Study finds exposure to maternal antibodies affects behavior

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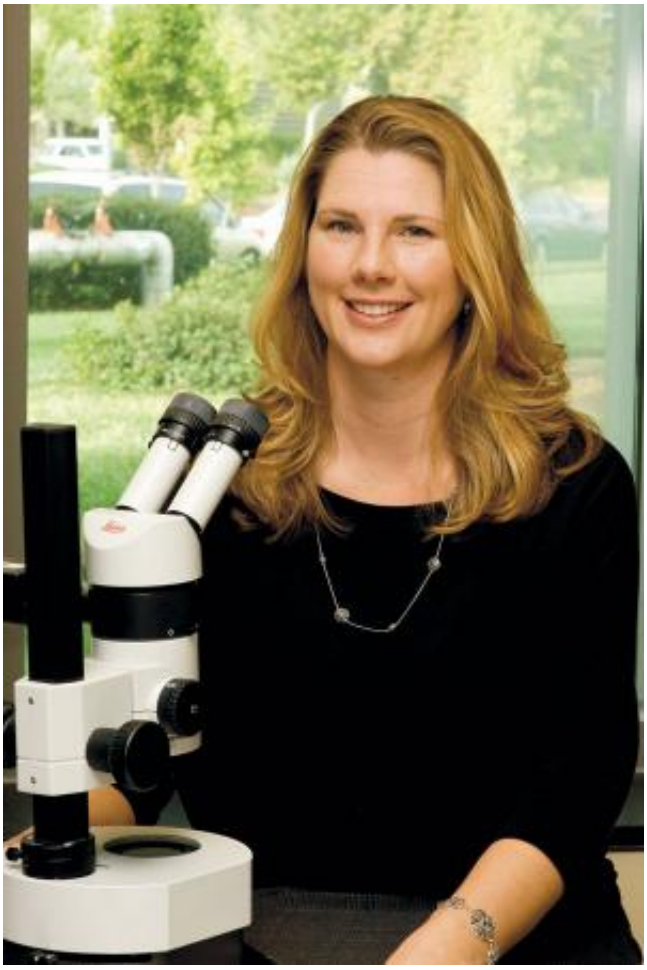

This is Assistant Adjunct Professor Melissa Bauman, University of California - Davis. Credit: UC Regents

Researchers with the UC Davis MIND Institute have found that prenatal

exposure to specific combinations of antibodies found only in mothers of children with autism leads to changes in the brain that adversely affect behavior and development.

The researchers said that the highly specific immunoglobulin-G (IgG) autoantibodies cross the placenta during pregnancy to impact fetal brain development, resulting in a form of autism that the researchers now are calling maternal antibody-related (MAR) autism. The researchers said that MAR autism cases could represent as much as 23 percent of all autism cases.

The research is published online today in *Translational Psychiatry*, a *Nature* journal.

During gestation, maternal IgG antibodies normally cross the placenta and protect the fetus, conferring the mother's immunities to the developing child. However, in addition to protective antibodies, autoantibodies that react to fetal proteins can also cross the placenta, essentially attacking fetal tissue.

The current study is an extension of an earlier study conducted in 2008. It explores the effects of the autism-specific IgG antibodies in a non-human primate model. Non-human primates live in complex social groups and use many forms of social communication. In addition, portions of the human brain, such as the prefrontal cortex, are poorly developed in other animal models, such as rodents, but are highly developed in the rhesus monkey.

For the study, a group of pregnant female monkeys were exposed to IgG purified from mothers of children with autism that exhibited fetal brain reactivity—the IgG-ASD group; a second group of pregnant female monkeys received IgG antibodies from the mothers of typically developing children. The third group included untreated animals that did

not receive antibodies.

The study's lead researcher is Melissa D. Bauman, UC Davis assistant adjunct professor in the UC Davis Department of Psychiatry and Behavioral Sciences, and a faculty member at the MIND Institute. To evaluate development in the IgG-ASD offspring, Bauman and her colleagues carried out a comprehensive evaluation of behavioral development and periodically conducted longitudinal magnetic resonance imaging (MRI) of the monkeys' brain development during the first two years of life.

"The offspring of IgG-ASD antibody treated mothers consistently deviated from species-typical behavioral development of young rhesus monkeys," Bauman said. Early in development, the monkey mothers treated with IgG-ASD antibodies were much more protective of their offspring. For example, the IgG-ASD treated mothers more frequently approached and contacted their infants and remained in close proximity to them.

The mothers may have detected behavioral abnormalities in their IgG-ASD offspring that were so subtle that they escaped the researchers' attention, Bauman said. "The heightened protectiveness of the monkey mother's was observed only when other animals were present, suggesting that the mothers perceived a greater risk to their IgG-ASD treated infants," she said.

Other alterations in behavior were observed as the animals matured. For example, the offspring of the IgG-ASD antibody-treated animals more frequently approached other infants in their rearing group. "Even more strikingly, as they grew older, the IgG-ASD offspring increased their approaches to unfamiliar peers," she said. "Inappropriately approaching a novel animal is highly unusual and potentially dangerous for young rhesus monkeys."

Social interactions such as grooming or playing often occur when a young rhesus monkey approaches a peer. Despite the higher frequency of their approaches, the IgG-ASD offspring did not interact socially with peers more often than did the offspring whose mothers did not receive IgG-ASD antibodies. "In fact, there actually was a trend for the IgG-ASD offspring to receive less grooming from their same-age peers," she said. "It is possible that there were subtleties in the demeanor of the IgG-ASD offspring that dissuaded their peers from interacting with them."

These new behavioral findings build upon previous studies exploring the role of maternal antibodies in autism, including a pilot study conducted in non-human primates in 2008. During the past five years, study co-author Judy Van de Water and her colleagues have made substantial progress in characterizing which maternal antibodies are highly specific to autism. Van de Water with colleagues Rob Berman and Daniel Braunschweig recently reported that mouse offspring prenatally exposed to these autism-specific antibodies exhibit altered physical and social development, including anxiety and social behavior.

"The non-human primate study provides an exciting look at the pathologic effect of these autism-specific maternal antibodies," said Judy Van de Water, who originally described the association between maternal antibodies to fetal brain proteins and ASD.

In addition to the behavioral changes, MRI analysis of the brains revealed altered patterns of neurodevelopment in the monkey offspring exposed to the IgG-ASD antibodies. The rate of brain growth was significantly faster in the male, but not female, IgG-ASD offspring, when compared with that of the control offspring. The total brain volume of the male IgG-ASD offspring also was significantly greater than normal, the researchers found.

While it is not clear why prenatal exposure to these antibodies only alters

brain volume in the male offspring, a similar trajectory of abnormal brain development has been observed in male children with autism. Recent research from the MIND Institute has reported that boys with autism who were exposed prenatally to the same antibodies have significantly larger brains than boys with autism born to mothers without the IgG-ASD antibodies and typically developing control groups.

"The combination of brain and behavioral changes observed in the nonhuman primate offspring exposed to these autism-specific antibodies suggests that this is a very promising avenue of research." Bauman adds that this unique interdisciplinary study requires a team of researchers with expertise in immunology, animal behavior and neuroscience thus "highlighting the collaborative efforts that characterize research at the UC Davis MIND Institute."

David Amaral, research director of the MIND Institute and senior author of the paper, noted "that much research remains ahead of us to identify the mechanisms by which the antibodies affect brain development and behavior. But, this program of research is very exciting, because it opens pathways to potentially predicting and preventing some portion of future autism cases."

Provided by UC Davis