CASE REPORT

Ovarian teratoma associated with anti-NMDA (N-methyl D-aspartate) receptor encephalitis

Nellihela LEEL,[1] Hemanshoo, S Thakkar,[1] David Drake,[2] Nordeen Bouhadiba[1,3]

[1]Department of Paediatric Surgery, Guy's and St Thomas's NHS Foundation Trust, London, UK
[2]Paediatric Surgery, Evelina Children's Hospital, London, UK
[3]Evelina London Children's Hospital, Guy's and St Thomas NHS foundation Trust, London, UK

Correspondence to
Dr Nordeen Bouhadiba, nordeen.bouhadiba@gstt.nhs.uk

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SUMMARY

Anti-N-methyl D-aspartate receptor (NMDAR) encephalitis is a paraneoplastic, immune-mediated encephalopathy with a known association with ovarian teratomas. We present the first case in the UK of a 7-year-old patient presenting with this condition. Having been previously fit and healthy, the patient presented with an acute onset of cognitive disturbances. The initial suspicion was that of an infective encephalopathy; however, the lumbar puncture results were negative. Electroencephalography reported diffuse background slowing, supporting a diagnosis of encephalopathy. Extensive autoimmune screening was done and found to be positive for anti-NMDAR antibodies. A whole body MRI found a right adnexal lesion consistent with ovarian teratoma. At laparoscopy, the right ovary was excised and histology confirmed a mature cystic teratoma with neural tissue. There were no postoperative complications with the patient's neurology recovering progressively at follow-up.

BACKGROUND

Although the association between anti-NMDA (N-methyl D-aspartate) encephalitis and ovarian teratomas is well documented in the adult literature, no such cases have previously been reported in the paediatric population in the UK. This case will be of interest to both paediatricians as well as surgeons who may encounter a similar presentation in the future. Furthermore, it demonstrates the importance of actively screening non-infective encephalitis for an autoimmune reaction to neuronal tissue in teratomas. We have also discussed successful management of this pathology through minimally invasive surgery and noted reversibility of the neurological symptoms.

CASE PRESENTATION

A previously fit and healthy 7-year-old girl presented with an acute onset of increasing cognitive dysfunction, including deteriorating memory, agitation, stuttering speech and altered sensorium. Three days later she developed dystonic posturing of her face and limbs. Subsequently she was admitted to her local hospital with suspected infective encephalopathy. There was no other relevant medical, personal or familial history.

She was started on a local management protocol with ceftriaxone, aciclovir and clarithromycin. On day 7 of her admission, her Glasgow Coma Score fell to 7/15 (E4 V1 M2). She was subsequently intubated and ventilated for transfer to our tertiary centre for further management. In view of her electroencephalography (EEG) and brain MRI results, an extensive autoimmune screen was sent and found to be positive for anti-NMDA receptor (NMDAR) antibodies. Subsequently, a whole body MRI was performed, which identified a right adnexal lesion consistent with an ovarian teratoma (figure 1). On day 9, she was started on a 5-day course of methylprednisolone and plasmapheresis. On day 10 she proceeded with laparoscopic oophorectomy (figure 2). There were no postoperative complications.

Histopathology confirmed the diagnosis of a mature cystic ovarian teratoma with neural tissues and no immature elements, yolk sac component or lymphocytic infiltration (figures 3 and 4). At her

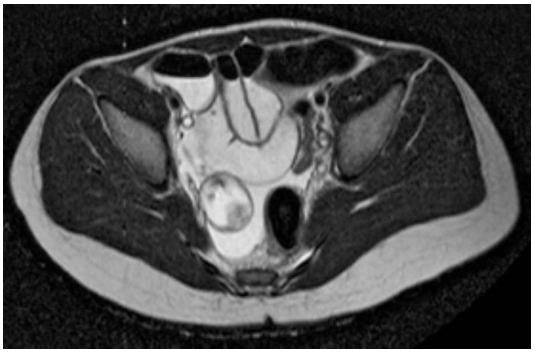

Figure 1 Preoperative MRI scan (T1-weighted) showing the right adnexal lesion.

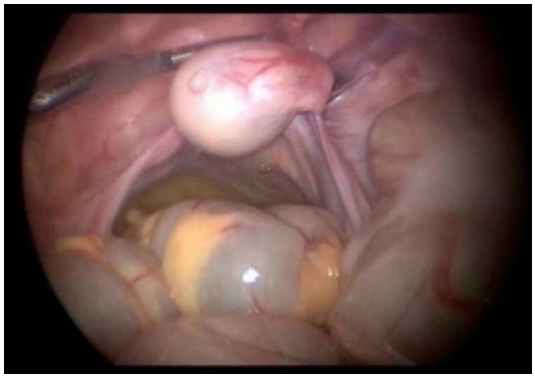

Figure 2 Intraoperative photography of the ovarian teratoma.

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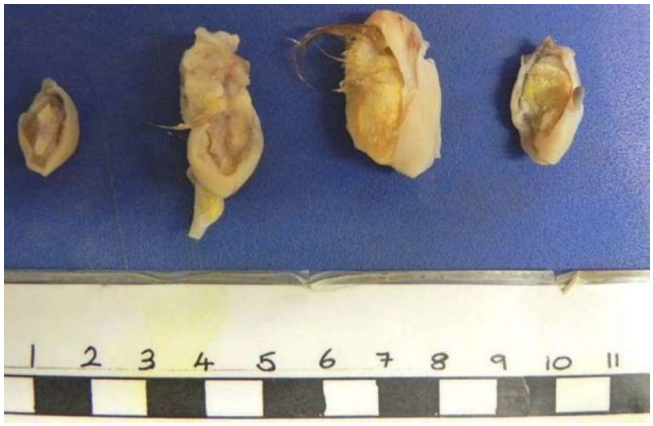

Figure 3 Macroscopy of the specimen (90×58 mm).

most recent follow-up 2 years after surgery, she was clinically well with minimal residual neurological symptoms.

INVESTIGATIONS

Her initial cerebrospinal fluid results showed a white cell count of 25 $\times 10^9$/L (90% lymphocytes), red cell count of 0, protein of 0.29 g/L and glutamine of 4.8 mg/L . Her culture results were negative. An EEG reported diffuse background slowing with suspected encephalopathy. An MRI head scan reported possible venous thrombosis and/or encephalitis.

DIFFERENTIAL DIAGNOSES

- bacterial encephalopathy
- viral encephalopathy.

TREATMENT

Surgical excision of the lesion.

OUTCOME AND FOLLOW-UP

Clinically improving at last follow-up 2 years postsurgery.

DISCUSSION

We presented the first paediatric case in the UK of autoimmune encephalitis associated with ovarian teratoma. In 2007, Dr Josep Dalmau and colleagues[1] discovered the antibodies against NR1/NR2 heteromers of the NMDAR. However, the association of psychiatric and neurological symptoms in patients with ovarian teratoma had previously been observed as early as 1997 in Japan[2] and Hong Kong.[3] The overall incidence of the condition is unknown, but it is found to be higher in those of Asian or African origin.[3]

Anti-NMDAR encephalitis is an acute form of encephalitis which could be fatal. It is caused by an autoimmune reaction, primarily against the NR1 subunit of the NMDAR.[4] The disorder can be considered to be paraneoplastic due its association with tumours, most commonly teratomas of the ovary. However, there are a number of cases that have been reported with no detectable tumour.[4]

Our patient first presented with cognitive symptoms followed by dystonic posturing of the face and limbs. The prominent orofacial and limb dyskinesia is typical for anti-NMDAR encephalitis, in addition to other neurological manifestations including autonomic dysfunction, cerebellar ataxia as well as a catatonia.[5]

Initially in our patient viral encephalitis was suspected, but viral testing was negative. Many patients are known to suffer from non-specific prodromal symptoms of fever, fatigue and headache in the preceding 2 weeks of illness.[6] This was however not the case with our patient. It is however plausible for such an infectious process to trigger an immunological response.[6] Movement disorder relapses after herpes simplex virus 1 (HSV1) encephalitis have been hypothesised to be secondary to postviral autoimmunity.[6] Recently, a proportion of patients with HSV1 encephalitis were shown to produce autoantibodies against NMDAR.[6] In cases where a tumour is demonstrated, surgical removal should eradicate the source of autoantibodies and reduce the risk of relapse. Furthermore, if a tumour is detected, its removal should occur in conjunction with first-line immunotherapy. This involves steroids to suppress the immune system, intravenous immunoglobulin and plasmapheresis. A study of 577 patients showed that over 4 weeks, about half the patients improved after receiving first-line immunotherapy.[7]

Anti-NMDA encephalitis has a gradual recovery process, which has been seen in our patient.

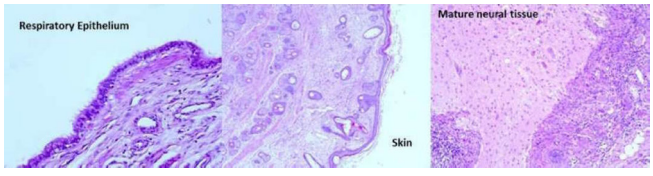

Figure 4 Histopathology of the specimen.

Learning points

- Anti-NMDA (N-methyl D-aspartate) receptor encephalitis is associated with occult teratoma.
- In female patients presenting with limbic encephalitis, initial bloods tests should include a bacterial and viral septic screen, immunological screen, and neurological testing with electroencephalography. MRI of the head should be performed to look for primary intracranial pathology. An assessment of the thorax should be done to exclude a primary infective focus. If no other cause is found, ultrasound or MRI of the pelvis is obligatory.
- Neurologists and intensivists should have a high index of suspicion of a gynaecological cause for a female patient presenting with limbic encephalitis. A multidisciplinary meeting should take place to plan the appropriate management.
- Primary treatment is a combination of symptom control, immunotherapy, plasmapheresis and surgical excision of the tumour.

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