Study: Multiple sclerosis blood antibodies found to be toxic to neurons

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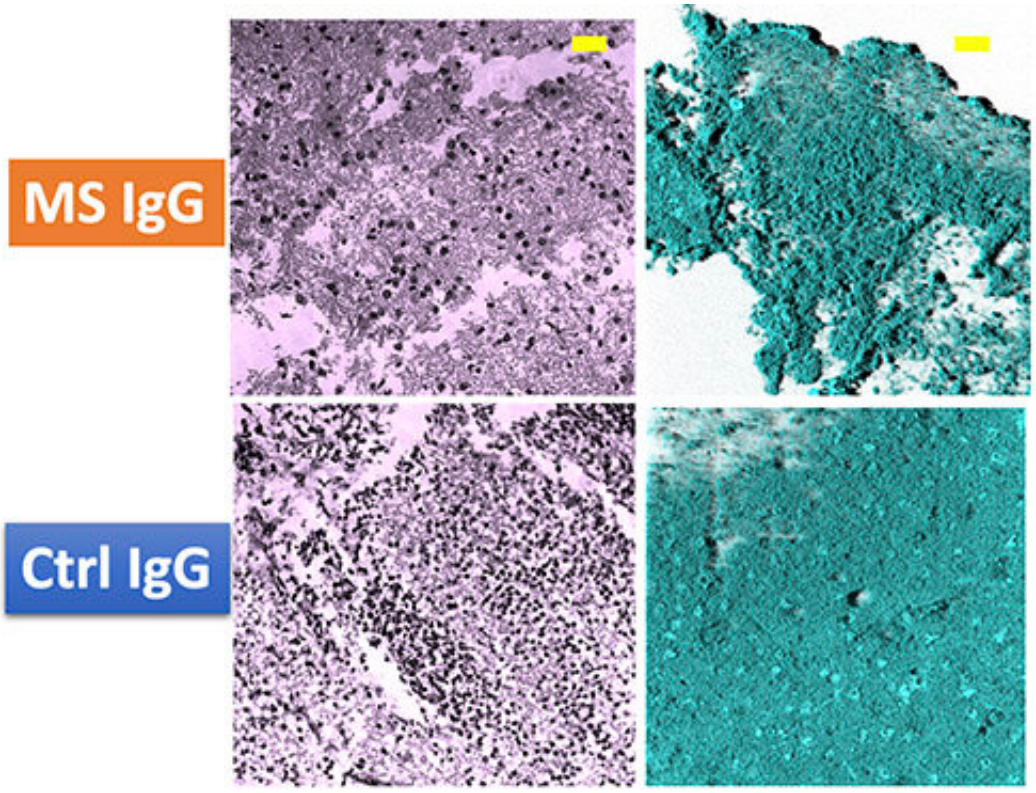

The difference in neuronal death between plasma IgG samples from MS patients and control samples. Credit: CU Anschutz Medical Campus

A University of Colorado Anschutz Medical Campus research team has discovered that the immunoglobulin G (IgG) antibodies in the plasma of multiple sclerosis (MS) patients are toxic to neurons, a finding the lead investigator said could transform the field of study.

The team found that plasma IgG aggregates—antibody clusters formed by individual IgG molecules that are at least six times bigger than the individual IgG—are behind the neuronal death.

"This is the discovery of my entire research career," said Xiaoli Yu, Ph.D., an associate professor in the Department of Neurosurgery at the University of Colorado School of Medicine. "I think these findings could represent a paradigm shift in MS research."

MS, an autoimmune disease characterized by neuronal loss and demyelination in the central nervous system, currently has no cure. Yu said her team's study, recently published in *Cell Death & Disease* titled "Multiple sclerosis plasma IgG aggregates induce complement-dependent neuronal apoptosis," offers a novel mechanism of neuron death that could lead to new effective treatments and therapies.

"We still don't know why the molecules aggregate in this way," she said, "but that's the nature of science: You discover one layer, and then you go to the next."

Nearly 1 million people in the United States and 2.8 million people worldwide live with MS. The disease damages nerves, disrupting signals between the brain and the rest of the body. MS is the most common disabling neurological disease of young adults, Yu said, with symptoms typically starting between the ages of 20 and 40.

In our interview, Yu talks about the study, why it's controversial, and how it could advance novel therapeutics that inhibit toxic antibodies. The interview has been edited and condensed.

Why is this study significant?

Our bodies produce antibodies—proteins that attack viruses and

bacteria. In the 1940s, Dr. Elvin Kabat (a leading quantitative immunochemistry researcher) developed the first reliable immunodiagnostic test for multiple sclerosis. He discovered that in most cases of MS, there was an increase in cerebrospinal fluid gamma globulin. He found that oligoclonal bands had a component containing IgG antibodies. Research continued over the years, and now it's well-established that either an elevated IgG index or oligoclonal bands are found positive in more than 95% of MS patients.

But there's been no definitive evidence showing whether those bands—those IgG antibodies—are toxic or not. I feel that ours is a definitive study.

I think the findings will fundamentally change the direction of MS research and provide novel drug-development strategies for progressive MS where current disease-modified therapies do not work.

How did you conduct your study?

We tested samples from 190 people with MS and 160 control samples. Our data support that IgG-induced neuronal death is MS-specific because we failed to see such effects in blood from other inflammatory diseases and neurological illnesses, including Parkinson's, West Nile, hypertension, Alzheimer's, lymphoma, viral meningitis and brain tumors (the latter plasma samples were obtained from the Department of Neurosurgery's Nervous System Biorepository).

We found no antibody-induced effect—no neuronal death—in any diseases or conditions outside of MS.

Why is your study considered controversial?

B cells are a type of white blood cell that make antibodies. Much of the study into MS therapeutics centers on B-cell therapy, which targets the B cells that harm the nerves in the brain and spinal cord. When you have MS, the B cells, which typically don't move from the blood into the brain or spinal cord, enter the central nervous system and damage the sheath protecting the nerves. While it's not a cure, B-cell therapy has been shown to reduce symptoms and relapses.

Our study suggests that new therapies should be developed to target the toxic antibodies, the product of B cells, not just the B cells. We've shown that blood plasma antibodies of this kind—unique features distinct in MS—kill astrocytes and mouse brain tissues. Previously, no researchers combined this with this much of a sample definitively.

It's also controversial because we don't yet know the mechanism that drives these antibody molecules to come together and form the aggregates. Also, how do these toxic aggregates get through the blood-brain barrier to reach the brain? They aren't supposed to get in. We still don't know the answer to those questions, so more study is needed.

More study is needed on why the MS-specific IgG antibodies form these aggregate complexes.

Does the toxicity of these antibody aggregates change the form of MS a patient has?

There are four forms of MS, including the form most people are initially diagnosed with—relapse-remitting (RRMS). In that form, symptoms arrive in intermittent flares. When a patient has a history of MS attacks but starts to develop steady symptoms, we call this secondary-progressive MS (SPMS). The two other forms are primary-progressive, where symptoms progressively worsen with no noticeable relapses, and

the rarest form—progressive-relapsing (steady worsening of symptoms with acute relapses).

Our study showed that the further the MS has progressed, the more toxic the antibodies in the plasma become. Suppose you compare the same amount of antibodies drawn from the progressive-form patient vs. a relapse-remitting patient. In that case, the antibodies are more toxic to the neurons in the progressive form.

What is the next step in your research?

The key is providing a novel approach to design drugs that inhibit these antibodies—prevent them from killing neurons.

If we have a drug to fight this, or at least provide early detection of this toxic antibody, it could provide early detection of what potentially might develop into progressive MS. Also, it could open the door to better treatment options. The earlier the diagnosis, the faster a patient may be able to receive an aggressive treatment that delays or even prevents the progression of MS.

Right now, there is no way to do any of that. It's all retrospective—the patient comes in, and the clinician says, "You're getting worse." There are no markers, nothing.

More information: Wenbo Zhou et al, Multiple sclerosis plasma IgG aggregates induce complement-dependent neuronal apoptosis, *Cell Death & Disease* (2023). DOI: 10.1038/s41419-023-05783-3

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