The Prenatal Environment and Neuroinflammation in Autism

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The neurobiological basis for autism remains poorly understood. However, research suggests that environmental and immunological as well as genetic factors are contributors.

Although most studies of the circulating immune system have found differences in autism, until recently studies of the brain have demonstrated few signs of immune activity. Our studies showed neuroinflammation (activation of neuroglia, immune cells called microglia and astroglia) and an increase in cytokines (immune chemicals) in the brains of autistic patients compared to controls.

Neuroglia are important in neuronal (nerve cell) function. Astroglia contribute to detoxification, produce growth factors, and secrete pro- or anti-inflammatory substances after injury or in response to neuronal dysfunction. Microglia are involved in responses to injury or dysfunction, and contribute to development of connections between neurons and the ability of the immune system of the brain to detect abnormal cells.

Both astrocytes and microglia are important in the developing brain, and alterations in their function can produce changes likely to contribute to brain dysfunction in autism. The neuroinflammation we found may result from external exposures, or from abnormal functioning of these or other brain cells.

Our research group is interested in the pregnancy environment in the development of autism. Maternal antibodies, produced by immune cells after external exposures, are of particular interest because they may affect fetal brain development.

The late Dr. Reed Warren and his colleagues originally demonstrated reactivity of mothers’ blood serum to their autistic children’s lymphocytes, meaning that the mothers’ immune systems responded to these blood cells in the children as though they were “invaders.” Similarly, maternal serum can cause antibody binding to Purkinje cells (a type of nerve cell that possesses a great deal of control over the refinement of motor activities) in
the cerebellum of the fetus—evidence of an immune reaction—when injected into pregnant mice.

Autoimmune disorders associated with antibodies, such as rheumatoid arthritis, lupus and thyroid disease, are increased among mothers and other family members of autistic children. Maternal antibodies, therefore, may influence fetal brain development during pregnancy by interfering with cell signaling in the developing brain and disturbing its organization. These antibodies also might result from environmental exposures in susceptible mothers during pregnancy.

Although it has been tempting to link abnormalities in circulating cells of the immune system in autism with differences in the brain, this has never been proven. Immune activation reported in autism brain and circulating immune system differences are more likely to develop in parallel, due to disturbances in mechanisms affecting development of both systems in the fetus.

All neurotransmitter systems interact to produce normal prenatal brain maturation, and abnormalities in one may impact the development of others. One example involves the B2AR (beta-2 adrenergic receptor), which is important for normal brain and tissue maturation. We have linked overstimulation of this receptor by terbutaline, a drug used for preterm labor, with concordance for autism in nonidentical twins. (“Concordance” for autism means that both twins have the disease, while “discordance” means that one does while the other does not.)

Our study found that half of the twin pairs concordant for autism had been exposed to terbutaline for two weeks or more, while only six of the 24 discordant pairs had been exposed to the drug for an extended period. We also found an increased frequency of specific polymorphisms, or variants of the B2AR gene, that may increase the susceptibility to autism.

Animal studies show that treatment of pregnant rats with terbutaline results in offspring with changes in the brain analogous to those in autism. Overstimulation of the B2AR with terbutaline, at an age in rats equivalent to the second trimester in humans, has also resulted in postnatal B2AR cell signaling in brain and other tissues of the offspring that is similar to the signaling that normally occurs during the fetal stage but not after birth. If this animal model proves comparable to autism, the abnormal persistence of fetal patterns of development could contribute to immune activation in the autism brain, and circulating immune system differences reported in this disorder.

Our group found neuroinflammation in this rat model of prenatal B2AR overstimulation, which can be used to investigate how neuroglial activation arises and persists beyond fetal brain development. We also found protein and lipid markers of oxidative stress in autism brain tissue. This finding may reflect a fetal pattern of cell functioning, in which tissue responses are too immature to handle “normal” exposures after birth.

It is important to note that the cellular effects from overstimulation of the B2AR may be an important process in the development of autism, more than terbutaline exposure alone, because additional factors, such as maternal stress, infections, heavy metal and pesticide exposure also might produce similar results. Interestingly, interference with B2AR signaling during fetal life may result in a “set-up” for susceptibility to environmental exposures after birth. Dr. Melissa Rhodes and colleagues at Duke University have shown that terbutaline exposure in rats (at the same age equivalent as above) followed by postnatal exposure to chlorpyrifos (a pesticide) results in synergistic, additive abnormal effects in brain and other tissues.

Interference with neurotransmitter signaling, such as the case with terbutaline and the B2AR system, may have relevance to findings from research on the immune system in autism. Disordered development of one important transmitter system may result in failure of the orderly maturation of others, resulting in increased susceptibility to environmental factors.


definitions

**Terbutaline**: A drug used to prevent or treat preterm labor.

**B2AR (Beta-2 Adrenergic Receptor)**: A protein that regulates cell signaling.

**Concordance**: The condition where both twins have a disease.

**Discordance**: The condition where one twin has a disease and the other does not.

**Polymorphisms**: Variations in the DNA sequence.

**Neuroinflammation**: Inflammation of the nervous system.

**Oxidative Stress**: Excessive production of reactive oxygen species.

**Synergistic**: Working together to produce a greater effect.

**Additive**: Having an effect that is equivalent to the sum of its parts.

**Drug-Induced Neurodevelopmental Effects**: The effects of terbutaline on brain development.

Authors

Susan L. Connors, M.D., is a board certified internist who has been doing research in the field of autism at the Kennedy Krieger Institute, while raising an autistic son. Connors has completed a study of prenatal drug exposure in twins with autism, using a clinical sample and the Autism Genetic Resource Exchange, and a study of polymorphisms of the beta 2 adrenergic receptor in fraternal twins with autism spectrum disorders.

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