Anti-N-Methyl-D-Aspartate receptor encephalitis

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ABSTRACT

Anti-N-methyl-D-aspartate (Anti-NMDA) receptor encephalitis is a rare and recently described disorder which presents with a variety of neuropsychiatric symptoms. Diagnosis is achieved by demonstrating the presence of anti-NMDA antibodies in the serum or cerebrospinal fluid. Early treatment with tumour removal (where indicated) and immunosuppression is associated with excellent outcomes. We report the case of a 30-year-old lady who presented with headache, auditory hallucinations and involuntary movements, and having initially been referred to the psychiatrist, was eventually diagnosed with anti-NMDA receptor encephalitis following further investigations.

Keywords: NMDA receptor, encephalitis, ovarian teratoma, dyskinesia

INTRODUCTION

Anti-N-methyl-D-aspartate (Anti-NMDA) receptor encephalitis may present with an array of neuropsychiatric symptoms, including involuntary movements, decreased level of consciousness, agitation or hallucinations. It has a known association with ovarian teratomas. [1] A high index of suspicion is important to avoid misdiagnosis, and early treatment carries a better prognosis. We report the case of a patient who was initially treated for anxiety, before further tests confirmed the diagnosis of anti-NMDA receptor encephalitis and the patient was then able to receive appropriate treatment.

CASE REPORT

A 30-year-old Chinese lady presented with a three-day history of headache, neck pain and dysarthria whilst on holiday in Bangkok with her friends. She then became occasionally forgetful, and started to have auditory hallucinations. She sought medical help upon returning to Malaysia a week later. Initial blood tests (full blood count, renal profile, liver function tests, C-reactive protein) revealed no abnormalities. A Magnetic Resonance Imaging (MRI) scan of the brain was also unremarkable, and she was subsequently referred to a psychiatrist.

Over the following days, she developed orofacial dyskinesia and choreoathetosis. She was commenced on anxiolytics. Despite two weeks of treatment, there was no improvement in her symptoms and her family sought a second opinion at another hospital. Over the following four days, further tests were performed; a second MRI brain was again reported as normal. An electroencephalogram (EEG) showed left temporal slowness. Thyroid function tests and connective tissue disease screening were normal. Hepatitis B and C, HIV serology and VDRL were negative. A lumbar puncture was performed, which came back positive for anti-NMDA receptor

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antibodies. Serum anti-NMDA receptor antibodies were negative. A computed tomography scan of thorax, abdomen and pelvis showed no evidence of ovarian teratoma or malignancy. Paraneoplastic screen was also negative.

She was immediately commenced on intravenous methylprednisolone for five days, followed by intravenous immunoglobulins for a further five days. With no improvement, she underwent one cycle of plasma exchange, followed by one dose of intravenous cyclophosphamide. She showed tremendous clinical improvement, and on discharge was able to follow one-step commands, communicate basic words and had no further involuntary movements. She has since had further cycles of cyclophosphamide and is under concurrent follow up with a rehabilitation unit, making steady clinical recovery. The patient is being closely followed up for evidence of tumour.

DISCUSSION

The current incidence of anti-NMDA receptor encephalitis is currently unknown. This clinical entity was first described in 2005 in four young women who presented with acute psychiatric symptoms, seizures, memory deficits and decreased level of consciousness. [2] They were found not only to have ovarian teratomas, but also antibodies which reacted with neuronal membranes in the brain. These antibodies were later shown to be autoantibodies targeting the NR1/NR2 heteromeric subunits of the NMDA receptor. [3] In a multicentre observational study of 577 patients with encephalitis who tested positive for NMDA receptor antibodies in the serum or CSF, the median age at disease onset was 21 years (range eight months to 85 years). Four hundred and sixty-eight patients (81%) were female. Two hundred and twenty (38.1%) patients had an underlying neoplasm, of whom 213 were female. Two hundred and seven (94.1%) of all tumours were ovarian teratomas. [4]

Analysis of CSF may show increased white blood cells, mild-to-moderate pleocytosis, and normal or mildly increased protein levels. Oligoclonal bands are positive in 60% of patients. [6] However, definitive diagnosis is made by identification of antibodies in the serum or the CSF to the NR1 subunit of the NMDAR. [5] Patients with a teratoma had higher antibody CSF titres than those without a teratoma. [6]

One third to one half of patients with NMDAR encephalitis have an abnormal MRI, which usually shows evidence of increased signal on T2 and fluid-attenuated inversion recovery (FLAIR), especially of the medial temporal lobes. [4, 6] Other regions involved were the periventricular white matter, cerebral cortex, cerebellum, brainstem, and basal ganglia. However, many of these patients will have a normal MRI at the onset of symptoms, and some remain normal throughout the disease course. [6]

CT of the thorax, abdomen and pelvis are essential due to its association with neoplasm, in particular ovarian teratoma. The most common tumour associated with this disorder is ovarian teratoma in women, but extra-ovarian teratoma, sex cord stromal tumour, neuroblastoma, Hodgkin lymphoma, lung cancer, breast cancer, thymic carcinoma, and pancreatic cancer have also been reported. [4-6] In a case series, several patients were found to have positive mycoplasma serology but negative CSF polymerase chain reaction (PCR). The association with mycoplasma infection is currently unclear as positive mycoplasma serology is common and may not be truly indicative of a current active mycoplasma infection especially with a negative CSF PCR result. [7]

Video EEG is a vital tool in the management of NMDAR encephalitis. The consistently predominant abnormality are nonspecific slowing or disorganised activity and much

less frequently epileptiform activity. [4, 6] During the catatonic stage slow, continuous, extreme delta brush or theta, rhythmic activity predominates. [5]

In the treatment, the first-line immunomodulation therapy during the acute phase of illness includes corticosteroids and intravenous immunoglobulin (IVIg) and/or plasmapheresis. [8] Response is often poor to first-line therapy, hence proceeding to second -line therapeutics rituximab and/or cyclophosphamide may improve outcomes. [4]

If a teratoma is identified, early resection (within four months) is associated with better outcomes. [6] Not removing a teratoma does not preclude clinical improvement but may delay recovery. Furthermore, not visualising a teratoma radiographically at time of diagnosis does not exclude the presence of a microscopic teratoma, [9, 10] and repeat surveillance imaging should be considered in patients who remain symptomatic or who have a recurrence of NMDAR encephalitis. [4]

Convulsive and non-convulsive seizures are common and may be treated with phenobarbital, pentobarbital, benzodiazepines, or levetiracetam. [4, 5] Psychiatric symptoms may be treated with psychotropic medications, although immunomodulation remains the most effective therapy. [11]

The prognosis depends on early diagnosis, treatment with appropriate immunomodulatory therapy, and early tumour removal in paraneoplastic cases. [12] Second-line immunotherapy with rituximab, cyclophosphamide, or both, improved the outcome of patients who do not respond to first-line treatment and reduced the occurrence of relapses. [5] Most patients make a full recovery or only have minor neurological deficits. [4-6] Recovery takes months, and requires a multidisciplinary approach including physical rehabilitation, occupational therapy, speech and language therapy, and psychiatric management. [5]

Recurrence is a recognised sequelae and some patients had relapses of varying severity, including 10% with relapses worse than their initial presentation. The risk for relapse was higher in those patients without tumor and was lower with the use of immunotherapy. [4]

In conclusion, anti-NMDA receptor encephalitis is an increasingly recognised cause of encephalitis, which may present with a variety of neuropsychiatric symptoms. Clinicians should maintain a high level of suspicion of this disorder as prompt recognition and appropriate treatment is associated with a better prognosis.

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