Study: First Evidence of Immune Response Targeting Brain Cells in Autism

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Evidence of T-lymphocyte attack on specific brain cells could explain more than half of all cases of autism and provide potential therapeutic targets

- Post-mortem analysis of brains of people with autism revealed cellular features not previously linked to autism.
- These cellular characteristics are

consistent with an immune response targeting on the brain cells that comprise a protective barrier between brain tissues and cerebral spinal fluid.
- The findings lend new insight to autism's origins and suggest potential means of improved diagnosis and care of people with autism.

BOSTON – Autism spectrum disorders affect one in 59 American children by age eight. With no known quantitative biological features, autism diagnoses are currently based on expert assessments of behavioral symptoms, including impaired social skills and communication, repetitive behaviors and restricted interests.

In a paper published in *Annals of Neurology*, Matthew P. Anderson, MD, PhD, a physician-scientist at Beth Israel Deaconess Medical Center (BIDMC), and colleagues report the presence of cellular features consistent with an immune response targeting specialized brain cells in more than two thirds of autistic brains analyzed postmortem. These cellular characteristics – not previously observed in autism – lend critical new insight into autism's origins and could pave the way to improved diagnosis and treatment for people with this disorder.

"While further research is needed, determining the neuropathology of autism is an important first step to understanding both its causes and potential treatment," said Anderson, who is Chief of Neuropathology in the Department of Pathology at BIDMC and an Associate Professor

of Pathology at Harvard Medical School. “Investigators typically aim potential treatments at specific pathologies in brain diseases, such as the tangles and plaques that characterize Alzheimer’s disease and the Lewy bodies seen in Parkinson’s. Until now, we have not had a promising target like that in autism.”

Anderson was examining brains donated to Autism BrainNet, a non-profit tissue bank, when he noticed the presence of perivascular lymphocyte cuffs – an accumulation of immune cells surrounding blood vessels in the brain. He also noted mysterious bubbles or blisters that scientists call blebs accumulating around these cuffed blood vessels. Anderson and colleagues subsequently found these blebs contained debris from a subset of brain cells called astrocytes.

Not previously linked to autism, perivascular lymphocyte cuffing is a well-known indicator of chronic inflammation in the brain. Lymphocyte cuffs in the brain are telltale signs of viral infections or autoimmune disorders. But the pattern Anderson observed did not match any previously documented infection or autoimmune disorder of the brain. In the brains Anderson examined, the cuffs were subtle but distinct. “I’ve seen enough brains to know you shouldn’t see that,” he said.

To find out if the perivascular lymphocyte cuffs in this sample of autistic brains were linked to autism spectrum disorder, Anderson and colleagues compared 25 brains from donors diagnosed with the disorder to 30 brains from

neurotypical brain donors. These neurotypical control cases were selected to approximate the age range and medical histories of the autism group. Present in more than two-thirds of the autistic brains, perivascular lymphocyte cuffing significantly surpassed that in the control cases.

In a second set of experiments, Anderson's team determined that the perivascular cuffs were made up of killer T-cells, a subset of immune cells responsible for attacking and killing damaged, infected or cancerous cells or normal cells in autoimmune diseases. With no apparent evidence of viruses known to infect the brain, the presence of these tissue-attacking immune cells throughout the autistic brains suggested one of two scenarios, explained Anderson. Either the T-cells are reacting normally to a pathogen such as a virus, or they are reacting abnormally to normal tissue – the definition of an autoimmune disorder.

"With this new research, we haven't proved causality, but this is one clue in support of the idea that autism might be an autoimmune disorder, just like multiple sclerosis is thought to be," said Anderson.

In future research, Anderson and colleagues will work to develop a genetically-engineered animal model of this T-lymphocyte cuffing neuropathology in which to conduct studies to determine mechanism as well as cause and effect. The team also plans to search for biomarkers – a measurable diagnostic signature in patients' urine or blood or other tissues – that may be used to identify these newly-documented

cellular features in living patients. In turn, these biomarkers could one day assist clinicians in the diagnosis and long-term care of people with autism.

In addition to Anderson, co-authors include Marcello DiStasio, MD, PhD, Ikue Nagakura, PhD, and Monica Nadler, PhD, all of Beth Israel Deaconess Medical Center.

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