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Do Maternal Anti–*N*-Methyl-D-Aspartate Receptor Antibodies Promote Development of Neuropsychiatric Disease in Children?

N-methyl-D-aspartate receptor (NMDAR) immunoglobulin G (IgG) is thought to be among the most frequent antineuronal antibodies in clinically asymptomatic individuals.[1,2] Whether maternal antibodies in asymptomatic NMDAR-IgG carriers reach the fetal brain and affect fetal development promoting neurodevelopmental disorders remain unknown. In this issue of *Annals of Neurology*, Jurek et al[3] establish a murine model of in utero exposure to human NMDAR antibodies to determine whether maternal autoantibodies are a risk factor for impaired brain development in the neonate.

NMDAR encephalitis is the most frequent antibody-associated encephalitis.[4] Evidence suggests that maternal immune responses against distinct neuronal proteins could influence development of autism spectrum disorder, learning disability, and schizophrenia.[5–8] Maternal transfer of antibodies occurs during the early stage of the second trimester of gestation, when the blood–brain barrier is still permeable,[9] creating a critical window for potentially harmful antineuronal antibodies to compromise fetal brain development. The seroprevalence of up to 1% creates a considerable subgroup of asymptomatic pregnant women at risk of transferring the NMDAR antibodies to the fetus.[1] Antibodies against the NR1 (GluN1) subunit of the NMDAR bind and crosslink the receptor, eventually leading to receptor internalization. The resulting alteration in postsynaptic currents and impairment of long-term potentiation lead to a characteristic clinical phenotype of progressive psychiatric symptoms, cognitive impairment, seizures, and speech problems.[4] To assess gestational antibody transfer, the authors established a mouse model of in utero exposure to human monoclonal NR1 antibodies. Recombinant human monoclonal NR1-reactive IgG antibodies, previously cloned from 2 female patients with acute NMDAR encephalitis,[10] were injected into the peritoneum at gestational days 13 and 17. Control mice were injected with an isotype-matched control antibody. Jurek et al observed that antibodies transferred across the placenta and bound to synaptic structures within the neonatal brain. Furthermore, NMDAR density was reduced and electrophysiological properties were altered in early postnatal life. Mortality was increased in NR1 antibody–exposed offspring. Surprisingly, maternal anti-NMDAR antibodies delayed neurodevelopment in neonates, reduced anxiety behavior, and impaired prepulse inhibition in adult offspring.

To translate these finding from a murine model to a clinical setting, the authors compared serum anti-NR1 IgG reactivity by flow cytometry in mothers of children with psychiatric disorders to those of mothers with healthy children. NMDAR antibody titers were slightly higher in the mothers of affected children, suggesting that asymptomatic mothers of affected children may transmit antibodies vertically to the unborn fetus, predisposing their offspring to a spectrum of psychiatric disorders.

Diaplacental antibody transfer is a key mechanism of maternal immune protection of the fetus. Maternal IgG is transferred via neonatal Fc-receptor at the beginning of the second trimester (Fig). However, only limited data are available regarding gestational transfer of maternal antibodies in diseases with antineuronal antibodies.[5–8,11] Maternal–fetal antibody transfer has been shown to have deleterious effects in murine models of anti-NR2B (GluN2B) antibodies, anti-Caspr2 antibodies, and anti–fetal brain antibodies from mothers of children with autism spectrum disorder. Pathogenic mechanisms of these transferred antibodies include disruption of NMDAR currents and NMDAR hypofunction. One could envisage that NMDAR hypofunction at a critical gestational age could lead to persistent neurologic deficits that predispose to neuropsychiatric disorders that may occur long after antibody clearance. However, there are several issues that need to be addressed. First, although the elevation in NMDAR antibodies in asymptomatic mothers was statistically significant, it was quite small. Thus, it is important to replicate the findings in this investigation and confirm the effect size. The authors provide evidence that diaplacentally transmitted NMDAR antibodies accumulate

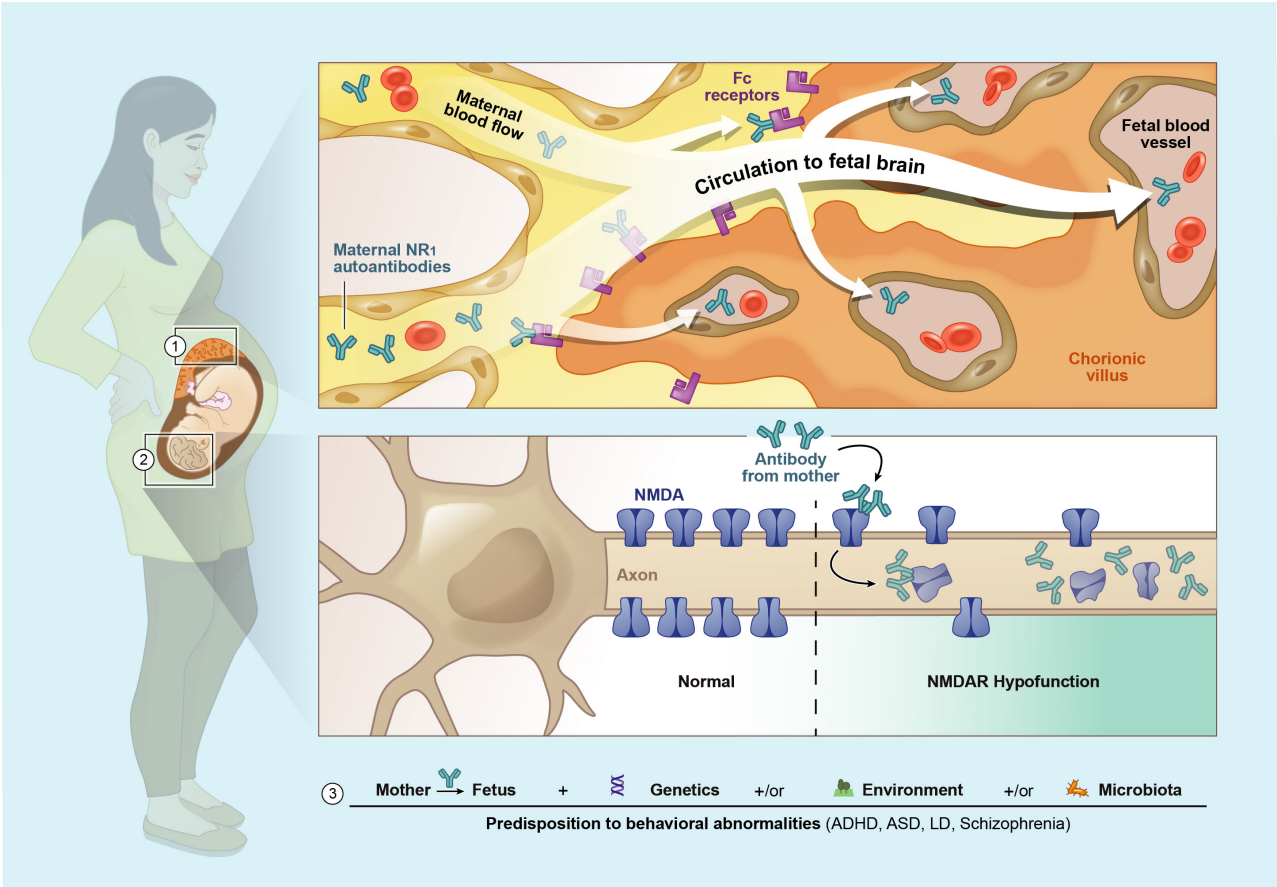

FIGURE: Model illustrating how maternal–fetal transfer of human anti–*N*-methyl-D-aspartate receptor (NMDAR) antibodies may lead to downregulation of NMDAR and development of neuropsychiatric abnormalities. (1) Maternal autoantibodies targeting the NR1 subunit of the NMDAR are diaplacentally transferred during pregnancy via neonatal Fc receptors on chorionic villi. (2) Enrichment of maternal anti-NMDAR antibodies in the fetal brain results in reduction and hypofunction of NMDARs. (3) In association with genetic and environmental risk factors (eg, microbiota), NMDAR hypofunction may predispose to neuropsychiatric diseases during childhood and adolescence, including attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorder (ASD), learning disabilities (LD), and schizophrenia.

in the fetus, a possibility that should be addressed more thoroughly in animal models. Finally, the observed spectrum of associated neuropsychiatric diseases is very broad and only a small subgroup of children become symptomatic, as suggested by previous case studies,[12] raising the question about additional predisposing factors such as genetics and environmental variables including gut microbiota (see Fig). Systematic testing of the blood of newborns from NMDAR-seropositive asymptomatic mothers as well as longitudinal follow-up of the children is clearly needed in future studies.

The identification of maternal–fetal transfer of NMDAR antibodies from asymptomatic mothers to the fetus and the potential transmission of NMDAR encephalitis is an important step forward in our understanding of NMDAR antibody–associated pathophysiology and the potential risks that are associated with a large percentage of asymptomatic carriers. Uncovering the contribution of passively transferred anti-NMDAR antibodies to the offspring may be vital to our understanding of the pathophysiology of neuropsychiatric diseases, with potentially broad therapeutic implications.

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Potential Conflicts of Interest

S.S.Z. has served as a consultant and received honoraria from Biogen, EMD Serono, Genzyme, Novartis, Roche/Genentech, and Teva Pharmaceuticals.

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