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Contents

Antibody-mediated encephalitis and psychosis

The four cases of *N*-methyl-D-aspartate (NMDA) receptor antibody encephalitis with associated psychosis reported in December[1] raise an important and emerging issue and highlight that psychiatrists should include the condition in the differential diagnosis for patients presenting with acute psychosis. But there are some aspects that need clarification. The authors state that 'this case series demonstrates a new and treatable cause of psychosis', inferring that the association of psychosis with these antibodies was previously unknown. However, since the first 100 patients with NMDA receptor antibody encephalitis were reported in 2008,[2] this association has been well documented; psychosis is typically the first presentation and many cases were seen by psychiatrists before neurologists become involved.[2,3]

The association of these antibodies with psychosis is highly relevant because they bind to key neuronal surface proteins and are therefore likely to be pathogenic. Indeed, NMDA receptor antibody encephalitis is a condition that responds to immunotherapy and, importantly, there is thought to be an initial 'treatment window' for optimal immunomodulation.[4,5] The authors[1] speculate that 'there may be a pure psychiatric presentation associated with lower antibody titres'. Indeed, a recent study found that 3 out of 46 patients with first-episode psychosis (with no neurological or other clinically distinguishing features) had NMDA receptor antibodies.[6] One patient made a significant clinical improvement with plasmapheresis and steroid treatment. An additional patient had voltage-gated potassium channel antibodies, which can also be found in patients with other psychiatric presentations.[5,7] It now appears increasingly likely that other neuropsychiatric (e.g. catatonia) and psychiatric (e.g. obsessive–compulsive) symptoms may be associated with cell-surface neuronal antibodies.[8]

As Barry *et al*[1] point out, the condition does indeed provide some support for the NMDA receptor hypofunction hypothesis for psychosis. Some proponents of this theory have linked NMDA receptor hypofunction to first-rank psychotic symptoms in particular.[9] It is important that future studies of auto-antibody-associated psychosis characterise symptomatology in full, as this could allow for a level of clinical–pathological correlation rarely attained in psychiatry.

Declaration of interest

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1 Barry H, Hardiman O, Healy DG, Keogan M, Moroney J, Molnar PP, et al. Anti-NMDA receptor encephalitis: an important differential diagnosis in psychosis. *Br J Psychiatry* 2011; **199**: 508–9.

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6 Zandi MS, Irani SR, Lang B, Waters P, Jones PB, McKenna P, et al. Disease-relevant autoantibodies in first episode schizophrenia. *J Neurol* 2011; **258**: 686–8.

7 Spinazzi M, Argentiero V, Zuliani L, Palmieri A, Tavolato B, Vincent A. Immunotherapy-reversed compulsive, monoaminergic, circadian rhythm disorder in Morvan syndrome. *Neurology* 2008; **71**: 2008–10.

8 Kayser MS, Kohler CG, Dalmau J. Psychiatric manifestations of paraneoplastic disorders. *Am J Psychiatry* 2010; **167**: 1039–50.

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Authors' reply: We thank Pollak *et al* for reiterating that anti-NMDA receptor encephalitis should be included as a differential diagnosis for patients presenting with acute psychosis. The association of anti-NMDA receptor encephalitis with psychosis is new, having been identified only as recently as 2008,[1] although the disorder has likely gone unrecognised and indeed untreated previously. Although to date there are no estimates regarding population prevalence rates of anti-NMDA receptor encephalitis, the California Encephalitis Project retrospectively screened 3000 patients with idiopathic encephalitis (with dyskinesia or movement disorders) and identified 10 (0.3%) anti-NMDA receptor-positive cases.[2] Examining the incidence of catatonia in psychosis, Fink & Taylor estimate a prevalence of between 9 and 17% of patients in academic psychiatry in-patient units,[3] while Peralta *et al* found that 31% of drug-naive patients with first-onset psychosis demonstrated at least one catatonic symptom, and found an interesting subgroup that showed a clear association with disorganisation and dyskinesia.[4]

The neuropsychiatric presentation underlying NMDA receptor encephalitis has only recently been published in the psychiatric literature.[5] Consequently, this clinical presentation involving psychiatric symptoms in approximately 77% of affected individuals has not been widely disseminated among psychiatrists. This was the driving force behind the publication of our case series.

Pollak *et al* restate our view that 'there may be a pure psychiatric presentation associated with lower antibody titres', and point to their own recent work showing that 3 out of 46 patients with first-episode psychosis had NMDA receptor antibodies.[6] This extremely important finding has profound