Autoantibodies in pregnancy: A cause of behavioral disorders in the child?

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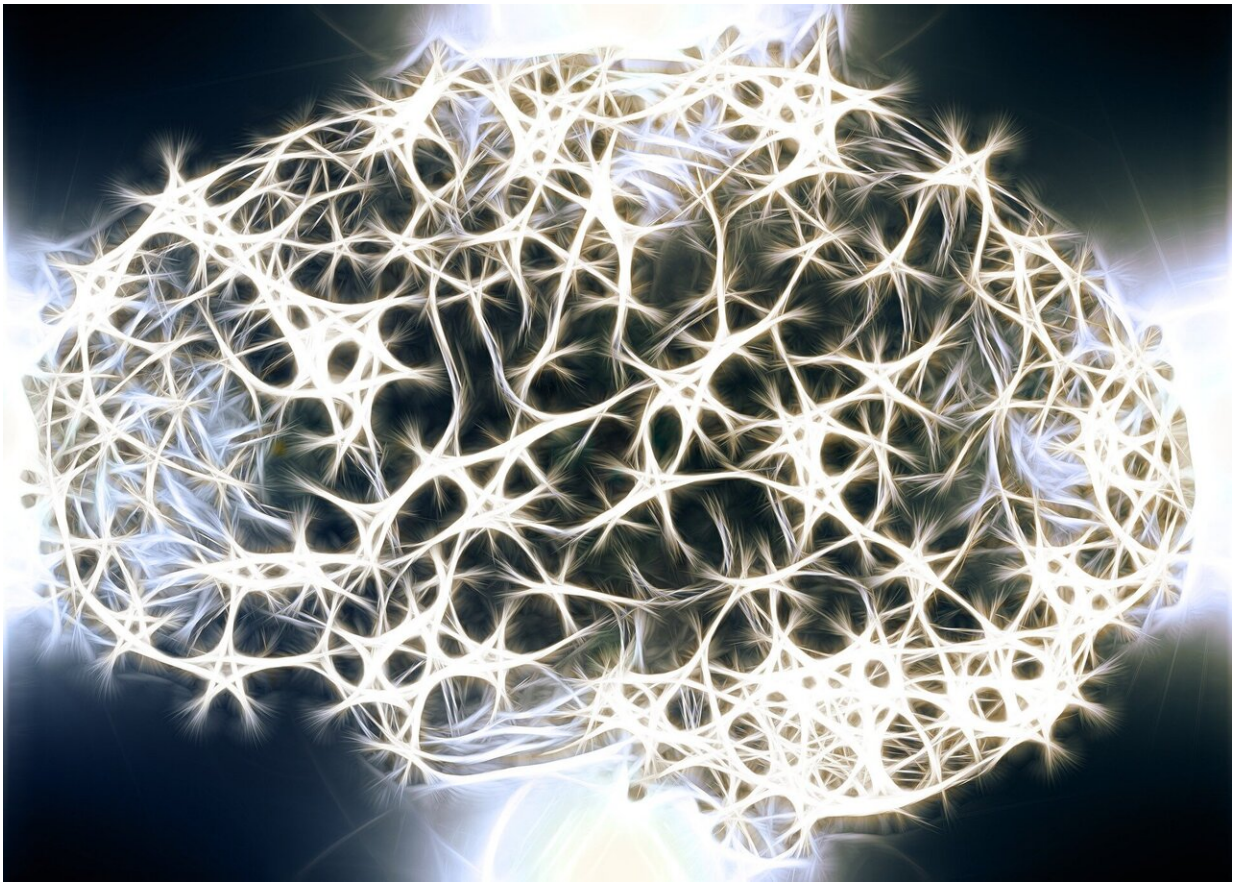

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Dysfunctions in the maternal immune system that occur during pregnancy could possibly lead to impaired brain development in the

unborn child. This is suggested by studies by the German Center for Neurodegenerative Diseases (DZNE) and Charite—Universitaetsmedizin Berlin, which are based on laboratory experiments and additional findings in humans. According to these studies, embryonic damage due to so-called autoantibodies could be a previously unnoticed cause of behavioral disorders that occur in diseases such as autism, schizophrenia and ADHD. The research results are published in the journal *Annals of Neurology*.

During pregnancy, antibodies from the mother's blood constantly enter the embryonic circulation via the umbilical cord to protect the developing child from infection. However, not all maternal antibodies are directed against foreign substances and serve to defend from pathogens. Some antibodies—known as autoantibodies—attack the body's own tissues. They may thus cause damage that can manifest, for example, as autoimmune diseases. Just like the beneficial antibodies, a pregnant woman passes on potentially harmful autoantibodies to her unborn child. This could promote the development of behavioral disorders in the child, as recent studies in animal models suggest. Initial data from studies in humans support these findings.

Dangerous Antibodies

The current study, led by Dr. Harald Pruess from the DZNE's Berlin site and the Department of Neurology with Experimental Neurology at the Charite, focused on an autoantibody that targets a specific protein on the surface of brain cells. This molecule, known as 'NMDA receptor', is essential for the interconnection of neurons and normal brain development. "The NMDA receptor antibody is a relatively common autoantibody. Data from blood donations suggest that up to one percent of the general population may carry this particular autoantibody in their blood. The reasons for this are largely unclear," said Pruess. If this autoantibody reaches the brain, serious inflammations can arise.

However, most carriers are free of such symptoms because the blood-brain barrier—a filtering tissue that surrounds the brain's blood vessels—is usually hardly penetrable for antibodies. Unless this barrier is damaged or, as with an embryo in early pregnancy, not yet fully developed.

"We investigated the hypothesis that NMDA receptor antibodies reach the brain of the embryo and cause subtle but lasting impairments during this important phase of brain development," explained Pruess. Indeed, in mice, large quantities of maternal autoantibodies were found to reach the brain of the embryo. This resulted in a reduction of NMDA receptors, altered physiological functions and impaired neuronal development. The offspring showed abnormalities in behavior and some areas of their brains were smaller compared to healthy animals. "This hitherto unknown form of pregnancy-associated brain diseases is reminiscent of psychiatric disorders caused by rubella or chickenpox pathogens. These types of infections also have a temporary effect on the brain that can have lifelong consequences," said Pruess.

Findings in humans

In humans, initial analyses of data from a group of 225 mothers suggest that these autoantibodies occur more frequently in women who have a child with a neurodevelopmental disorder or psychiatric disease. The mothers seem to be protected by the blood-brain barrier. "Further studies will be needed in order to confirm the link between maternal NMDA receptor antibodies and human psychiatric disorders in humans," Pruess emphasized. "However, should future research results confirm our hypothesis, tests for such antibodies in pregnant women would have to be included in prenatal screenings. Where necessary, this would allow to initiate treatments to remove the autoantibodies in order to prevent the child from suffering potentially life-long adverse health effects."

The current results may explain why previous studies have failed to demonstrate a clear link between NMDA receptor antibodies and psychiatric diseases such as schizophrenia. In newborns, the antibodies transferred by the mother are broken down within a matter of weeks. Most patients in existing studies were young adults. Therefore, when the testing for these autoantibodies took place, they had long since disappeared.

More information: Betty Jurek et al, Human gestational N -methyl- d -aspartate receptor autoantibodies impair neonatal murine brain function, *Annals of Neurology* (2019). DOI: 10.1002/ana.25552

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