First evidence of immune response targeting brain cells in autism

Autism Featured Neurology Neuroscience · October 17, 2019

Summary: *Examining postmortem brains of ASD patients, researchers discover an accumulation of immune cells surrounding blood vessels in the brain. They also found blebs accumulating around blood vessels that contained astrocyte debris. The findings suggest autism may be an autoimmune disorder.*

Source: *BIDMC*

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.

ABOUT THIS NEUROSCIENCE RESEARCH ARTICLE

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"T-lymphocytes and Cytotoxic Astrocyte Blebs Correlate Across Autism Brains". Marcello M. DiStasio MD, PhD Ikue Nagakura PhD Monica J. Nadler PhD Matthew P. Anderson MD, PhD.

Annals of Neurology doi:10.1002/ana.25610.

Abstract

T-lymphocytes and Cytotoxic Astrocyte Blebs Correlate Across Autism Brains

Objective

Autism spectrum disorder (ASD) affects 1 in 59 children yet, except for rare genetic causes, the etiology in most ASD remains unknown. In the ASD brain, inflammatory cytokine and transcript profiling show increased expression of genes encoding mediators of the innate immune response. We evaluated post-mortem brain tissue for adaptive immune cells and immune cell-mediated cytotoxic damage that could drive this innate immune response in the ASD brain.

Methods

Standard neuropathology diagnostic methods including histology and immunohistochemistry were extended with automated image segmentation

to quantify identified pathologic features in the postmortem brains.

Results

We report multifocal perivascular lymphocytic cuffs contain increased numbers of lymphocytes in ~65% of ASD compared to control brains in males and females, across all ages, in most brain regions, and in white and grey matter, and leptomeninges. CD3+ T-lymphocytes predominate over CD20+ B-lymphocytes and CD8+ over CD4+ T-lymphocytes in ASD brains. Importantly, the perivascular cuff lymphocytes numbers correlate to the quantity of astrocyte-derived round membranous blebs. Membranous blebs form as a cytotoxic reaction to lymphocyte attack. Consistent with multifocal immune cell-mediated injury at perivascular CSF-brain barriers, a subset of white matter vessels have increased perivascular space (with jagged contours) and collagen in ASD compared to control brains. CSF-brain barrier pathology is also evident at cerebral cortex pial and ventricular ependymal surfaces in ASD.

Interpretation

The findings suggest dysregulated cellular immunity damages astrocytes at foci along the CSF-brain barrier in ASD.

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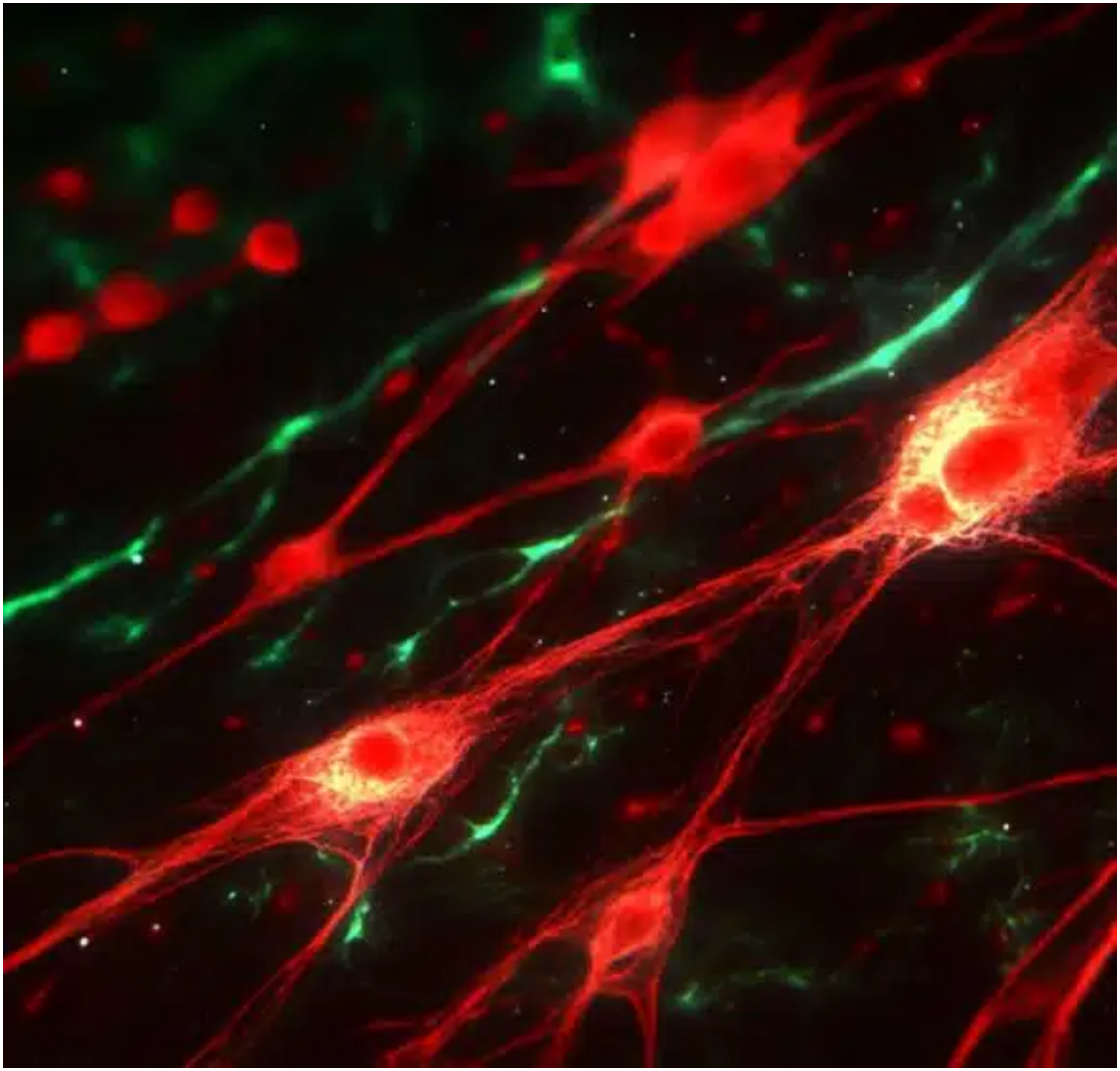

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One Comment

Rosie BazarWard

October 29, 2019 at 8:17 pm

So autoimmune drug therapy? I finally sat down and watched ‘Brain on Fire.’ The main character was successfully treated and recovered from her autoimmune encephalitis with autoimmune drug therapy. Do you really have to get a brain biopsy for this kind of treatment? Do you really have to shell out a million dollar workup to even be considered? Can’t a kid who regressed into

autism be lumped into this kind of treatment? This isn't just the first time someone discovered inflammation is going on in ASD.

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