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Prenatal exposure to maternal antibodies linked to autistic behaviors in offspring

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New research from the UC Davis M.I.N.D. Institute shows that an interaction between fetal brain cells and maternal antibodies could be linked with the repetitive behavior – also called stereotypies – that is characteristic of autism. While additional studies are needed to confirm the outcome, this result leads investigators to suspect that brain-directed antibodies during the prenatal period could be a causal factor for the disorder. The study appears online now and will be published in a future issue of Brain, Behavior and Immunity.

The study builds on recent research led by UC Davis immunologist Judy Van de Water (to be published in the March 2008 issue of *Neurotoxicology*) showing that IgG antibodies from the blood of mothers of children with autism react against fetal brain proteins. The outcome was predominant with IgG samples from mothers of children with the regressive form, rather than the early onset form, of the disorder. Her outcome raised the possibility that some cases of autism may be linked to antibody transplacental transfer during pregnancy which, in turn, affects the growing brain.

“Dr. Van de Water’s result implicated maternal immune system factors with at least one form of autism,” said neuroscientist David Amaral, research director of the M.I.N.D. Institute and senior author of the current study. “We wanted to take that important finding a step further and find out if IgG exposure during pregnancy could cause the kinds of changes in social interactions or behavior we see in children with autism.”

To test this hypothesis, Amaral and his research team at the California National Primate Research Center exposed eight rhesus monkeys to human IgG at three times during the end of the first trimester of pregnancy. Four monkeys received IgG from mothers of children with autism, while four received antibody isolated from the blood of mothers of typically developing children to ensure that any potential outcomes were not due to human IgG exposure. Five monkeys received no treatment whatsoever and were included as study controls. The behavior and social interactions of all 13 offspring were then carefully observed and recorded over the course of a year-and-a-half in a variety of familiar and novel settings.

The team identified only mild social alterations in the four monkeys treated with IgG from mothers of children with autism. The monkeys' behavior, however, was notably distinct, since all of them exhibited repetitive activities such as pacing, backflipping, twirling and swinging with much greater frequency and for longer periods of time than other monkeys in the study. The stereotypies were most pronounced after weaning and were even more striking in unfamiliar settings.

"The major significance of this study is that it links exposure to abnormal immune system factors during pregnancy with specific behavioral outcomes in offpsring," said Amaral. "The monkeys' behavior is profoundly changed from normal, and those changes are similar to impairments that we see in children with autism. The study adds to increasing evidence that immune system factors of mothers could contribute to the development of some forms of autism."

While the finding is remarkable, the results must be replicated in a larger, more comprehensive study before prenatal IgG exposure can be confirmed as a risk factor for autism. At that point, the researchers are hopeful that clinical protocols can be developed to identify this risk factor during pregnancy.

“We started with a small study to see if our assumptions had merit, and that definitely proved to be true,” said Amaral. “If a more exhaustive study has the same results, we will be able to say with confidence that we’ve identified a causal factor for some cases of autism. The goal after that will be to define blood tests that isolate IgG as a diagnostic marker.”

One of many forms of antibodies in blood serum, IgG typically crosses the placenta as a protective agent for the growing fetus and newborn child. However, antibodies formed against one’s own body (autoantibodies) are implicated in disorders such as lupus, multiple sclerosis and arthritis. The known links between IgG and the prenatal environment and autoimmune-mediated disorders is what originally persuaded Van de Water to test the potential role of fetal-brain-specific IgG in autism.

The presence of stereotypies is part of one major symptom category – in addition to social deficits and language impairments – of the autism diagnosis. Clinicians do not know for certain why children with autism tend to repeatedly, for instance, rock, flap their hands, twirl objects or walk on their toes. It has been surmised that the repetition might help reduce anxiety or could be related to damage in specific parts of the brain. This new research provides evidence that brain-directed antibodies in the immune systems of mothers may provide part of the answer.

“If we confirm that these antibodies are a risk factor for autism, it’s possible that they could be removed through treatments much like those used for autoimmune and inflammatory diseases,” said study lead author Martin, who is now an assistant professor in the Department of Psychology at Azusa Pacific University and was a postdoctoral fellow in the Amaral lab when the study was conducted. “It’s early in the research process to consider specific therapies, but it is clear that our result should lead to a much greater emphasis in autism science on immune

system links to the disorder.”

Source: University of California - Davis