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Rare disease

Appearance of anti-NMDAR antibodies after plasma exchange and total removal of malignant ovarian teratoma in a patient with paraneoplastic limbic encephalopathy

Sarah M Wali, Andrew Cai, Alexander M Rossor, Christopher Clough

Department of Neurology, King's College Hospital, London, UK

Correspondence to Sarah Wali, sarah.wali@kcl.ac.uk

Summary

A 29-year-old female was admitted under section 2 of the mental health act with an acute psychosis. Her condition deteriorated as she developed a fever and worsening hallucinations. Brain imaging was normal but a lumbar puncture revealed a reactive cerebrospinal fluid. A transvaginal ultrasound revealed a left ovarian mass suggestive of a teratoma. A diagnosis of anti-N-methyl-D-aspartic acid receptor (NMDAR) limbic encephalitis was made but the anti-NMDAR antibody was found to be negative. The patient proceeded to a laparoscopic oopherectomy and a 5-day course of plasma exchange. The patient has made a gradual improvement and the anti-NMDAR antibody has since become positive.

BACKGROUND

Anti-N-methyl-D-aspartic acid receptor (NMDAR) encephalitis is a rare and recently described disease that is characterised by a neuropsychiatric syndrome and associated with ovarian teratomas. Early diagnosis is important since patients can recover with immunotherapy and tumour resection. We present a case where the diagnosis was antibody-negative only to, unusually, become antibody-positive after treatment suggesting either the assay for the antibody is insensitive or the presence of the antibody is an epiphenomenon. The case is also important in that it highlights the need to search for an 'organic' cause in cases of acute psychosis. It also illustrates the need to consider a paraneoplastic cause in young patients presenting with encephalitis.

CASE PRESENTATION

A 29-year-old nulliparous female was admitted to the local accident and emergency department with an acute psychosis. Her medical history was notable for the removal of a dermoid cyst 3 years ago. She appeared febrile, confused, tremulous and was noted to have auditory and visual hallucinations. She was admitted to the psychiatric unit under section 2 of the Mental Health Act (1983).

Her condition continued to deteriorate as she became disinhibited, agitated and violent. Following a fall, she was transferred from the psychiatric ward to A&E where she underwent a CT scan of her head and a lumbar puncture under general anaesthetic. Her CT scan was unremarkable, and cerebrospinal fluid (CSF) analysis showed an elevated white blood cell count of 31 cells/ml (95% lymphocytes) and a normal protein and glucose. Extensive bacteriological, virological and immunological studies performed on serum and CSF were all negative. This included a cell-based assay with immunofluorescent anti-NMDA receptor antibody staining.

The patient was later transferred to a neurological centre where she displayed a persistent short-term memory deficit, and experienced fluctuations in alertness, orientation and concentration. She then became aphasic after the third day and eventually required nasogastric feeding. Although the clinical examination was limited by the patient's behaviour, her cranial nerve examination was mostly normal, except that her swallow was found to be unsafe. There was normal tone and power in all limbs although the patient would perform stereotyped cycling movements of the lower limbs, with both arms raised in the air.

INVESTIGATIONS

An MRI of the brain was normal. Considering her gynaecological history of a benign right ovarian dermoid cyst, removed laparoscopically 3 years ago, a trans-vaginal ultrasound was performed which revealed a new left ovarian cyst measuring 4×5×5 cm.

DIFFERENTIAL DIAGNOSIS

In view of the new ovarian cyst, a clinical diagnosis of paraneoplastic limbic encephalitis (PLE) was considered, despite a negative screen for cell membrane antigen antibodies, including voltage-gated potassium channel antibodies and NMDAR antibodies.

TREATMENT

The patient underwent a 5-day course of plasma exchange and an emergency laparoscopic oophorectomy. The ovarian cyst was subsequently found to be a malignant ovarian teratoma on pathology examination. Moreover, a repeat serum anti-NMDA antibody test performed 10 days post-operation, revealed a low positive result, further confirming the diagnosis.

OUTCOME AND FOLLOW-UP

Following her operation, the patient made slow but steady clinical improvements. Her recovery was noted for the development of frequent episodes when she would become unresponsive for several seconds. An interictal EEG showed frequently superimposed left temporal sharp waves and epileptiform discharges on a mildly slowed background. In view of the EEG, it was felt that the episodes were most likely to be epileptic in origin and the patient was commenced on levetiracetam. The patient's neurological state continued to improve slowly and she was transferred to the oncology team. She later started a course of adjuvant chemotherapy (Bleomycin, Etoposide and Cisplatin) after surgery.

At follow-up 5 months post-oophorectomy, the patient continued to make good improvement. She was conversant with family and staff, and able to feed herself. There have been no further reports of seizures and she remains on levetiracetam. However, she still suffers with anterograde and retrograde amnesia. A third serum anti-NMDA antibody test was found to remain positive. She was also noted to be hypotensive (80/45mm Hg), and was commenced on fludrocortisone for postural hypotension.

DISCUSSION

Anti-NMDAR encephalitis is a subset of paraneoplastic neurological syndromes (PNS) initially manifesting with behavioural changes and psychosis, followed by memory disturbances, confusion, dystonia, aphasia, diskinesias, seizures, hypoventilation and sometimes dementia. In a case series of 100 patients with anti-NMDAR encephalitis, 53 out of 58 (91.4%) women were found to have an ovarian teratoma.[1]

In retrospect, diagnosis in the present case was made by; a compatible clinical picture; the presence of a malignant ovarian teratoma; exclusion of other neuro-oncological complications; CSF with inflammatory changes (CSF evidence of inflammation is reported in 80% of limbic encephalitis)[2] and an encephalopathic EEG. Moreover, neurological improvement was noticed after tumour resection and plasma exchange.

However, at the time, diagnosis was particularly difficult as the neuropsychiatric dysfunction preceded the detection of the tumour and without the detection of onconeural antibodies. The absence of serum antineuronal antibodies to both known intracellular and cell membrane antibodies is a common occurrence in ~40% of cases of proven PLE,[3] and thus their absence does not exclude the diagnosis of definite or possible PNS (including anti-NMDAR encephalitis).[3]

Learning points

- An acute psychosis with no preceding history should always prompt a search for an 'organic' cause.
- A paraneoplastic cause should be considered even in young patients with an encephalitis as the prognosis is significantly improved by early diagnosis.
- The initially negative anti-NMDAR antibody assay suggests that either the assay is not sufficiently sensitive or that the antibody is not pathogenic and its presence is merely an epiphenomenon.

Competing interests None.

Patient consent Obtained.

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