Maternal immune response to fetal brain during pregnancy a key factor in some autism

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New studies in pregnant mice using antibodies against fetal brains made by the mothers of autistic children show that immune cells can cross the placenta and trigger neurobehavioral changes similar to autism in the mouse pups.

A report on the research from investigators at the Johns Hopkins Children's Center published online in the *Journal of Neuroimmunology* expands on a 2008 report from the same team showing that mothers of autistic children tested positive for fetal brain antibodies. Antibodies are proteins the body naturally makes to attack foreign tissues, viruses or bacteria. Because a growing fetus is not "rejected" by the mother's immune system even though some of its DNA is "foreign" (from the father), scientists have long suspected that some combination of maternal and fetal biological protection is at work. The new research from Hopkins, however, suggests that the protective system is not perfect and that antibodies are not only made but are re-circulated back to the fetus through the placenta, possibly triggering inflammation in the brain and leading to a cascade of neurological changes resulting in neurodevelopmental disorders, such as autism.

Despite this new evidence, the researchers warn against over-interpreting the results, saying prenatal exposure to maternal antibodies is likely only one of several factors implicated in autism.

"Autism is a complex disorder and it would be naďve to assume there's a single mechanism that can cause it," says Harvey Singer, M.D., director of pediatric neurology at Hopkins Children's. "It's most likely the cumulative result of several factors, including genes, metabolism and environment. We believe we have identified one of these factors."

For the new study, Singer and colleagues injected antibodies from mothers of autistic children into pregnant mice and used several standard neurobehavioral tests to identify neurobehavioral changes in the pups. As control groups, they used offspring of mice injected with antibodies from mothers of nonautistic children and the offspring of mice who received no injections.

"Comparing mice to humans is tricky, and we should be cautious anytime we do so, but our findings strongly suggest that the behaviors we observed in the offspring of mice injected with fetal brain antibodies from human mothers did behave in a manner that mimics some behaviors seen in people with autism," Singer says.

Following the mice throughout adolescence (four to six weeks) and adulthood (four to six months), the Hopkins team measured novelty-seeking (or willingness to explore unfamiliar open spaces), response to loud noise, sociability and anxiety-like behavior.

Overall, mice exposed prenatally to antibodies from mothers of autistic children behaved more anxiously, spent less time in open spaces when placed in an elevated maze, and were overall more hyperactive, fretting back and forth between open and closed spaces in the maze and in an open field environment, both behaviors that in humans would equal abnormal activity.

Again, compared to control mice, the mice exposed to antibodies from mothers of autistic children were also more easily startled by loud noises

and were less social, choosing to spend more time visiting an empty cage rather than one with a live mouse in it.

The differences among groups were less pronounced in the adolescent mice, but as the mice aged, researchers observed an increase in autism-like symptoms, a finding consistent with neurodevelopmental disorders in humans, who tend to develop new or more pronounced symptoms over time, investigators point out.

Comparing brain tissues from all groups of mice, researchers observed markedly more activation of microglia -- immune cells in the central nervous system activated during inflammation - in the brain tissues of the group injected prenatally with antibodies from mothers of autistic children.

In further studies, the Hopkins scientists hope to identify which specific brain proteins the antibodies affect and to correlate changes in brain anatomy and function to changes in behavior.

Ultimately, researchers hope to develop ways to detect and analyze culprit antibodies in pregnant women and prevent them from binding to fetal brain proteins.

The causes of autism, a disorder manifesting itself with a range of brain problems, impaired social interactions, communication disorders and repetitive behaviors, remain unknown for an estimated 90 percent of children diagnosed with it. Genetic, metabolic and environmental factors have been implicated in various studies of autism, which affects an estimated 1 in 150 U.S. children, according to the Centers for Disease Control and Prevention.

Source: Johns Hopkins Medical Institutions