

# One Brain, Two Specialties, Converging Mechanisms: Neuronal Autoantibodies as a Rare Cause of Postpartum Psychosis

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The onset of severe psychotic and affective symptoms within the first 4–6 weeks after childbirth, termed postpartum or puerperal psychosis, is one of the most striking phenotypes in psychiatry and neurology (1). The onset is typically abrupt, and the decline rapid (1). Postpartum psychosis is a psychiatric emergency and can be incredibly disruptive to the mother, child, and family alike. Sadly, postpartum psychosis can also be destructive via maternal self-harm (2) and, very rarely, infanticide (3).

In this issue of the *Journal*, Bergink et al. (4) identify neuronal autoantibodies linked to autoimmune encephalitis as a specific, albeit rare, cause of psychosis in the postpartum period. The authors collected serum samples from 96 consecutive women with postpartum psychosis evaluated in a specialized mother and child inpatient psychiatric unit in the Netherlands between 2005 and 2012. Antibodies against the GluN1/NR1 subunit of the *N*-methyl-D-aspartate (NMDA) receptor were identified in two (2%) of the women with postpartum psychosis, including one who had experienced a prior episode of postpartum psychosis. Neither woman had an ovarian teratoma, and neither exhibited other classic features of anti-NMDA receptor encephalitis, such as seizure, amnesia, autonomic instability, or coma. However, the observed antibody reactivity was typical of what is seen in anti-NMDA receptor encephalitis, an autoimmune encephalitis syndrome with prominent psychiatric features (5). An additional two (2%) women exhibited abnormal neuropil staining indicative of abnormal autoantibody reactivity to an unidentified extracellular antigen(s). By contrast, none of the 64 healthy postpartum women exhibited neuronal cell-surface antibodies or neuropil reactivity on serum testing. The authors conclude that NMDA receptor antibodies were likely causative of or contributory to the postpartum psychiatric syndrome in these select cases and that testing for NMDA receptor antibodies should become part of the diagnostic evaluation for postpartum psychosis (4).

The emerging recognition that autoantibodies can target neuronal cell-surface and synaptic CNS antigens and cause brain dysfunction has revolutionized clinical neurology (6, 7). Autoantibodies from patients have been identified against several synaptic receptors, such as NMDA, AMPA, GABA<sub>A</sub>, GABA<sub>B</sub>, mGluR5, and glycine, as well as ion channel and

associated membrane proteins, such as LGI1 and CASPR2. The practical implication is that many cases of encephalitis that at one time might have been called “viral” or “idiopathic” are now recognized to be autoimmune in origin and are generally responsive to immunosuppression.

By contrast, classical “paraneoplastic” disorders associated with antibodies against intracellular antigens, such as Hu and CRMP-5, are highly correlated with the presence of a tumor, tend to respond poorly to immunosuppression, and exhibit pan-neuronal destruction with prominent T-cell infiltration. Unlike neuronal cell-surface antibodies, antibodies to intracellular antigens in classical paraneoplastic syndromes are probably not directly pathogenic but are rather humoral markers of an antitumoral immune response (8).

Anti-NMDA receptor encephalitis is an archetypical autoimmune encephalitis syndrome. It is a disease of the young; 95% of cases occur in patients under age 45 and 37% in children under age 18 (5). There is a female predominance (5). Patients with NMDA receptor encephalitis tend to exhibit a characteristic

clinical syndrome heralded by a vague prodrome of headache, fever, nausea, vomiting, and upper respiratory infection-type symptoms, followed by the acute onset of prominent psychiatric symptoms, including agitation, anxiety, disordered thinking, hallucinations, delusions, and unusual behavior (9). Some patients with anti-NMDA receptor encephalitis may even get triaged initially to a psychiatric service. The syndrome usually progresses within days to include prominent amnesia, language dysfunction, and seizures (9). A subset of patients will decline rapidly with autonomic dysfunction and reduced level of consciousness to the point of coma, requiring extended stays in the intensive care unit sometimes for months on end (9). Abnormal movements are common. CSF examination usually reveals a pleocytosis and oligoclonal banding (5, 9). Brain MRI is usually normal or nonspecific but can show focal T<sub>2</sub>/fluid-attenuated

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inversion recovery hyperintensities or contrast-enhancing lesions (5). Electroencephalography usually shows slowing or epileptiform activity. Diagnosis is confirmed by identification of IgG antibodies to the NR1 subunit of the NMDA receptor in CSF or serum. About 10% of patients with NMDA receptor encephalitis will have positive CSF antibody testing when serum is negative (5). Immunosuppression with high-dose glucocorticoids and intravenous immunoglobulin or plasma exchange, followed in severe cases by B-cell depletion with rituximab and/or cytotoxic therapy with cyclophosphamide, appears to improve outcomes in observational analyses (5).

The pathogenicity of NMDA receptor autoantibodies in anti-NMDA receptor encephalitis is supported by elegant in vitro and in vivo models, in which antibodies purified from patients were shown to negatively affect neuronal function (10). Ovarian teratomas (which express neuronal tissue) are found in over half of adult women with the disease, but in less than 6% of children under age 12 (5). Anti-NMDA receptor encephalitis can also occur weeks to months after recovery from proven herpes-simplex encephalitis, illustrating the potential role for a postinfectious autoimmune trigger (11).

Clinical laboratory testing for neuronal autoantibodies is now widely available through commercial laboratories and national reference laboratories. Unlike enzyme-linked immunosorbent assay or western blot approaches, reliable detection of neuronal cell surface antibodies requires assays in which the antigen can be expressed in its native three-dimensional conformation. These include 1) a “cell-based assay” in which the antigen is expressed in HEK-293 cells, 2) immunohistochemical staining in cultured rodent hippocampal neurons, and 3) immunohistochemical staining against fixed rodent brain slices. Confirmation of reactivity using more than one method improves confidence in the finding.

The availability of a biomarker like the NMDA receptor antibody allows for identification of attenuated or *forme fruste* phenotypes that might otherwise fly under the diagnostic radar (6), which in the case of anti-NMDA receptor encephalitis has so far included new-onset seizure disorders and milder encephalitis presentations. Clinical correlation must guide interpretation of antibody testing, and clinicians should be cautious about inferring causation when the phenotype is novel or improbable, when serum testing is positive only at low titer, when antibody reactivity is not confirmed through complementary laboratory techniques, and/or when CSF testing is normal. The study by Bergink et al. screened serum samples against rat brain slices and confirmed the presence of NMDA receptor antibodies using cultures of live hippocampal neurons and HEK-293 cells recombinantly expressing the NMDA receptor. A major limitation of the study is the lack of CSF confirmation (as CSF was not collected), but the serum testing that was done is compelling methodologically. Furthermore, the observed acute, self-limited neuropsychiatric phenotype would certainly be consistent with an attenuated form of classical anti-NMDA receptor encephalitis, although the lack of other typical features of anti-NMDA receptor encephalitis

in these women raises the bar for inferring causation. It will be important to evaluate the CSF in subsequent patients with postpartum psychosis who test positive for NMDA receptor antibodies. Detailed clinical phenotyping in such cases is also likely to be informative.

In the study by Bergink et al., two additional women exhibited abnormal neuropil staining on brain slices in a pattern typical of extracellular antigen binding; testing for known antigens using cell-based assays was negative (4). Screening patient serum or CSF against fixed rodent brain slices immunohistochemically can enable detection of abnormal staining patterns suggestive of an antibody response against an extracellular antigen. Clinical laboratories, however, will not typically report out such reactivity without being able to confirm binding against a validated antigen. The implication of such staining is to provide evidence of, or at least the potential for, abnormal neuroinflammation. The clinical significance of reactivity against brain slices in the absence of a known antigen requires further study both generally and in the postpartum context.

Many commercial laboratories have begun to offer neuronal autoantibody order panels categorized by phenotype (i.e., autoimmune encephalitis, epilepsy, dementia, and ataxia) or clinical context (i.e., paraneoplastic). As the diagnostic endeavors of neurology and psychiatry reconverge and pathophysiological mechanisms are clarified, it will be increasingly important for psychiatrists to be aware of autoimmune encephalitis syndromes with prominent psychiatric features and available antibody testing. Further study and validation is needed, but psychiatrists and neurologists should consider the potential role of abnormal brain inflammation—and anti-NMDA receptor encephalitis specifically—in the evaluation of women with postpartum neuropsychiatric syndromes.

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