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CASE REPORT

Behavioural disturbance requiring medical referral: A case of anti-N-methyl-D-aspartate receptor encephalitis in the emergency department

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Abstract

A 17-year-old woman presented to the ED with behavioural disturbance and psychotic features. Brief dystonic jerks were noted so she was referred to the medical team. A diagnosis of anti-N-methyl-D-aspartate receptor encephalitis was made. Immunotherapy was instituted early and the clinical outcome was excellent. It is important to consider this condition in young women presenting with acute behavioural or psychotic symptoms.

Key words: *catatonia, dyskinesia, encephalitis, N-methyl-D-aspartate receptor, ovarian teratoma.*

Introduction

Anti-N-methyl-D-aspartate (NMDA) receptor encephalitis is an autoimmune condition that is potentially reversible if diagnosed early. Classically, it presents with a combination of psychiatric, neurological and autonomic features (Table 1). Psychiatric manifestations predominate. These might include personality and behavioural changes, memory loss, hallucinations, psychosis and even catatonia. Neurological signs might include dyskinesia, dystonia, rigidity, ataxia, seizures and reduced conscious state.[1] Central hypoventilation requiring ventilator support might occur.[2,3] Most cases are preceded by a viral prodrome.[1]

Case report

A 17-year-old woman was brought to the ED by her parents because of bizarre behaviour. She was having difficulty sleeping and had been continually turning a light switch on and off. This was accompanied by repetitive verbalisation (e.g. 'can't stop'). Although her eyes were open, she was not interacting normally with her parents. She reported a feeling of not having 'control' of her actions. She had experienced some intermittent dizziness in the few days before her presentation.

Ten days before presentation, the patient had completed a triathlon. There was no significant past medical history. She was in year 12 at secondary school with no reported social stressors. She denied alcohol or illicit drug usage. There was no history of oral or genital herpes and she was not sexually active.

On examination, she was afebrile with a GCS of 15/15 and normal oxygenation. Her pulse rate was 90/min and blood pressure was 124/65 mmHg. She had no meningism and her gait was mildly ataxic, but there were no other findings.

On mobilising in the ED, she was witnessed to hold onto a desk and lower herself to the floor. At this time,

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Table 1. Clinical presentation of 100 patients with anti-N-methyl-D-aspartate receptor encephalitis (the median age in this population was 23 years)[1]

Characteristics	Percentage
Female	91
Prodromal symptoms	86
Psychiatric presentation	77
Neuropsychiatric presentation	23
Seizures	76
Dyskinesia	86
Autonomic dysfunction	69
Central hypoventilation	66

jerky myoclonic arm movements were noted for approximately 5 s. She reported associated dizziness with this event. In light of this evidence, a provisional diagnosis of encephalitis was made. She was commenced on i.v. aciclovir, computed tomography (CT) head was organised and a referral was made to the medical team.

Subsequently, CT head was normal. Cerebrospinal fluid (CSF) showed an elevated white cell count of 74×10^6/L (<5), all mononuclear cells, with 6×10^6/L red cells (<5). CSF protein and glucose were normal. CSF herpes simplex virus (HSV) polymerase chain reaction (PCR) testing and CSF paraneoplastic and autoimmune antibodies were requested.

On day 1 of admission, she remained agitated demonstrating unusual behaviours and perseveration of thought. Electroencephalogram (EEG) showed slow wave disturbance focally over the right posterior temporal region. Magnetic resonance imaging (MRI) brain scan was normal. HSV PCR testing was negative on the CSF.

The following day (day 2), a repeat CSF examination was obtained, primarily with the purpose of repeating the HSV PCR. It is well documented that this test can be negative in the first 24 to 48 h of illness with herpes encephalitis.[4] The second CSF contained 102×10^6/L (<5) white cells (100% mononuclear cells) and 1×10^6/L red cells. That afternoon, just over 48 h after admission, the original CSF proved positive for NMDA receptor antibodies. Aciclovir was ceased and directed therapy instituted that evening. Subsequently, the second CSF HSV PCR was also negative.

She was treated with intravenous immunoglobulin (IVIg), 0.4 g/kg/day for 5 days, and methylprednisolone, 1 g daily for 3 days. Pelvic ultrasound and MRI scans failed to detect a teratoma. She responded well to treatment and was discharged home 8 days after presentation. A single maintenance dose of IVIg was given fortnightly for 3 months.

Two months out from her presentation, a neuropsychology report highlighted a severe impairment in the areas of dual attention and flexibility of thought. Her parents subjectively reported increased difficulty 'reasoning' with her. At 6-month follow up, she was performing well functionally. She attended school and is expected to complete grade 12 this year. She exercised regularly and had obtained her learners' drivers' licence. However, she continued to experience some obsessive behaviour, intermittent insomnia and flashbacks to her illness. Her parents remain vigilant for signs that might indicate a relapse of her illness.

Discussion

Anti-NMDA receptor encephalitis was first described in 2005 by Vitaliani *et al*.[3] Although the true incidence is unknown, it is being increasingly recognised because of wider availability of antibody testing. Dalmau *et al*. reported 400 patients over 3 years suggesting that it is not a rare condition.[5] Approximately 80% of patients are female, with a median age in the early 20s.[1] It is often associated with an underlying neoplasm, particularly ovarian teratoma. The risk of underlying neoplasia is age, sex and ethnicity dependent.[1]

N-methyl-D-aspartate receptors are found throughout the central nervous system. They play a role in synaptic transmission and neuronal plasticity. These cellular mechanisms are vital for memory and learning.[6] In anti-NMDA receptor encephalitis, antibodies are directed against the NR1 subunit of the NMDA receptor. The depletion of NMDA receptors is thought to be responsible for the characteristic symptoms of this illness.[5]

Cerebrospinal fluid is abnormal in 80% of patients.[1] Findings include CSF pleocytosis, increased protein and CSF-specific oligoclonal bands.[1] Anti-NMDA receptor antibodies are diagnostic when found in the CSF but might also be present in the serum.[5,7] MRI brain is unremarkable in 50% of cases, with the remainder showing minor, non-specific changes.[8] EEG is abnormal in 77% with non-specific slowing or disorganised activity.[1]

There are no randomised controlled trials evaluating the management of anti-NMDA receptor encephalitis. First-line treatment generally includes i.v. corticosteroids and immunoglobulin or plasma exchange. Rituximab and cyclophosphamide might be used as

second-line therapy.[5,9] Surgical excision is recommended if an underlying tumour is present.[1,2]

The prognosis is thought to be dependent on time to treatment initiation. Currently, the NMDA receptor antibody assay is performed in only a handful of laboratories in Australia creating potential for sample transport delays. In addition, being an expensive assay, it might be run either daily or second daily at the laboratory depending on demand. The minimum 'turnaround time' for this test is generally 24 h. However, as in this case, despite this diagnosis being considered among the initial differential, a positive result might not be available for 2 days. For the patient described here, treatment was commenced that evening, as soon as the result was known.

Unfortunately, diagnosis within a few days of symptom onset is very uncommon in reported cases. If the diagnosis and treatment occurs within weeks of symptom onset, as is more usual, approximately 75% of patients will still show a good outcome with mild or no residual sequelae. The prognosis appears to be worse if diagnosis, and thus treatment, is delayed for months after onset of illness. Mortality or severe deficit occurs in up to 25%.[1] Relapses occur in 20–25% of affected patients. For these individuals, continuous immunosuppression might be considered.[9]

The 17-year-old woman reported here presented with a behavioural disturbance because of anti-NMDA receptor encephalitis. The predominance of behavioural and psychiatric features, in the absence of other symptoms, could easily be misinterpreted as an acute psychiatric illness. Awareness of this condition in the ED allows for a high index of suspicion and appropriate medical, rather than psychiatric, referral. This condition poses a diagnostic challenge for the emergency physician, as well as the inpatient physician or paediatrician.

Competing interests

None declared.

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