Anti-N-methyl-D-aspartate (NMDA) receptor encephalitis is a severe form of encephalitis associated with antibodies against NR1 and NR2 subunits of the NMDA receptor and occurs primarily in women. It is characterised by psychotic symptoms, motor changes such as catatonia, seizure-like activity and dyskinesias. There are also behavioural changes, autonomic dysfunction and impaired consciousness.

We present four patients with anti-NMDA receptor encephalitis (see online Table DS1 for summary). In each case, patients were considered by their medical teams to have a primary psychiatric disorder at varying points over the course of their illness. None had any prior history of psychosis or history of substance misuse.

Case study 1

A 19-year-old female with no psychiatric history presented to her district general hospital with a 2-week history of slurred speech and difficulties with concentration and word finding. Routine investigations were normal and a provisional diagnosis of conversion disorder was considered. On transfer to our tertiary neuroscience centre she rapidly deteriorated and demonstrated behavioural changes which included aggression towards staff, sexual disinhibition and kneeling to pray in the corridor. Her affect was labile and infantile. She was treated with haloperidol 1–2 mg twice daily and lorazepam 1–2 mg twice daily as required. Seizure-like activity was noted, as were prominent orofacial dyskinetic movements. An electroencephalogram (EEG) showed non-specific slowing and CSF showed leucocytosis (13 cells/high power field (hpf); 100% lymphocytes). Soon afterwards she developed autonomic instability and status epilepticus and was transferred to the intensive care unit for ventilation. On resolution of her seizures, she remained mute for 2 weeks. Following confirmation of diagnosis and treatment with intravenous immunoglobulin (IVig) and steroids she gradually improved and was discharged. Neuropsychological assessment at that time demonstrated slight language deficits but overall she returned to her premorbid level of functioning. However, 12 months after presentation she experienced re-occurrence of some symptoms including decreased energy, myoclonic jerks, and reduced coordination and clarity of speech. Anti-NMDA receptor antibody test has remained positive since presentation and she was commenced on the immunosuppressant mycophenolate 720 mg twice daily with initial improvement. As symptoms did not fully resolve she was treated with additional IVIg. She was discharged but remains on mycophenolate.

Case study 2

A 28-year-old female was admitted with a generalised tonic-clonic seizure on a background of a 3-week history of lethargy and hypersomnia followed by a 3-day history of behaviour change characterised by irritability, confusion, agitation, visual hallucinations and a delusion that she had cancer. On admission, further seizure-like activity (i.e. rhythmic arm movements and cycling movements of her legs) was observed, although no epileptiform activity on EEG was noted. She was violent and was sexually disinhibited, with a marked diurnal pattern to behaviour, sleeping during the day but hyperkinetic and behaviourally disturbed throughout the night. An EEG recorded intermittent slowing with no epileptiform activity and CSF analysis showed raised white cell count (209 cells/hpf; 100% lymphocytes). Other investigations were negative. Following confirmation of anti-NMDA receptor encephalitis, a partially necrotic dermoid ovarian cyst was identified on ultrasound and removed surgically. Escalating psychotic symptoms and behavioural disturbance prevented plasma exchange and she was treated with steroids and IVIg. However, the severity of her behavioural disturbance subsequently necessitated transfer to a psychiatric hospital for further behaviour management. As olanzapine was ineffective she was switched to aripiprazole 30 mg and trazodone 75 mg nocte. After a 2-month admission she was returned to the medical unit for further IVIg and was eventually discharged. Cognitive assessment showed an overall good level of recovery with slight residual weakness in motor speed, visual planning and visual memory. Psychotropics were discontinued and psychotic symptoms resolved completely. Subsequently, she was readmitted with recurrent seizures and was treated with a further course of IVIg. She has deferred returning to college as she has not returned to her previous level of functioning and remains anti-NMDA receptor antibody positive.

Case study 3

A 29-year-old female who was 12 weeks postpartum presented to her district general hospital with seizure-like activity, i.e. cycling leg movements which were considered to be non-epileptic and non-organic in origin. An EEG showed mild slowing. She became confused with bizarre behaviour – dancing, giggling, echolalia,
echorpraxia, posturing and cycling leg movements. She showed delusional thinking, which centred on thoughts that her baby was dead and that her partner was conspiring against her. Following a battery of normal physical investigations including CSF, she was transferred to our centre for further assessment. She subsequently became stuporous, alternating between periods of excitement and agitation, and was transferred to a psychiatric hospital for further behavioural management. In addition, she was treated with amisulpride 50 mg twice daily and haloperidol 2.5 mg twice daily. On confirmation of anti-NMDA receptor encephalitis 2 months after initial presentation, she was returned to the medical unit for IVlg and steroid treatment. During the acute phase of the illness, behavioural disturbance precluded formal cognitive assessment. However, on discharge she scored 28/30 on the Mini-Mental State Examination. She was discharged home and has discontinued all psychotropic medication but has limited recollection of the 3-month hospital admission.

Case study 4

A 20-year-old female presented to her district general hospital with slurred speech and fatigue of 2 weeks’ duration and was treated for presumed viral encephalitis. One month later her behaviour deteriorated and she became emotionally labile, agitated and at times disorientated. Her EEG recorded slowing, brain magnetic resonance imaging showed non-specific white matter abnormalities and CSF showed lymphocytosis (45 cells/hpf; 100% lymphocytes). She was transferred to our centre and was noted to be distracted in manner, to have coarse dyskinetic movements of her hands and feet, and to have psychomotor retardation. A primary central nervous system vasculitis was suspected and a brain biopsy of the right frontal area was taken. Following biopsy and initiation of high-dose steroids, she developed paranoid delusions and believed that she was being poisoned. She also developed a delusion that she was unable to move her limbs, although she was observed to move them spontaneously. Olanzapine 2.5 mg twice daily was prescribed and steroid medication was reduced to exclude an iatrogenic aetiology for her psychotic symptoms. Brain biopsy revealed neuronal loss and lymphocytic infiltrate (see online Fig. DS1 (a)–(d) for details of histological examination). On confirmation of anti-NMDA receptor encephalitis she was treated with plasmapheresis (to which she responded rapidly) as well as prednisolone, IVlg and mycophenolate. Approximately 15 months after initial presentation she describes resolution of symptoms and plans to return to college. She continues on mycophenolate but remains anti-NMDA receptor antibody positive.

Discussion

This case series demonstrates many of the core features of anti-NMDA receptor encephalitis, the diagnosis of which requires a positive finding of antibodies to the NMDA receptor subunit. Critically, in all four cases, a psychiatric diagnosis was among the initial provisional diagnoses, indicating that clinicians need to be highly aware of this disorder. Behavioural disturbance had an impact on the ability to deliver immunomodulatory therapy in all cases. Although routine physical investigations were normal, all patients had mildly slowed EEGs, one had ovarian pathology, one was 12 weeks postpartum, and three patients had lymphocytosis in CSF. Sequential phases of the clinical presentation have been described previously. Most notably, Iizuka and colleagues described distinct prodromal, psychiatric, unresponsive, hyperkinetic and recovery phases. Although the cases in our series replicated these symptoms, the overall pattern was less clearly differentiated. Recovery is not always to the premorbid level, and in Dalmau et al’s case series, 25 out of 100 patients had severe deficits or died. Of note, despite immunomodulatory therapy, all patients remain anti-NMDA receptor positive. The clinical symptoms of this disorder correlate with antibody levels. Treatment options to date involve immunomodulatory agents, including plasmapheresis, high-dose steroids and IVlg. Although benzodiazepines and electroconvulsive therapy are known to be effective in mood and psychotic disorder-related catatonia, little is known about their effectiveness in the treatment of catatonia in the context of this condition. Anti-NMDA receptor encephalitis is associated in some cases with ovarian pathology, in particular teratomas: it is considered that the antibodies develop in response to this abnormal tissue.

The abnormal movements, which developed prior to the introduction of antipsychotic medications, can broadly be divided into dyskinesia and catatonia types. The dyskinesias noted included choreoathetoid mouth and facial movements, and cycling arm and leg movements. These movements were similar to partial seizures but had no epileptic activity on EEG. Catatonic abnormalities included posturing, echorpraxia and muscular rigidity rapidly alternating with hyper-reflexia. The combination of psychotic symptoms with catatonia and indicators of dopaminergic involvement (orofacial dyskinesias) are all consistent with the effects of the NMDA receptor antagonist phencyclidine, which replicates many aspects of the presentation of schizophrenia. The psychiatric presentations of these cases of anti-NMDA receptor encephalitis thus provide important support for the NMDA receptor hypofunction hypothesis for psychosis, and the possibility that auto-antibodies to the NMDA receptor subunits may be implicated in the development of psychosis is novel.

In summary, this case series of anti-NMDA receptor encephalitis demonstrates a new and treatable cause of psychosis. Our understanding is preliminary and it is possible that the disorder is underrecognised. It is also unclear whether there is a psychiatric presentation associated with lower antibody titres. Our cases suggest that a new onset of psychosis presenting with the combination of catatonia, seizures and dyskinesias should prompt referral to neurology for consideration of this disorder.

References

### Table DS1 Characteristics and clinical features of case studies 1 to 4

<table>
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<th>Case</th>
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<th>Neuropsychiatric symptoms</th>
<th>Catatonia or reduced responsiveness</th>
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<th>Recovery/ complication</th>
<th>Positive findings</th>
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<tbody>
<tr>
<td>1</td>
<td>Conversion disorder Encephalitis</td>
<td>Slurred speech, concentration impairment</td>
<td>Disinhibition, aggression</td>
<td>Mutism</td>
<td>Orofacial dyskinesia</td>
<td>Less severe relapse</td>
<td>EEG slowing, status epilepticus, raised leucocytes in CSF</td>
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<td>2</td>
<td>Psychotic disorder Meningoencephalitis/ limbic encephalitis</td>
<td>Lethargy, hypersomnia</td>
<td>Irritability, agitation, delusions, visual hallucinations</td>
<td>Cycling leg and arm movements with no EEG epileptiform activity</td>
<td>Some cognitive deficits</td>
<td>EEG slowing, necrotic dermoid ovarian cyst, CSF lymphocytosis</td>
<td></td>
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<tr>
<td>3</td>
<td>Conversion disorder Postpartum psychosis Encephalitis</td>
<td>Sudden onset</td>
<td>Delusions, mood lability</td>
<td>Echopraxia, echolalia, posturing</td>
<td>Cycling leg movements with no EEG epileptiform activity</td>
<td>Recovery to baseline</td>
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<td>4</td>
<td>Viral encephalitis Psychotic disorder</td>
<td>Slurred speech, fatigue</td>
<td>Mood lability, agitation, delusions</td>
<td>Slowed in speech and movement</td>
<td>Coarse leg and arm movements</td>
<td>Gradual recovery, remains on immunosuppressant</td>
<td>EEG slowing, white matter abnormalities on brain MRI, lymphocytic infiltrate on brain biopsy, CSF lymphocytosis</td>
</tr>
</tbody>
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CSF, cerebrospinal fluid; EEG, electroencephalograph; MRI, magnetic resonance image.

Neuropsychiatric symptoms, catatonia/reduced responsiveness and hyperkinesis/seizure-like movements overlapped and were non-sequential.
Fig. DS1  Histological analysis of encephalitis.

(a) Right frontal sample. Neurons displayed various abnormalities. The most striking pathology was vacuolisation of the perikaryon and most of the vacuoles contained small granules (granulovacuolar degeneration; a phenomenon not known in this age group). The granules were often amphophilic, or light eosinophilic, rarely basophilic (see arrow in insert top left. Luxol Fast Blue). Lymphoplasmacytic inflammation was seen mostly within the Virchow–Robin spaces as well as in the leptomeninges (see inset bottom left). (b) CD20 antibody decorates B lymphocytes. (c) CD3 immunohistochemistry. T-cells (brown, positive reaction product) slightly outnumber B-cells (negative with this antibody), but this difference is insignificant. (d) Glial fibrillary acidic protein immunohistochemistry specifically and strongly decorates richly arborised reactive astrocytes.
Microscopic examination

Microscopic examination of serial paraffin sections revealed normal dura mater with negligible perivascular lymphocytic accumulation. Normal neocortical cytoarchitecture was observed. The Virchow–Robin spaces were widened and often contained variable numbers of regularly shaped small lymphocytes. Mild microglial activation and somewhat increased perineuronal satellitosis without neuronophagia were noted. Neuronal necrosis, red neurons, inclusions were not observed. Scattered neurons with granulovacuolar degeneration were conspicuous.

Immunohistochemistry

Diffuse, strong leucocyte common antigen decoration, with partial CD20 and CD3 positivity characterised the lymphocytes with slight T-cell dominance. Activated microglial cells and a few macrophages were highlighted by KP1 and PGM1 antibodies. Glial fibrillary acidic protein showed richly arborised reactive astrocytes. Synaptophysin, S-100 and chromogranin A reactions were normal. Luxol Fast Blue staining did not show demyelination. NeuN, NF52 and NF312 antibodies revealed no pathognomonic neuronal changes.
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