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Maternal immune dysfunction linked to risk of autism with intellectual disability in children

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Pregnant women with higher levels of inflammatory cytokines and chemokines, proteins that control communication between cells of the immune system, may be at significantly greater risk of having a child with autism combined with intellectual disability, researchers with the UC Davis MIND Institute have found.

The research also suggests a potential immune profile for the differentiation of autism combined with intellectual disability, as distinct from either autism or developmental disability alone.

"Inflammation during the second trimester in the mothers of children with autism who also have intellectual disability was significantly greater than in mothers of children autism without intellectual disability in our study," said Judy Van de Water, professor of Internal Medicine in the Division of Rheumatology, Allergy and Clinical Immunology and a researcher affiliated with the UC Davis MIND Institute.

"However, equally significant was that profiles of mothers whose children go on to be diagnosed with autism and intellectual disability differed markedly from those whose children have intellectual disability without autism, as well as from the typically developing general population," said Van de Water, director of the UC Davis Center for Children's Environmental Health and the study's senior author.

"Their profiles are distinct from all of the other groups that we studied, based on their cytokine and chemokine profiles," Van de Water continued. "This finding suggests an avenue that we will explore to potentially identify possible markers to separate sub-phenotypes in the autism population."

The study is published online in *Molecular Psychiatry*, a Nature publication.

Chemokines have been shown to regulate the migration, proliferation and differentiation of neuronal cells, and studies have identified the roles of specific cytokines during neurodevelopment, such as influencing neurogenesis, neuronal and glial cell migration, proliferation, differentiation and synaptic maturation and pruning.

The large, diverse, population-based study was conducted using blood serum samples obtained from the California Department of Public Health of mothers in the Kaiser Permanente Early Markers for Autism Study -- 184 whose children developed autism and intellectual disability (previously known as mental retardation), 201 who had children with autism without intellectual disability, 188 whose children had developmental disability alone and 428 general population control participants.

The largely Southern California-based study was designed to evaluate biomarkers for autism. Women were eligible for participation if they delivered their infants between July 2000 and September 2003. The participants were largely from Orange, San Diego or Imperial counties.

The researchers examined the mothers' mid-gestational blood serum levels of 22 different cytokines and chemokines, including GM-CSF, IL-1Alpha, IL-6, and IFN-Gamma.

"The fact that we see this increase in inflammatory markers with the autism/intellectual disability group compared with all of the other reference groups is striking, because the ones we're seeing that are affected are usually down-regulated during the second trimester of pregnancy," said Karen L. Jones, study first author and a post-doctoral fellow in the Division of Rheumatology, Allergy and Clinical Immunology. "This really is suggesting that there is a lack of the immune regulation in these moms that is typically associated with a healthy pregnancy."

The authors postulate that alterations in the gestational immune environment among mothers of children autism with intellectual disability may lead to alterations in the neurodevelopmental trajectory of the developing fetus, which may subsequently result in the altered behavioral phenotype characteristic of children with autism and intellectual disability.

The researchers noted that maternal immune activation represents one of several pathways that can result in differences in maternal cytokines, including environmental toxicants such as pesticides, polychlorinated biphenyls and polybrominated diphenyl ethers. Mid-gestational maternal cytokine and chemokine levels also may interact with

other potential risk factors, such as parental genetics.

"It is particularly exciting that this work does start to tease apart a potential source of differences in autism with and without intellectual disability, as well as from intellectual disability without autism," Jones said.

"This study is incredibly valuable because it helps us understand more about the sources of variability within autism spectrum disorder, providing important insights into the different neurobiological mechanisms underlying important subtypes of the disorder," said Leonard Abbeduto, director of the MIND Institute.

"At the same time, the study reinforces the importance of the maternal immune system in to a host of child outcomes. Most importantly, this study brings us closer to knowing how to prevent adverse developmental outcomes," he said.

Source:
University of California - Davis Health System
