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Fact or Fiction? Examining a Role for *N*-Methyl-D-Aspartate Receptor Autoantibodies in Psychiatric Illness

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There is a pressing need in psychiatry to establish biologically based disease subtypes, which might allow for more specific diagnosis and effective intervention. An active area of investigation in this realm has been autoimmunity and mental illness. The discovery and characterization of anti–*N*-methyl-D-aspartate receptor (NMDAR) encephalitis has led the resurgent effort into understanding whether specific autoantibody syndromes might define a subset of patients with psychiatric diagnoses or symptoms, such as schizophrenia or psychosis. Numerous groups have attempted to detect disease-causing autoantibodies in adults; in this issue of *Biological Psychiatry*, Pathmanandavel *et al*. (1) take an important step in searching for autoantibodies associated with a first episode of psychosis in a pediatric population.

Anti-NMDAR encephalitis is a synaptic autoimmune disorder caused by immunoglobulin (Ig) G–type antibodies against the extracellular N-terminal of the GluN1 subunit of the NMDA-type glutamate receptor. The syndrome occurs most commonly in young women and can be associated with the presence of an ovarian teratoma (2). From a clinical perspective, anti-NMDAR encephalitis is of particular interest to psychiatrists because it begins with prominent neurobehavioral symptoms, most notably psychosis, changes in mood, and aggression (3). In most cases, these early psychiatric manifestations are followed by severe neurologic illness, including seizures, movement abnormalities, and autonomic instability (2). Prompt detection of antibodies is imperative because tumor removal (if present) and immunosuppression lead to positive outcomes, with ~80% of patients returning to baseline function (2).

Do NMDAR autoantibodies cause psychiatric symptoms in isolation, leading to patients harboring these antibodies being given a misdiagnosis of a primary psychiatric illness? Focusing on patients with anti-NMDAR encephalitis (presence of IgG GluN1 antibodies in cerebrospinal fluid [CSF]), ~5% experience only psychiatric symptoms either at initial presentation or during relapse, indicating proof of principle that these antibodies can cause episodes that do not progress to include neurologic involvement (4). Do some patients with a

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diagnosis of a primary psychiatric illness actually have this or another autoantibody disorder? This question has been addressed repeatedly in recent years, and what has become clear is that the evidence is murky. To understand the debate, one must understand some details about how the antibodies are detected.

First, the initial seminal articles describing anti-NMDAR encephalitis detected antibodies using three core approaches: incubation of patient CSF and serum with 1) sections of rat brain; 2) cultured nonpermeabilized, live, rat hippocampal neurons; and 3) non-neuronal cells that express the NMDAR (3). These approaches tell us three things about patient CSF in the syndrome: 1) It strongly reacts with the hippocampus, an area of brain densely populated with neurons expressing NMDARs; 2) autoantibodies react with a punctate, synaptic distribution on the surface of neurons in culture; and 3) the antibodies appear similar to commercially available GluN1 NMDAR antibodies from an immunohistochemical perspective. However, not all groups use all these approaches; many have used only the third approach, which when applied to serum only can result in nonspecific reactivity. This lack of specificity brings us to the second issue.

As might be expected in assessing a psychiatric population, all of the studies so far have examined serum, not CSF, in the search for NMDAR autoantibodies; however, the sensitivity and specificity of antibodies in serum do not approach the sensitivity and specificity of CSF (2). It is not even known whether the presence of serum NMDAR antibodies is relevant to what goes on in the brain. Research has hypothesized that serum antibodies affect brain function in the context of trauma and blood-brain barrier disruption (5), but there is no evidence that antibodies are present in CSF even in such a circumstance.

Finally, antibody subfamily and NMDAR subunit matter. In anti-NMDAR encephalitis, IgG antibodies targeting the GluN1 subunit are disease-causing (3). The relevance of other antibody subtypes (IgA, IgM) is unknown even if they are in CSF, much less serum. Likewise, antibodies targeting other NMDAR subunits might be associated with many other known or as-yet-unknown syndromes, but these do not cause anti-NMDAR encephalitis, with its prominent psychiatric symptoms, well-characterized disease course, and recently described treatment approach.

Armed with this information, how does the work of Pathmanandavel *et al.* fit into the recent spate of studies examining NMDAR autoimmunity in psychiatric illness? Masdeu *et al.* (6) examined serum collected at symptom onset from 80 adults with a first episode of psychosis who met criteria 1 year later for schizophrenia spectrum illness and found no evidence of IgG GluN1 antibodies in patients or control subjects. Similarly, other groups have not detected these antibodies in serum from patients with a diagnosis of schizophrenia or when examining patients predominantly with chronic psychosis. In contrast to these negative findings, Zandi *et al.* (7) reported IgG antibodies against NMDAR subunits (not specifically GluN1) in serum from 3 of 46 patients specifically with early-onset schizophrenia. However, the same authors recently found similar serum NMDAR antibodies in 23% of patients who had disorders considered unlikely to be immune mediated (8), raising questions about the disease relevance in the initial report. Zandi *et al.* (8) modified the interpretation of their assay scoring system so that at least one of the three patients with schizophrenia

initially reported to harbor autoantibodies would currently be considered unlikely to have an immune-associated disorder.

Steiner *et al.* (9) tested serum from 459 patients with either schizophrenia or other psychiatric disorders for the presence of NMDAR autoimmunity. They found two patients with GluN1 IgG antibodies, but both had classic anti-NMDAR encephalitis with neurologic features, and their conditions had been misdiagnosed. Other immunoglobulin subtypes were detected in 10% of patients with schizophrenia in the initial report (IgA or IgM antibodies, or both, reacting with GluN1/GluN2 NMDAR subunits). However, subsequent work found that the frequency of IgA and IgM antibodies recognizing NMDARs is similar in control and healthy individuals (10), again casting doubt on the clinical relevance of these NMDAR antibody subtypes—a conclusion consistent with work by Hammer *et al.* (5), also showing ~10% serum positivity of IgM and IgA NMDAR antibodies in patients and control subjects.

Pathmanandavel *et al.* (1) tested for the presence of NMDAR autoantibodies in a population of pediatric patients with a first episode of psychosis; they also looked for autoantibodies recognizing the dopamine-2 receptor (D2R), which have been associated with movement and psychiatric symptoms in pediatric patients. The authors detected antibodies in patients' serum using reactivity with rodent neurons and non-neuronal cells expressing NMDARs or D2R; in addition, the authors used flow cytometry, another approach to serum antibody detection. They reported IgG GluN1 antibodies in 5 of 43 patients and D2R IgG in 3 of 43 patients, with neither IgG GluN1 antibodies nor D2R IgG present in control subjects. Patients' antibodies reacted with the cell surface of either fixed or live cultured rodent neurons, and preabsorption of the antibodies eliminated neuronal immunostaining. The authors also found that patients' serum and commercially available antibodies yielded a similar pattern of immunostaining. There were no clinical differences in the patient versus control population regarding mild neurologic or psychiatric symptoms, and given the retrospective nature of the study, no patients were treated with immunomodulatory therapies.

The work by Pathmanandavel *et al.* is exciting because of their focus on a pediatric patient population and because they specifically demonstrate the presence of IgG GluN1 autoantibodies in serum, as opposed to only IgA or IgM subtypes. However, the results must be interpreted cautiously. First, after acceptance but before publication of this work, many issues have arisen with the approach and results the authors cite extensively as supporting their finding of serum NMDAR antibodies in a population of patients with psychosis. Although these issues do not call into question the results of Pathmanandavel *et al.*, they do raise concerns about some of the methodologic approaches taken. Second, as the authors point out, the clinical relevance of serum NMDAR antibodies is unknown, again emphasizing the need for careful examination and clinical correlation of CSF.

In conclusion, Pathmanandavel *et al.* have made an advance toward addressing whether NMDAR autoantibodies are detected in serum of patients with psychiatric disorders. The field of psychiatry still awaits whether these antibodies are the mark of a clinically relevant subset of patients and, if so, whether immunosuppressive therapies will show efficacy as they do in classic forms of anti-NMDAR encephalitis.

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