Not hysteria: ovarian teratoma-associated anti-*N*-methyl-D-aspartate receptor encephalitis

R Roberts, N J J MacDougall, P O'Brien, K Abdelaziz, J Christie and R Swingler

Ninewells Hospital, Dundee, Scotland, UK
E-mail: rachelroberts2@nhs.net

Abstract

We report a case of a 33-year-old nulliparous woman who, following a short prodromal illness, experienced a series of psychiatric and behavioural symptoms. These included states of terror, insomnia, delirium, self-harm and suicidal ideation, facial dyskinesias, verbigeration, cognitive impairment, reduced responsiveness, violence and paranoia. A diagnosis of anti-*N*-methyl-D-aspartate (NMDAR) encephalitis was made 50 days after symptom onset. Early tumour removal is associated with an improved prognosis and a laparoscopic oophorectomy was performed following detection of a dermoid cyst. Within 24 hours of the operation there was marked improvement in cognitive function and appetite.

Keywords: ovarian teratoma, dermoid cyst, anti-NMDAR encephalitis, autoimmune encephalitis

Case report

A fit and healthy 33-year-old woman presented to her out-of-hours general practitioner with confusion, dizziness, shaking and hyperventilation. She had been vaguely unwell prior to this with abdominal pains. Over the two months prior to this she had been undergoing intrauterine insemination (IUI) following normal day 21 progesterone and hysterosalpingogram. She experienced dysmenorrhoea, but there was no other past medical history of note. Her initial symptoms had given her some hope that IUI had been successful and that she may have been experiencing some symptoms of pregnancy. Her urine pregnancy test was negative, but dipstick was suggestive of infection. She was diagnosed with a urinary tract infection and was sent home. The following day she was seen again, this time with pyrexia and vomiting and her diagnosis was flu. On her third assessment she was once again experiencing confusion, shaking and hyperventilation. She was discharged with antibiotics, but her condition continued to deteriorate.

Over the course of the next few weeks she became mute and confused, repeating words such as 'cup', 'tea' and 'drink'. At times she was found in a state of terror, screaming and burning herself. Self-harm elevated to suicidal ideation as she expressed that she wanted to cut her wrists or jump off a bridge. She experienced involuntary elevation of her eyebrow, flickering of her eyelids, facial distortion and developed a short stepped gait where she would stop for no reason. She forgot how to perform various routine tasks such as brushing her teeth. Her sleep cycle was disturbed and she may have had seizures, although these episodes did not involve tongue biting, falls or incontinence.

After admission to the Neurology Ward she became violent, abusive and paranoid. She required 24-hour psychiatric nurse input as well as high doses of haloperidol and lorazepam to maintain a safe environment. She had a markedly reduced oral intake. Her treatment was performed under the Adults with Incapacity Act (Scotland) with close involvement with her partner and family members.

Initial blood tests transiently revealed a slightly elevated white cell count. Her computerized tomography (CT) head was normal.

Following admission to Neurology, six weeks after the onset of her illness an electroencephalogram (EEG) was normal. Lumbar puncture showed high protein levels (823 mg/L) and oligoclonal bands with no corresponding bands in serum; this indicates inflammation, causes of which include autoimmune disease, infection and demyelinating disease. Although viral polymerase chain reaction was negative, she was given acyclovir as a standard treatment for herpes simplex encephalitis. A blood test for *N*-methyl-D-aspartate (NMDA) receptor antibodies was sent on the day of her admission to Neurology.

Her magnetic resonance imaging (MRI) revealed one or two tiny foci of increased signal on the fluid attenuation inversion recovery (FLAIR) sequence in each frontal lobe; the study was degraded by patient movement and sedation was required to complete the test.

A CT scan was done 12 days after admission revealing a 2.5-cm dermoid cyst on the right ovary. The Ca 125 was 11 U/mL. The CT result was available before the positive anti-NMDA receptor arrived.

At 50 days after symptom onset the NMDA receptor antibody was found to be positive. She was treated with

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intravenous methylprednisolone for five days followed by high-dose oral prednisolone.

Anaesthetic assessment was performed and a decision was made to use total intravenous anaesthesia with propofol and remifentanil for induction as well as rocuronium for muscle relaxation. This plan was based upon a case report describing anaesthetic experience with an anti-NMDA receptor antibody patient.[1] A bispectral index monitor was used throughout the procedure to monitor the depth of anaesthesia. Despite having an intensive care bed on standby, the entire procedure was uneventful and the patient returned to the Neurology Ward postoperatively.

At laparoscopy there were multiple vesicular, pale peritoneal deposits and a small dermoid cyst on the right ovary. Peritoneal washings, peritoneal biopsies and oophorectomy were undertaken. Plans to commence intravenous immunoglobulin treatment were delayed until the effects of surgery had been assessed.

An immediate improvement was seen following oophorectomy with the patient seeming calmer, more responsive, gaining eye contact, increasing appetite and walking with a more normal gait. Despite this improvement and a marked reduction in antipsychotics, there seemed to be little changes beyond the first postoperative day. Intravenous immunoglobulin was commenced at five days postoperative for a total of five days.

Histopathology revealed a benign mature cystic teratoma that contained neural tissue. There were foci of endometriosis and mesothelial inclusion cysts.

The patient continued to recover and within two weeks of the operation she was able to spend weekends at home. Although the postoperative improvements were marked, her ongoing recovery has been more gradual. She is now having plasmaphoresis. She remains on a maintenance dose of prednisolone. Her behaviour is more normal, although she has still not fully regained her premorbid cognitive function and personality. She has been assessed by the neuropsychology team who feel that she is likely to have good cognitive outcome in the long term. We will follow her up every year with ultrasound to detect any further dermoid cysts.

Discussion

It is thought that around 8% of encephalitis cases are associated with specific antibodies directed against neuronal proteins which are treatable with immunotherapy. Without treatment there can be permanent cognitive dysfunction, seizures and ultimately death.[2]

Anti-NMDAR encephalitis has multiple features from psychosis and memory problems, advancing to seizures, dyskinesias and autonomic instability requiring prolonged intensive care. The case described had many of the typical features of this condition, but the autonomic disturbances were less pronounced. This may be because the diagnosis was made relatively quickly in comparison to many of the cases in the literature; 80% of patients are female and 20–50% will have an identifiable tumour, the most common being an ovarian teratoma.[3] The detection of a tumour varies with age, sex and ethnicity with younger patients having fewer detectable tumours.[4] Perioperative care in patients with this condition needs to be addressed with caution due to the potential autonomic complications.

As illustrated in this case the majority of patients have a prodromal illness within two weeks of presentation and many will initially present to psychiatry.

MRI is unremarkable in 50% cases and in the other 50% there is increased FLAIR or T2 signal in one or several brain regions,[4] which are mild or transient, as in this case. EEG and cerebrospinal fluid (CSF) analysis is usually abnormal and NMDAR antibodies can be detected in CSF.

In a case series of 100 patients, 25 had severe neurological deficits or died.[5] The estimated mortality is 4%.[4] There is agreement that management should combine immunosuppression and the removal of a teratoma to speed recovery and reduce relapse. Recovery may occur without tumour removal, but the severity and extended duration of symptoms support excision.[6] Treatments have been used including steroids, immunoglobulins and plasma exchange as first lines and then rituximab or cyclophosphamide if additional treatment is required.

Our knowledge comes from case reports and case series and the optimal sequence and timing of treatments are not known. The decision to perform an oophrectomy rather than a cystectomy was taken to ensure a complete excision was achieved. Histopathological analysis of tumours has revealed neural tissue with strong expression of NMDAR.[4,7] In this patient the neural tissue found in the teratoma probably acted as an initial substrate for the generation of anti-NMDA receptor antibodies.

This condition should be considered in patients presenting with mood or behavioural changes and severe psychiatric symptoms. Making the diagnosis allows implementation of treatments that speed recovery and reduce recurrence.[7] Gynaecologists need to be aware of this condition and our important contribution towards patient recovery. Its incidence is unknown, but as over 400 cases have been diagnosed within three years by Dalmau *et al.*[4] it may be more prevalent than any other paraneoplastic encephalitis. It is likely that many women have died from this treatable condition before it was fully characterized and that others are suffering in psychiatric care when the diagnosis can give the potential to lead a normal life once again. The recognition and diagnosis of this condition will remain delayed unless awareness of it increases.

Conflicts of interest: None.

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