


A case of non-paraneoplastic anti-N-methyl D-aspartate receptor encephalitis presenting as a neuropsychiatric disorder

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Abstract

N-methyl D-aspartate receptor antibody encephalitis can often be a paraneoplastic manifestation of occult malignancy such as ovarian teratoma and rarely teratoma of mediastinum or testis and small cell lung carcinoma. We report a case of non-paraneoplastic anti-N-methyl D-aspartate receptor antibody-positive autoimmune encephalitis in a young patient who presented with neuropsychiatric features and made a very good recovery following treatment with intravenous immunoglobulin and steroids. The case highlights the need for increased vigilance for the condition in young females with or without a previous psychiatric history and emphasises the need for a multidisciplinary approach in the management of this challenging disorder with a good prognosis.

Keywords

Autoimmune encephalitis, neuropsychiatric encephalitis, anti-N-methyl-D-aspartate receptor encephalitis

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Introduction

Most cases of the N-methyl-D-aspartate (NMDA) receptor antibody encephalitis are paraneoplastic, reported mainly in association with ovarian teratoma and rarely with teratoma of testis or mediastinum and small cell lung carcinoma.^{1,2} Cases of non-paraneoplastic autoimmune NMDA receptor encephalitis have been increasingly recognised recently.^{1,3} A retrospective study of 505 patients aged 18–35 years admitted to an intensive care unit (ICU) showed it to be the cause of illness in about 1%.³ The cause of the disorder remains unknown, although autoimmune activation has been proposed as a possible mechanism and previous viral illnesses like Epstein-Barr virus (EBV) infection have been implicated as a trigger for autoimmune activation.^{1,4,5} EBV infection has been implicated in the pathogenesis of other immune-mediated disorders such as lymphoma, systemic lupus erythematosus (SLE), rheumatoid arthritis (RA) and multiple sclerosis (MS). Diagnosis may often be delayed because of its low incidence and the presence of previous psychiatric history in some patients.⁶ Because early diagnosis leads to better outcome,^{1,6} increased vigilance is necessary.

We report a case of a young woman with non-neoplastic NMDA receptor antibody encephalitis presenting with

neuropsychiatric symptoms and neurological manifestations and a positive serum antibody.

Case history

A 21-year-old Caucasian lady presented to the psychiatric ward with anxiety, agitation and an erratic speech pattern. She was treated for ‘acute psychosis’ with haloperidol. Two days later, she developed twitching of the eyelids with gaze fixed to the right upper quadrant. This was treated as oculogyric crisis secondary to haloperidol and treated with procyclidine. She was also commenced on olanzapine and sodium valproate. Apart from eating disorder, there was no past psychiatric illness or any family history.

For 2 weeks, she continued with pure psychiatric manifestations before developing pyrexia, tachycardia and cough. She was noted to have slow telegraphic speech and gegenhalten, but the rest of the neurological examination was

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normal. Soon after her conscious level dropped (Glasgow Coma Scale (GCS) 9), she was transferred to the high dependency unit with a diagnosis of aspiration pneumonia and Type 1 respiratory failure. Blood tests showed raised white blood cell (WBC) with neutrophilia and raised C-reactive protein (CRP). Chest X-radiograph was normal. Computed tomography (CT) of the head showed no abnormality, and a lumbar puncture showed a cerebrospinal fluid (CSF) WBC count of 38 (100% lymphocytes) with three red blood cells (RBCs), normal glucose and protein. Magnetic resonance imaging (MRI) of the brain was unremarkable. A transthoracic echocardiogram was normal. CT pulmonary arteriogram was suggestive of aspiration pneumonitis and features of mediastinal emphysema. Her breathing deteriorated requiring ventilation. She was given intravenous (IV) acyclovir and broad-spectrum antibiotics.

Three days later, she developed abnormal eye movements with divergence of both eyes, although pupils were equal and reactive. She had generalised hypertonia and hyper-reflexia with flexor plantar response bilaterally.

Further tests showed a weakly positive CSF polymerase chain reaction (PCR) for enterovirus but negative for herpes simplex virus, varicella zoster virus and cytomegalovirus. CSF angiotensin-converting enzyme, lactate, lactate dehydrogenase, virology and tests for tuberculosis, fungi and syphilis were negative. Monospot test for EBV was weakly positive. Thyroid functions, B12, ferritin, folic acid, autoimmune profile, HIV, antithyroid antibodies, T spot for tuberculosis, toxoplasma antibody, anti-voltage-gated potassium channel antibodies, antineuronal antibodies, anti-Purkinje antibody, cerebellar antibody and serological tests for syphilis were negative. Tumour markers were negative apart from Cancer Antigen (CA) 19-9 which was non-specifically raised at 62.8. Repeat CT and MRI of the head were normal. Electroencephalogram (EEG) showed runs of slow wave activity over both frontal areas consistent with encephalitis.

A diagnosis of a neuroinflammatory disorder was considered for which a 5-day course of IV 1 g methylprednisolone followed by oral prednisolone 60 mg once daily was given. She showed some improvement, and by the end of the third week of admission, she was alert but not following commands and had developed generalised rigidity and catatonia. She had a generalised tonic-clonic seizure following which she was treated with phenytoin. She had a tracheotomy as she remained ventilated. The results for anti-NMDA receptor antibody in the serum returned positive, and a diagnosis of 'Anti-NMDA receptor antibody-positive encephalitis' was made. Her CT of the abdomen and pelvis was normal, and fluorodeoxyglucose positron emission tomography (FDG-PET) of whole body showed no signs of malignancy.

She was given intravenous immunoglobulins (IVIGs) 0.4 mg/kg for 5 days and continued with oral steroids in a tapering dose through nasogastric tube, to which she responded slowly. Phenytoin was later changed to sodium valproate for its mood-stabilizing effect. The patient

continued to improve. One week later, psychiatrist review documented delusional beliefs with persecutory paranoid ideation. She was given another dose of IVIG, IV methylprednisolone for 5 days.

She continued to improve in the rehabilitation unit with regular input from the multidisciplinary team of neurologist, psychiatrist, oncologist, dietician, physiotherapist and occupational therapists and was discharged home after 3 months. She made a full recovery, and all medications were successfully withdrawn. No malignancy was found in the 2-year follow-up.

We confirm that patient's consent to report the case has been obtained. Institutional approval is not required for reporting this case.

Discussion

NMDA receptor antibody encephalitis is one of the autoimmune-mediated encephalitis described in recent times. It represents 1% of all the young patients admitted to the ICU.³ NMDA receptors are ligand-gated cation channels which bind glycine and glutamate and have crucial roles in synaptic transmission and plasticity.⁷ Anti-NMDA receptor encephalitis is associated with antibodies against NR1-NR2 heteromers and results in a characteristic neuropsychiatric syndrome with anxiety, agitation, paranoid thoughts, delusional beliefs and hallucinations. Patients are reported to have seizures, catatonia, orofacial and other forms of dyskinesia and autonomic instability resulting in hypersalivation, unstable blood pressure and dysrhythmias, and central hypoventilation requiring mechanical ventilation. Pseudo-seizures may occur.

It usually affects young female adults with a mean age of 23 years (range: 5–76 years). Most of the reported cases are paraneoplastic secondary to occult tumours, especially ovarian teratoma. Associations with teratoma in the mediastinum, testis and small cell lung carcinoma are rare.^{1,2} The illness may precede the underlying neoplasm; hence, periodic surveillance has been suggested for at least 2 years using MRI and ultrasound of the abdomen and pelvis in females of all ages. Guidelines for tumour surveillance for males are not clear, but some authors have considered 6 monthly ultrasound of testes and full-body PET scans.^{8,9}

The description of non-paraneoplastic anti-NMDA receptor encephalitis in the literature remains scarce and restricted to a few case reports. The clinical features and presenting symptoms are no different to those with underlying neoplasm, making it extremely difficult to recognise this as a specific entity; hence, in the vast majority, a search for underlying neoplasm may continue for years. The underlying mechanism is proposed to be autoimmune activation from underlying neoplasm at an early stage, although a trigger from non-paraneoplastic cases remains uncertain. EBV infection has been suggested as a trigger factor since it has been implicated in the pathogenesis of other immune-mediated conditions

such as lymphoma, SLE, RA and MS and may well be relevant in our case.^{1,4,5}

The CSF picture in our patient was consistent with the reported cases in the literature, although normal MRI is reported in 50%. EEG abnormalities have been reported during catatonia. Our patient had raised CA 19-9, reported in cases of gastrointestinal (GI) malignancies and inflammation of hepatobiliary system,¹⁰ but its significance in our patient remains unclear.

Prompt recognition is important since it is treatable and can be diagnosed serologically. The disorder typically has excellent prognosis in comparison with cases with underlying neoplasm although recovery is rather slow (1–18 months),¹¹ and symptoms may relapse. Around 25% may be left with severe disability, and mortality is uncommon. The management involves immunotherapy with IVIG, steroids and plasma exchange.² Additional immunosuppression with rituximab or cyclophosphamide or both has been suggested in some cases but was not required in our patient who showed good recovery with acute treatment.⁶ Treatments such as adrenocorticotrophic hormone (ACTH) has shown good results in paediatric patients,¹² and those with autonomic disability may require temporary cardiac pacemakers.^{1,6,13} Coenzyme Q10 has been reported to show improvement in a case where standard immunotherapy had failed.¹⁴

Conclusion

Our case highlights the importance of high vigilance in diagnosing anti-NMDA receptor encephalitis particularly in young females with neuropsychiatric manifestation even when there is premorbid psychiatric history. Investigations must be undertaken to identify an underlying neoplastic disorder, although the absence of an underlying neoplasm should not preclude this as a differential. Multidisciplinary approach is vital in the management. The complete recovery in our patient indicates a good prognosis in those with early diagnosis.

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Declaration of conflicting interests

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