NMDA receptor antibodies are found in a small subgroup of patients with first-episode psychosis, but their clinical relevance is unknown

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WHAT IS ALREADY KNOWN ON THIS TOPIC?

Antineuronal antibody-mediated encephalitis frequently presents with prominent psychiatric features. It has been hypothesised that antineuronal antibodies may play a pathophysiological role in subgroups of patients with psychotic disorders. Whereas a few large studies find a similar prevalence of antineuronal antibodies in patients with psychotic disorders, other psychiatric disorders and healthy controls,[1 2] there is some evidence of an increased prevalence of N-methyl-D-aspartate receptor (NMDAR) antibodies in patients with first-episode psychosis.[3 4] In their present study, the authors aimed to (1) investigate the prevalence of neuronal cell surface antibodies in patients with first-episode psychosis and healthy controls and (2) compare the clinical and cognitive profile of patient's with and without these antibodies.

METHODS OF THE STUDY

The subjects in this observational study were 228 patients with first-episode psychosis recruited from 35 early intervention, community or inpatient mental health services sites and 105 healthy controls from the general population in the UK. Patients were 14–35 years old, had less than 6 weeks on antipsychotic medication and a score >3 on one or more of the following Positive and Negative Syndrome Scale (PANSS) items: delusions, hallucinations, grandiosity, suspiciousness and unusual thought content. Exclusion criteria were drug-induced psychosis or the presence of a neurological disorder. Patients were assessed using standardised symptom rating scales (PANSS, Addenbrooke's Cognitive Examination-III, Bush-Francis Catatonia Rating Scale and Global Assessment of Functioning (GAF)) at baseline and with International Classification of Diseases 10 diagnosis and GAF at 6 months follow-up. Serum was tested for the presence of antineuronal IgG antibodies (NMDAR, leucine-rich glioma-inactivated protein-1, contactin-associated protein-like 2, γ-aminobutyric acid A receptor, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor and voltage-gated potassium channel complex) using live cell-based assays or a radioimmunoprecipitation assay.

WHAT THIS PAPER ADDS?

- This is the largest study examining the prevalence of antineuronal antibodies in patients with first-episode psychosis.
- Twenty (9%) of 228 patients had serum antibodies against one or more of the neuronal cell surface antibodies compared with four (4%) of 105 controls (unadjusted OR 2.4, 95% CI 0.8 to 7.3). These associations remained non-significant when adjusted for current cigarette smoking, alcohol consumption and illicit drug use.
- NMDAR IgG antibodies were more prevalent in patients with first-episode psychosis (seven patients, 3%) as compared with no healthy controls ($p=0.02$).
- Antineuronal antibody negative patients had statistically significant higher levels of psychotic (PANSS positive 21.8 vs 19.1 ($p<0.01$)) and catatonic (Catatonia Rating Scale 2.2 vs 0.6 ($p<0.01$)) symptoms than antineuronal antibody positive patients. The absolute difference in symptom scores are small, and the clinical significance of these findings is unclear.

LIMITATIONS

- The authors do not provide the number of patients asked to participate in the study (inclusion rate). A low inclusion rate would make the results more prone to selection bias (ie, inclusion of patients with less severe psychotic symptoms).
- Neurological examination, brain MRI, electroencephalogram and cerebrospinal fluid analyses were not performed, but would be necessary to definitely exclude neurological causes of first-episode psychoses, such as autoimmune encephalitis, multiple sclerosis and temporal lobe epilepsy.

WHAT NEXT IN RESEARCH?

The finding of an increased prevalence of NMDAR antibodies in patients with first-episode psychoses needs to be replicated in other cohorts using multiple confirmatory laboratory methods (ie, live vs fixed cell-based assays vs immunohistochemistry). These studies should also include thorough somatic examinations including cerebrospinal fluid analyses. Further, it is important to evaluate the use of immunotherapy in patients with first-episode psychosis serum positive to antineuronal antibodies in randomised controlled trials (RCTs). RCTs investigating the feasibility, safety and efficacy of using immunotherapy to treat such patients are currently being performed by the researchers behind the present study (http://www.sinapps.org.uk/studies/4589969048).

DO THESE RESULTS CHANGE YOUR PRACTICE AND WHY?

Not yet. There is some evidence of an increased prevalence of NMDAR IgG antibodies in patients with first-episode psychosis. The clinical relevance of these antibodies is, however, still unknown. The authors of the original paper suggest that all patients with first-episode psychosis should be screened of NMDAR IgG antibodies. However, the effect of immunotherapy in NMDAR IgG positive patients with psychiatric disorders (and no evidence of autoimmune encephalitis) has not been investigated in RCTs. In our opinion, RCTs need to prove benefit of immunotherapy in these patients before routine screening can be recommended. Until such evidence exists, we suggest that antineuronal antibody testing should be restricted to patients with a clinical suspicion of autoimmune encephalitis.[5]

Competing interests None declared.

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