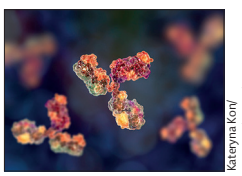
NMDAR antibodies in patients with psychosis



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The concept of a relevant contribution of immunological and inflammatory factors to psychiatric disorders such as schizophrenia was postulated more than 100 years ago.[1] It has since been supported by increasing evidence, including the association of infections, autoimmune disorders, and elevated inflammation markers with schizophrenia. Recent studies have identified alterations of blood cytokine networks and increased microglial activity in patients with schizophrenia,[2] and reports of post-infectious psychosis cases following the 1918 Spanish influenza pandemic are particularly interesting given the current COVID-19 pandemic.[3]

Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis is an autoimmune encephalitis that is caused by NMDAR IgG antibodies in the cerebrospinal fluid (CSF) of patients.[4] At onset, the disease frequently manifests with psychiatric symptoms such as agitation, hallucinations, delusions, or depressed mood. The encephalitis then typically progresses to include neurological symptoms, including seizures, movement disorders, autonomic dysfunction, and cognitive impairment. In rare cases (about 4%), patients present with isolated psychiatric symptoms. Patients with suspected NMDAR encephalitis require rapid CSF antibody testing and immunotherapy.

The frequent psychotic symptoms at the onset of NMDAR encephalitis have raised the question of whether NMDAR antibodies can be detected in patients with isolated psychosis. This question has been addressed repeatedly in the past decade—in different patient populations, using different methods, and yielding considerably varying results. In their meta-analysis in *The Lancet Psychiatry*, Alexis Cullen and colleagues[5] investigated the effect of these different methods and patient factors on NMDAR IgG antibody detection in the serum of patients with psychosis in 14 cross-sectional and 14 case-control studies.

The authors observed that serum NMDAR IgG antibodies were detected in 0·73% (95% CI 0·09–1·38) of patients with psychosis, and that patients with psychosis were not significantly more likely to be seropositive than were healthy individuals (OR 1·57, 95% CI 0·78–3·16).[5] Using meta-regression, Cullen and colleagues showed a significant effect of assay type on antibody detection rate, with live cell-based assays (CBAs) being associated with significantly higher pooled prevalence estimates in patients with psychosis than were fixed CBAs (2·97% [95% CI 0·70 to 5·25] *vs* 0·36% [–0·23 to 0·95]). In addition, live CBAs showed significant differences in odds ratios (ORs) between patients and controls (OR 4·43, 95% CI 1·73 to 11·36), which was not the case for fixed CBAs (OR 0·65, 0·33 to 1·29). Furthermore, in cross-sectional studies, antibody prevalence was higher in patients with first-episode psychosis than in multi-episode or mixed samples, whereas no effect of disease stage was found in case-control studies. Finally, a significant effect of study quality was observed with low-quality case-control studies yielding higher ORs than high-quality studies did for the detection of antibodies in patients with psychosis relative to controls (OR 3·80 [95% CI 1·47 to 9·83] *vs* 0·72 [0·36 to 1·42]). There was no significant effect of study quality in cross-sectional studies.

Assay type (live *vs* fixed CBA) showed the largest effects on heterogeneity and was the only variable to have a significant impact on effect sizes in both cross-sectional studies (prevalence) and case-controls studies (ORs). Indeed, the two studies with the largest weights included in the meta-analysis used different assays and showed opposing results. This difference could indicate that live CBAs produce more false positive results than fixed CBAs. However, in this case, one would expect similarly high rates in patients and healthy controls and not—as was observed in the meta-analysis—increased ORs for patients in comparison with controls. In contrast to this observation, in patients with anti-NMDAR encephalitis, fixed CBAs detected more positive serum samples than did live CBAs.[6] Further differences between assays of different laboratories that could contribute to heterogeneous findings include the number of plasmids in transfected human embryonic kidney 293 cells in live CBAs, differences in the interpretation of CBAs, and differences in test cutoff values. This fundamental and ongoing debate on the advantages and disadvantages of different assays can, by design, only be addressed on a study level and not by meta-analyses. Therefore, further studies are needed that compare NMDAR antibody frequencies using different assay types in all enrolled patients and control participants, ideally in serum and CSF.

A recent study,[7] which was also included in the meta-analysis, offers additional insight into characteristics of serum NMDAR antibodies in patients with schizophrenia. In this study, NMDAR IgG antibodies were detected in 19% of patients using a live CBA.[7] Antibodies were found only in serum (not in CSF), had substantially lower titres in comparison with samples from patients with anti-NMDAR encephalitis, and were directed against different glutamate receptor ionotropic NMDA 1 epitopes, as shown using immuno-competition assays. However, NMDAR antibodies from patients with schizophrenia modified surface dynamics and the nanoscale organisation of NMDARs and its anchoring partner, the ephrinB2 receptor, suggesting a pathogenic role of these antibodies.

The meta-analysis by Cullen and colleagues identified disease stage as significant effect in cross-sectional studies, but this analysis was limited by incomplete primary data with poor reporting of patient characteristics in the studies included. As the authors state, it is also concerning that low-quality case-control studies yielded significantly higher ORs than high-quality studies. For most studies, inadequate clinical information led to these low-quality scores. These two points illustrate the importance of increasing the quality of reporting in studies—from the recruitment strategy to the analysis plan—to allow a solid interpretation of results and to enable robust meta-analyses.

In summary, this meta-analysis identifies the pain points in the analysis of serum NMDAR antibodies in patients with psychosis, namely assay types, disease stage, and reporting quality. Further studies are now needed that compare NMDAR antibody frequencies using different assays (live *vs* fixed CBAs) in both patients and controls, preferably in serum and CSF. Such studies should also assess differences in the clinical presentation between antibody-positive and antibody-negative patients, for example by regarding the clinical spectrum of psychotic symptoms and additional symptoms such as cognitive impairment, and they should follow the temporal dynamics of symptoms in longitudinal study designs.

I declare no competing interests.

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