Case report

Early recognition of anti-N-methyl D-aspartate (NMDA) receptor encephalitis presenting as acute psychosis

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Abstract

Objective: We present a case of anti-N-methyl D-aspartate (NMDA) receptor encephalitis that illustrates the dilemma that psychiatrists face in evaluating patients with first episode psychosis.

Conclusions: The discovery that acute psychosis can be the presenting feature of autoimmune encephalitis (in particular encephalitis caused by anti-NMDA receptor antibodies) has both practical and theoretical consequences. First, this condition is an important, but often overlooked, differential diagnosis of first episode psychosis. Antibody testing is not currently part of routine screening, though delayed (or missed) diagnosis can lead to prolonged hospital stay, medical complications and incomplete or delayed recovery. Widespread screening of patients with first presentation psychosis for anti-NMDA receptor and anti-voltage-gated potassium channel (anti-VGKC) antibodies is warranted for a number of reasons: to expedite appropriate treatment, to determine the true proportion of patients with these conditions presenting as psychosis, and to help elucidate the neurochemical causes of psychosis.

Keywords: anti-N-methyl D-aspartate receptor encephalitis, first episode psychosis

The discovery that acute psychosis can be the presenting feature of autoimmune encephalitis (in particular encephalitis caused by NMDA receptor antibodies) has both practical and theoretical consequences. First, this condition is an important, but often overlooked, differential diagnosis of first episode psychosis. Antibody testing is not currently part of routine screening, though delayed (or missed) diagnosis can lead to prolonged hospital stays, medical complications and incomplete or delayed recovery.

Second, the recognition that limbic encephalitides, involving autoantibodies to neuronal receptors, can present as schizophreniform psychosis raises the possibility that a proportion of people thought to have schizophrenia may in fact have one of these conditions. Third, the fact that these autoimmune disorders can present identically to otherwise typical psychoses sheds new light on pathophysiological theories of psychosis and schizophrenia.

In addition to anti-NMDA receptor encephalitis, limbic encephalitis presenting as psychosis can also be caused by voltage-gated potassium channel (VKGC) complex

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antibodies,[1] and glutamic acid decarboxylase antibodies.[2] Presumably other hitherto uncharacterised antibody-mediated limbic encephalitides also exist. We present an illustrative case.

Case vignette

A 27-year-old Aboriginal female was brought to a South Australian tertiary hospital emergency department by police after she was found singing and dancing in front of cars on a busy city street. She was disorientated, paranoid and agitated. She was unable to recount the events prior to her presentation or how she came to hospital. She was observed to be responding to auditory and visual hallucinations. She appeared easily frightened by noises or other people. She repeatedly tried to abscond in a state of terror and agitation. Her speech was disorganised with loosening of associations, echolalia and derailment. She lamented the recent death of a friend, continually mumbling his name, juxtaposed with periods of loud screaming and singing. She initially reported extreme hunger, then suddenly ceased oral intake entirely.

There was a family history of schizophrenia and depression. Collateral history revealed a recent relationship breakup and a past history of depression and substance use. Her initial neurological examination, blood screens (biochemistry, septic, drug and infectious disease screens, thyroid function) and computed tomography (CT) head scan were normal. She was admitted to a psychiatric intensive care facility with a provisional diagnosis of first episode psychosis. Given that the presentation included past and family psychiatric history, and recent psychosocial stressors, this was a very typical presentation for an acute first episode psychosis.

She was treated with antipsychotic medication. She deteriorated over several days, becoming catatonic, mute then incontinent. She developed hypersalivation and orofacial dyskinesias consisting of repetitive semi-rhythmic grimacing and smiling. On day 6 she became transiently unresponsive and was referred back to the general hospital. The consulting neurology team observed the characteristic orofacial movements of NMDA encephalitis and immunotherapy was promptly commenced. Despite this, she deteriorated further requiring ventilator support in the intensive care unit. Three weeks after admission she was unresponsive and developed typical complex semi-rhythmic bulbar and limb movements.

Cerebrospinal fluid (CSF) examination revealed a lymphocytic pleocytosis (22 mononuclear cells/μl), raised immunoglobulin G/albumin ratio and unmatched oligoclonal bands. Magnetic resonance imaging (MRI) revealed diffuse sulcal hyperintensity, indicative of a generalized meningoencephalitis. Both CSF and serum samples were strongly positive for anti-NMDA receptor antibodies. An ovarian teratoma was confirmed on pelvic ultrasound and removed on day 12 of her illness. Management included intravenous methylprednisolone, immunoglobulin and the anti CD-20 monoclonal antibody rituximab. After five weeks she underwent plasmapheresis. After nine weeks she was weaned off sedation and she has continued a slow recovery.

Clinical presentation and course of anti-NMDA encephalitis

Anti-NMDA receptor encephalitis was first recognised in 2005 as a distinctive clinical syndrome.[3] It was initially thought to occur only in young women with ovarian teratoma, but the condition has since been described in both genders and across the lifespan, including children and the elderly. The classic presentation is psychosis, following a non-specific prodrome (often headache and malaise). The psychosis is characterised by delusions, hallucinations, sleep disturbance, disordered behaviour and catatonia. Three-quarters of patients are initially admitted to psychiatric units, usually diagnosed as first episode psychosis and treated with antipsychotic drugs and sometimes electroconvulsive therapy (ECT). A complex movement disorder then develops in association with an altered conscious state (often a 'wakeful coma'). Central respiratory dysfunction, autonomic instability, hypersalivation and severe semicontinuous dyskinesias frequently necessitate prolonged intensive care admission.[4,5]

Females represent approximately 80% of cases and of these, 44–50% have an ovarian teratoma.[4] Rarely other occult malignancies may be present. Other less specific, early findings include a CSF pleocytosis, detected in 80% of cases initially (rising with time), non-specific abnormalities on appropriate MRI sequences in around half of cases, and an elevated creatine kinase.[4] The electroencephalogram (EEG) most commonly demonstrates diffuse slowing.

Although patients may require months of support in an intensive care unit and then several more months in rehabilitation, remarkable recoveries are more the rule than the exception. Seventy-five percent of survivors recover to baseline or near baseline function.[4] The extent and speed of recovery is enhanced if immunotherapy is commenced and the tumour (if present) is removed within the first month.[6,7]

Although the overall prevalence of the condition is unknown, international studies suggest anti-NMDA receptor encephalitis is found in up to 20% of patients with immune-mediated encephalitis[8] and in young adults it is more common than enteroviruses or herpes simplex virus-1 (HSV-1) encephalitis.[9] At the South Australian tertiary hospital to which the patient described above presented, three typical cases, all in young women with ovarian teratomas, have been retrospectively identified over the preceding 15 years.[10] All patients were initially admitted to psychiatric wards and one received ECT for psychosis with catatonic features. All were initially indistinguishable from other cases of first episode psychosis.

Pathophysiology of limbic encephalitis

Finelli[2] divides limbic encephalitides into viral or autoimmune forms, with the latter being either paraneoplastic or idiopathic. Young women who develop anti-NMDA receptor antibody encephalitis commonly have an ovarian teratoma. These teratomas contain neural tissue expressing NMDA receptors, which elicit an immune response with the formation of anti-NMDA receptor antibodies. The antibodies bind and cap the surface NMDA receptors in the central nervous system, prompting internalisation and subsequent glutaminergic neuronal hypofunction.[11] The trigger for NMDA encephalitis in patients without evidence of tumours bearing the NMDA receptor is not known.

Implications for psychiatric practice

Early recognition of this condition by psychiatrists would permit more rapid institution of appropriate immunotherapy and tumour removal (if a tumour is present), which may limit or prevent prolonged intensive care admission and reduce the need for neuroleptic exposure.

While florid cases requiring ventilator support will eventually be transferred to intensive care units (where this disease is increasingly recognised), it is probable that more benign, chronic and incomplete forms of the syndrome exist. If encephalitis is not considered in the differential diagnosis, such cases would most likely be assumed to be due to chronic schizophrenia.

The presence of soft neurological signs in many people with schizophrenia, and the propensity of many antipsychotics to cause movement disorders, complicates recognition of milder forms of anti-NMDA receptor encephalitis. The side effect profile of antipsychotic drugs used in acute psychosis can confound the clinical picture and delay recognition of the encephalitis. Additionally, given that NMDA receptors are found in the highest densities in the frontotemporal regions and hippocampus,[11] it is possible that a more slowly progressive form of anti-NMDA receptor encephalitis might present as frontotemporal dementia. As with the more florid forms of the disorder, it is likely that early recognition and treatment would lead to improved long-term outcome, as chronic antibody-mediated attack on NMDA receptors may lead to irreversible changes over time.[12]

To date, there has only been one small study reporting the prevalence of these autoantibodies in people presenting with first episode psychosis.[13] Apart from this, testing has only been performed sporadically or in patients with a diagnosis of encephalitis. This small German study provided 'proof of concept' that routine antibody testing in patients with first presentation of psychosis may be worthwhile. In this study 6.5% had serum anti-NMDA receptor antibodies.[13] The identified cases of anti-NMDA encephalitis were indistinguishable clinically from the other cases of psychosis and fulfilled Diagnostic and Statistical Manual for Mental Disorders IV (DSM IV) criteria for schizophrenia. All had paranoid delusions and most were unmotivated and had poor self care in keeping with the negative symptoms of schizophrenia. CSF was not examined in these patients, and it may be that CSF testing would have shown a higher prevalence, as false negative serum results would be expected to be more likely in milder forms of the disease. Furthermore, the anti-NMDA antibodies levels in serum decline with time and thus using serum assays as the indicator of the disease may under-estimate the true prevalence.

With increasing recognition of the syndrome, the diagnostic anti-NMDA receptor antibody assay is becoming more readily available. Laboratories in Brisbane and Perth perform this test fortnightly, at a Medicare claimable cost of approximately $34, with the result available in 2–3 days [Tidswell, J: personal communication]. Recent international reviews of the assay detection revealed a serum antibody sensitivity of 85% and CSF sensitivity of 100%.[7] Data from the major laboratory used in Australia, Pathology Queensland, shows a lower sensitivity in serum analysis to that reported in the literature, which may be explained by the use of different assays, but they have a comparable CSF assay sensitivity.[14] Therefore, in high cases where there is a high index of suspicion, a lumbar puncture for CSF should be performed.

Other forms of limbic encephalitis are probably also under-recognised when they present psychiatrically. In all of these conditions similar non-specific CSF, EEG and MRI abnormalities are detected. Antibody assays for VGKC antibodies are similarly available in Australia, and we suggest that all first-presentation psychoses should have serum anti-NMDA and VGKC antibodies added to their medical investigations and cases with a high index of suspicion should undergo a lumbar puncture for CSF analysis. Additionally, testing these specimens for IgG/albumin ratio and unmatched oligoclonal bands may suggest an alternate, as-yet-undiagnosable autoimmune encephalitis. Broad uptake of these readily available and relatively inexpensive tests ($130) seems appropriate given the potentially devastating clinical and financial outcomes of missing this diagnosis.

Population-based studies of the prevalence of autoantibodies to central nervous system neurreceptors in patients with first-presentation psychosis are urgently required. In one of the larger case series to date,[15] 77 of 100 cases were first seen by a psychiatrist. Psychiatrists are therefore at the front line in diagnosing autoimmune psychoses. While, with time, it will become clearer whether some patient groups do not require testing, given the relatively low cost of the test, the readily available and effective treatment and the high cost of acute and chronic psychosis we argue that anti-NMDA and VGKC antibody testing should become a routine part of the initial assessment of people presenting with first episode psychosis.

Implications for theoretical understanding of the aetiology of schizophrenia

There is now considerable evidence concerning the role of the glutamate system in schizophrenia. NMDA receptors, found in high densities in the frontotemporal regions and hippocampus also have a large role in learning and memory.[11] Ketamine, an NMDA antagonist, can cause an acute psychosis.[12] These observations help to explain the psychotic features in patients with anti-NMDA encephalitis, but as noted above also raise the possibility that some cases of schizophrenia may in fact be due to chronic, reversible autoimmune encephalitis.

The case presented above illustrates the conceptual limitations of previous classifications of psychosis as 'organic' or 'non-organic'. Despite some understanding of the biochemical disturbances in the psychotic brain including the role of disturbed glutaminergic transmission, the aetiology of these neurochemical imbalances is unknown. Perhaps researchers should be looking more closely at autoimmune mechanisms, considering the possible role of autoantibodies in at least some cases of first presentation psychoses. Beyond the autoantibodies already identified in the literature, such as antibodies to the NMDA receptor, VGKC-complex, gamma-aminobutyric acid (GABA) receptor and glutamate receptor 1 and 2 subunits of the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA) receptor,[16] there is a possibility further antibody targets will be found and implicated in the pathophysiology of schizophrenia.

Conclusion

Our case illustrates the dilemma that psychiatrists face in evaluating patients with first episode psychosis. The fulminant clinical syndrome of anti-NMDA receptor encephalitis becomes apparent over time but serum immunoassays can be sensitive and specific early in the disease, when only neuropsychiatric symptoms may be present. Widespread screening of patients with first presentation psychosis for anti-NMDA receptor and anti-VGKC antibodies is warranted for several reasons: to expedite appropriate treatment, to determine the true proportion of patients with these conditions presenting as psychosis, and to help elucidate the neurochemical causes of psychosis.

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Disclosure

The authors report no conflict of interest. The authors alone are responsible for the content and writing of the paper.

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