bilateral ovaries	Not tested	IVIg Left salpingo-oophorectomy and bilateral tumour resection	Minimal deficits	Termination of pregnancy at 10 weeks
Kumar *et al*[9] 2010	19	17	Abnormal behaviour	Nil	Not tested	IV Methylprednisolone	Normal	Normal vaginal delivery at 37 weeks gestation. Normal baby
Shahani L[10] 2015	26	22	Headache, delusions, abnormal behaviour	Nil	Not tested	IV Methylprednisolone Oral corticosteroids Plasmapheresis	Normal	Normal vaginal delivery at 37 weeks gestation. Normal baby
McCarthy *et al*[11] 2012	32	8	Psychotic, catatonia, autonomic disturbance	Left ovary	Not tested	IV methylprednisolone Plasmapharesis Left oophorectomy at 32 weeks + C-section delivery	Normal	C-section delivery at 32 weeks gestation. Normal
Ito *et al*[12] 2010	19	17	Oral dyskinesia, abnormal behaviour	Nil	Not tested	Corticosteroids	Normal	Normal vaginal delivery at 37 weeks. Normal baby.
Xiao *et al*[13] 2017	24	28	Psychiatric symptoms –visual and auditory hallucinations	Nil	Not tested	IVIg IV-Methylprednisolone Bilateral ovarian wedge resection	Normal	Emergency C-section at 33 weeks gestation. Normal baby

IVIg, intravenous immunoglobulin.

treatments, second-line therapy, including rituximab and cyclophosphamide, can give a good response.[23]

Due to concerns around teratogenicity, cyclophosphamide is avoided in pregnancies where the fetus is viable.[20] The safety of rituximab is less clearly defined; its use is still not recommended in pregnancy except where the potential benefit to the mother justifies the potential risk to the fetus. However, rituximab has a low transplacental transfer rate in the first trimester of the pregnancy, and thus has been used preconceptually and antenatally in various autoimmune conditions, with good pregnancy outcomes.[23] Some literature suggests that termination of pregnancy can hasten recovery, but more recent case analysis suggests that an elective preterm delivery may improve maternal and fetal prognosis.[13] While pregnancy is a potential trigger of anti-NMDA receptor encephalitis relapses in certain case series, several reports have suggested that good maternal and newborn outcome may follow anti-NMDAR encephalitis.[13]

Regarding preconceptual planning in women who have recovered from NMDAR encephalitis, there are no current guidelines. However, it appears that the best maternal and fetal outcomes are linked to achieving and maintaining a negative autoantibody status before conception and maintenance of this throughout pregnancy, with immunotherapy as required. Fortunately, thus far, our patient remains antibody-negative off all treatments. Periodic screening for ovarian teratomas is recommended for at least 2 years following anti-NMDAR encephalitis, and it would seem intuitive to screen patients ultrasonographically at a higher frequency throughout pregnancy. We would recommend that this be discussed frankly with women before conception, as well as the risk of developmental difficulties in children born to mothers with this condition.[6 8] Post partum we would recommend that the baby be referred to paediatrics to detect and act on any developmental issues promptly.

Early immunotherapy and prompt identification and removal of an associated ovarian teratoma, in our case, gave a favourable response, negating the need to consider second-line therapies. This suggests that early treatment with immunotherapy and tumour resection can lead to good fetal and maternal outcomes, particularly if a negative antibody status can be achieved by approximately 13 weeks' gestation. Furthermore, despite displaying severe symptoms and requiring admission to an intensive care unit—factors associated with poor outcome—this patient delivered a healthy baby and fully recovered post partum.

Key points

- Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis may be triggered by pregnancy.
- Thorough assessment for an underlying tumour is essential in anti-NMDAR encephalitis; when found, prompt removal is probably important in inducing remission.
- Anti-NMDA-receptor encephalitis presenting in pregnancy can have a good maternal and fetal outcome with prompt diagnosis, immunotherapy and removal of any paraneoplastic source.

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