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Excessive cerebral spinal fluid, enlarged brain size in infancy are potential biomarkers for autism

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Children who were later diagnosed with autism spectrum disorder had excessive cerebral spinal fluid and enlarged brains in infancy, a study by a multidisciplinary team of researchers with the UC Davis MIND Institute has found, raising the possibility that those brain anomalies may serve as potential biomarkers for the early identification of the neurodevelopmental disorder.

The study is the first to follow the brain-growth trajectories from infancy in children who later develop autism and the first to associate excessive cerebrospinal fluid during infancy with autism. "Early Brain Development and Elevated Extra-Axial Fluid in Infants who Develop Autism Spectrum Disorder," is published online today in the neurology journal *Brain*, published by Oxford University Press.

"This is the first report of an infant brain anomaly associated with autism that is detectable by using conventional structural MRI," said MIND Institute Director of Research David Amaral, who co-led the study.

"This study raises the potential of developing a very early method of detecting autism spectrum disorder. Early detection is critical, because early intervention can decrease the cognitive and behavioral impairments associated with autism and may result in more positive long-term outcomes for the child," Amaral said.

The study was conducted in 55 infants between 6 and 36 months of age, 33 of whom had an older sibling with autism. Twenty-two infants were children with no family history of the condition.

The researchers reported that the brain anomaly was detected significantly more often in the high-risk infants who were later diagnosed with autism between 24 and 36 months. Prior research by Sally Ozonoff, the vice chair for research and professor in the Department of Psychiatry and Behavioral Sciences, who co-led the study, has shown that the risk of autism is nearly 20 times greater in siblings of children with autism than in the general population. The U. S. Centers for Disease Control and Prevention puts the overall incidence of autism at 1 in 88.

The excessive cerebrospinal fluid and enlarged brain volume were detected by periodically measuring the infants' brain growth and development using magnetic resonance imaging (MRI), and by regularly assessing their cognitive, social, communication and motor development. Both the high- and low-risk infants underwent their first MRI scans at 6 to 9 months. The second MRI scans occurred when they were 12 to 15 months old. The third was conducted between 18 and 24 months. The MRIs were conducted while the infants were sleeping naturally, without the need for sedation or anesthesia.

At 6 months, the researchers began intensive behavioral assessments of the infants' development. Their parents also periodically completed questionnaires about their babies' behaviors. These tests were conducted until the infants were 24 to 36 months old, when each child was evaluated as having autism spectrum disorder, other developmental delays, or typical development.

In addition to the 10 children diagnosed with autism, 24 percent of the high-risk and 13.5 percent of the low-risk infants were classified as

having other developmental delays. Some 45.5 percent of high-risk and over 86 percent of low-risk babies were found to be developing normally.

The researchers found that by 6 to 9 months of age, the children who developed autism had elevated cerebrospinal fluid levels in the "extra-axial" space above and surrounding the brain, and that those fluid levels remained abnormally elevated between 18 to 24 months of age. The more fluid during early infancy, the more severe were the child's autism symptoms when diagnosed, the study found.

In the infants who would go on to be diagnosed with autism, the "extra-axial" fluid volume was, on average, 33 percent greater at 12 to 15 months and 22 percent greater at 18 to 24 months, when compared with typically developing infants. At 6 to 9 months, the extra-axial fluid volume was 20 percent greater, when compared with typically developing infants.

The study also provided the first MRI evidence of brain enlargement in autism prior to 24 months. The infants in the study diagnosed with autism had, on average, 7 percent larger brain volumes at 12 months, compared with the typically developing infants.

The excessive extra-axial fluid and enlarged brain volume were detected by brain imaging before behavioral signs of autism were evident. "The cause of the increased extra-axial fluid and enlarged brain size is currently unknown", Amaral said.

Early diagnosis may be of particular benefit to infants whose older siblings have been diagnosed with autism, but the researchers caution that this finding must be replicated before it could aid in the early diagnosis of ASD. The MIND Institute is currently collaborating with other research institutions to replicate these findings and to evaluate how

well the potential biomarker can accurately predict a later diagnosis of ASD.

"It is critical to understand how often this brain finding is present in children who do not develop autism, as well," said Ozonoff. "For a biomarker to be useful in predicting autism outcomes, we want to be sure it does not produce an unacceptable level of false positives."

"If this finding of elevated extra-axial fluid is replicated in a larger sample of infants who develop autism, and it accurately distinguishes between infants who do not develop autism, it has the potential of becoming a noninvasive biomarker that would aid in early detection, and ultimately improve the long-term outcomes of these children through early intervention," said Mark Shen, UC Davis graduate student and the study's lead author.

Provided by UC Davis