Serum NMDA receptor antibodies do not predict treatment response in a sample of people with first episode psychosis

Natalie Shoham

NIHR Doctoral Fellow in Psychiatry

Affiliations:

1) University College London, Division of Psychiatry, 6th Floor Maple House, 149 Tottenham Court Road, London. W1T 7NF

2) Camden and Islington NHS Foundation Trust

natalie.shoham.16@ucl.ac.uk

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Autoimmune encephalitis is a rare but potentially life-changing illness, in which antibodies damage healthy brain cells. It can present with a wide range of neurological and psychiatric symptoms, from seizures and autonomic instability to depression and anxiety (1). It can also mimic schizophrenia and other psychotic illnesses (1). Since the 1950s, an array of potentially causative autoantibodies have been identified (1), but the N-Methyl-D-Aspartate Receptor (NMDAR) antibody is the type most consistently associated with psychosis (2). NMDAR encephalitis was originally described as a paraneoplastic syndrome in a series of women with ovarian teratoma, but it also occurs in people with no malignancy (1).

Case series show that in selected patients with psychosis and serum NMDAR antibodies, remission of psychopathology occurs with immunological treatments, and that these may work best if started early (3). These patients are at risk of missed or delayed diagnosis of autoimmune encephalitis when their symptoms are attributed to functional psychiatric illness. The use of antipsychotic medications might be associated with both adverse effects and delay in receiving curative treatment (1). The question of when to screen for NMDAR and other autoantibodies in psychosis is therefore of great importance to psychiatrists. Routine screening might ultimately restore some patients to their previous level of functioning and avert permanent neurological deficit or even death, but it might also subject large numbers of patients to unnecessary and uncomfortable investigations, at a time when many lack capacity to consent.

Some authors have advocated for routine screening of serum for encephalitis-causing antibodies in all patients with first episode psychosis (3, 4). Guidelines from both the *American Psychiatric Association* and *British Association of Psychopharmacology* currently do not support this approach however, instead suggesting that screening should be targeted (5, 6). Features that might prompt consideration include reduced conscious level, seizures, adverse response to antipsychotics, and movement disorder (2). Consequently, which patients receive investigations, and the extent of investigation they receive, is largely left to the discretion of individual clinicians. The most convenient investigation is a simple blood test for serum NMDAR antibodies. Problematically however, a positive result does not necessarily indicate a clear course of action, as serum NMDAR antibodies have been found to occur in up to 10% of healthy individuals (7).

It is highly welcome then that in this issue, Pollak et al provide evidence regarding the clinical importance of serum NMDAR antibody positivity on routine screening in people with first episode psychosis (8). They used blood results from a sample of 387 participants in the international OPTiMiSE trial, the primary aim of which was to assess efficacy of two alternative antipsychotic treatment pathways in first-episode schizophrenia (9). The participants had blood tests at baseline.

Pollak et al investigated two hypotheses: 1) that presence of serum NMDAR antibodies would be associated with a shorter Duration of Untreated Psychosis (DUP); and 2) that it would be associated with poorer response and more frequent adverse events with antipsychotic medications. The implication of a shorter DUP would be that the psychosis was more rapidly progressive and therefore typical of autoimmune encephalitis psychosis. Response to antipsychotic medication was assessed using the Positive and Negative Syndrome Scale (PANSS) and Clinical Global Impression (CGI) scores after treatment with amisulpiride for four weeks.

At baseline, 15 out of 387 patients tested positive for serum NMDAR antibodies. Ninety-two in total were excluded from follow-up, meaning that the seropositive sample dropped to 11 for the purposes of hypothesis 2. Reassuringly, there was minimal difference between those who did and did not drop out in terms of serum status.

Some of the findings differed markedly from the authors' expectations. The median duration of untreated psychosis was 1.5 months in the seropositive group compared with 4 months in the seronegative group, consistent with the more subacute presentation proposed in hypothesis 1. The second hypothesis was not supported, however. In fact, the rate of remission in the seropositive group was higher, although this was not statistically significant. There was no difference between the groups in rate of adverse effects.

How to interpret these findings? One explanation for the lack of between-group difference in treatment response is that the antibodies were not causally relevant to the psychosis. This is considered the most likely explanation by the authors, who point to the comparable prevalence of such antibodies in healthy populations in some studies. A second possibility is that the seropositive patients had an autoimmune encephalitis which remitted spontaneously, with prescription of amisulpiride being coincidental. The authors consider this unlikely, although they acknowledge that spontaneous remission of NMDAR encephalitis has been reported. The fact that no patients had features suggestive of organic psychosis strongly goes against this. A third, albeit improbable explanation is that the seropositive patients had NMDAR encephalitis which responded to antipsychotics. Whilst this has also previously been reported, it is clear that in the majority of confirmed cases symptoms do not respond to antipsychotics (10).

Ultimately, it was not possible to conclude whether the NMDAR antibodies played a role in causing the psychosis in the seropositive group, as the trial did not conduct more invasive investigations such as lumbar puncture. It seems far more likely that they did not, given the consistent literature documenting a more severe course of illness in confirmed cases. Pollak et al's main conclusion is that prescription of antipsychotic medications is unlikely to be harmful in people with first episode psychosis and an incidental finding of NMDAR antibodies.

Some limitations are worth noting and well-described by the authors. The number with seropositivity was small, and the follow-up period was far shorter than the conventional 6-month period required to diagnose remission. Nevertheless, a high number of patients did achieve remission (69% and 82% in each group), suggesting that follow-up was adequate to assess the effects of treatment. The OPTiMiSE trial required patients to provide written informed consent and not be subject to coercive treatment (9). Since autoimmune encephalitis is associated with neurocognitive deficit, it is likely that these inclusion criteria excluded potential participants with this illness. A previous study of inpatients found that 5 out of 6 patients discovered to have autoimmune encephalitis were too unwell to consent to research participation except through a proxy decision-maker (3). It would be interesting to know how use of this entry pathway in the trial might have affected the results. Caution should be used when applying the results to more severely unwell patients. As the OPTiMiSE trial was for people with first episode psychosis, it is also unclear how the results might apply to people with longer, treatment-resistant illnesses. One interesting suggestion from the authors is that a longitudinal study could be conducted in which serum tests for NMDAR antibodies are taken each time a participant has a relapse of psychotic illness. This would help to establish whether seropositivity is a trait or state phenomenon; and whether it is likely to be a cause or even consequence of psychotic episodes not typical of encephalitis. Significant strengths of the paper include its large overall sample size. Additionally, serum status was ascertained after DUP and remission status had been recorded, eliminating the possibility for recall or assessor bias.

Pollak et al state that their findings support the use of further intensive investigations in patients with seropositivity for NMDAR antibodies, including electroencephalogram, magnetic resonance imaging, and cerebrospinal fluid analysis. In the UK however, serum results typically take several weeks, by which time many of the patients in the trial would have achieved remission. Another

interpretation of the findings could be that widespread screening of patients with first episode psychosis for serum NMDAR antibodies is not necessary, and that a more targeted approach which selects people with clinical 'red flags' is preferable. Considering the significant consequences for people with autoimmune encephalitis in whom the diagnosis is missed, replication of these results would be valuable, particularly in samples including more severely unwell patients. Pollak et al should be commended for conducting a rigorous study addressing a crucial issue. The findings are reminiscent of the adage that it is the patient, rather than the blood results, that we should be treating.

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