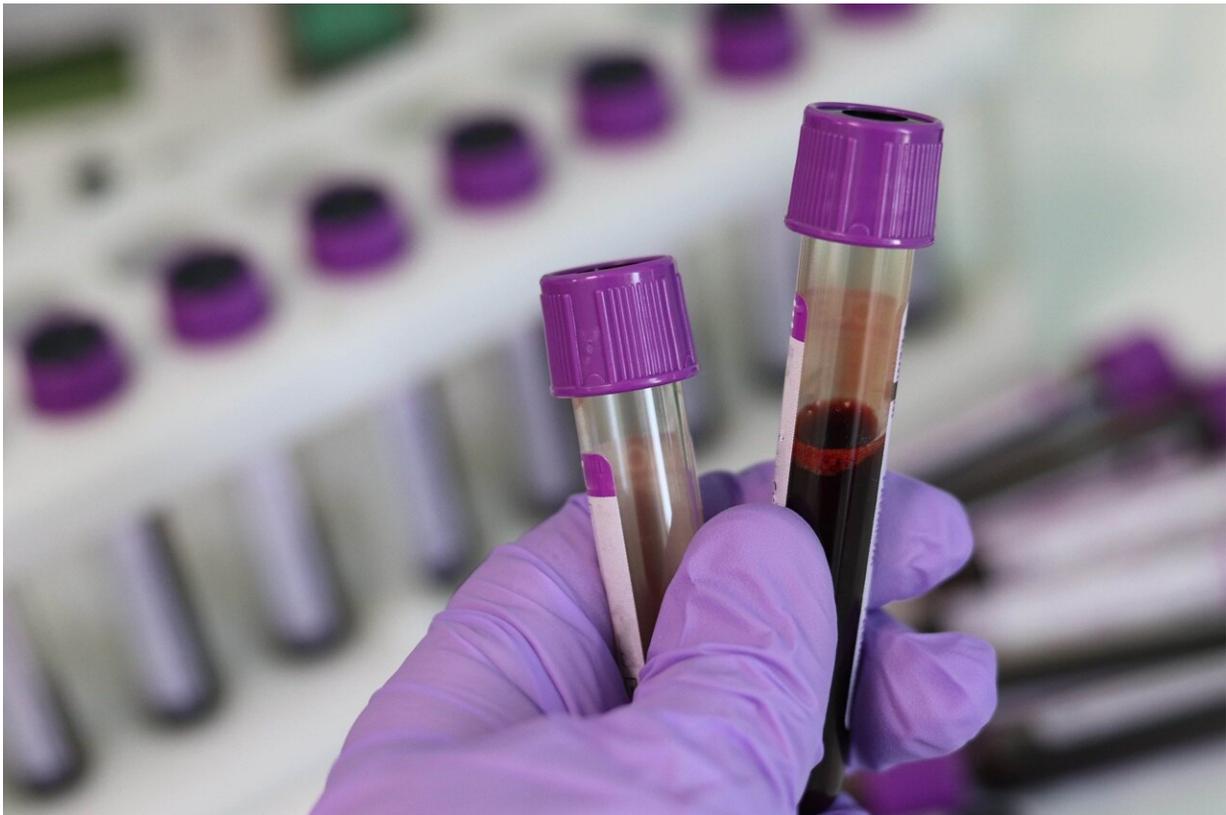


Signs of multiple sclerosis show up in blood years before symptoms, study finds

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In a discovery that could hasten treatment for patients with multiple sclerosis (MS), UC San Francisco scientists have discovered a harbinger in the blood of some people who later went on to develop the disease.

In about 1 in 10 cases of MS, the body begins producing a distinctive set of antibodies against its own proteins years before symptoms emerge. These [autoantibodies](#) appear to bind to both [human cells](#) and common pathogens, possibly explaining the immune attacks on the brain and spinal cord that are the hallmark of MS.

The findings were published in [Nature Medicine](#) on April 19.

MS can lead to a devastating loss of motor control, although new treatments can slow the progress of the disease and, for example, preserve a patient's ability to walk. The scientists hope the autoantibodies they have discovered will one day be detected with a [simple blood test](#), giving patients a head start on receiving treatment.

"Over the last few decades, there's been a move in the field to treat MS earlier and more aggressively with newer, more potent therapies," said UCSF neurologist Michael Wilson, MD, a senior author of the paper. "A diagnostic result like this makes such early intervention more likely, giving patients hope for a better life."

Linking infections with autoimmune disease

Autoimmune diseases like MS are believed to result, in part, from rare immune reactions to common infections.

In 2014, Wilson joined forces with Joe DeRisi, Ph.D., president of the Chan Zuckerberg Biohub SF and a senior author of the paper, to develop better tools for unmasking the culprits behind autoimmune disease. They took a technique in which viruses are engineered to display bits of proteins like flags on their surface, called phage display immunoprecipitation sequencing (PhIP-Seq), and further optimized it to screen [human blood](#) for autoantibodies.

PhIP-Seq detects autoantibodies against more than 10,000 human proteins, enough to investigate nearly any autoimmune disease. In 2019, they successfully used it to discover [a rare autoimmune disease that seemed to arise from testicular cancer.](#)

MS affects more than 900,000 people in the US. Its early symptoms, like dizziness, spasms, and fatigue, can resemble other conditions, and diagnosis requires careful analysis of brain MRI scans.

The phage display system, the scientists reasoned, could reveal the autoantibodies behind the immune attacks of MS and create new opportunities to understand and treat the disease.

The project was spearheaded by first co-authors Colin Zamecnik, Ph.D., a postdoctoral researcher in DeRisi's and Wilson's labs; and Gavin Sowa, MD, MS, former UCSF medical student and now internal medicine resident at Northwestern University.

They partnered with Mitch Wallin, MD, MPH, from the University of Maryland and a senior author of the paper, to search for autoantibodies in the blood of people with MS. These samples were obtained from the U.S. Department of Defense Serum Repository, which stores blood taken from armed service members when they apply to join the military.

The group analyzed blood from 250 MS patients collected after their diagnosis, plus samples taken five or more years earlier when they joined the military. The researchers also looked at comparable blood samples from 250 healthy veterans.

Between the large number of subjects and the before-and-after timing of the samples, it was "a phenomenal cohort of individuals to look at to see how this kind of autoimmunity develops over the course of clinical onset of this disease," said Zamecnik.

A consistent signature of MS

Using a mere one-thousandth of a milliliter of blood from each time point, the scientists thought they would see a jump in autoantibodies as the first symptoms of MS appeared.

Instead, they found that 10% of the MS patients had a striking abundance of autoantibodies years before their diagnosis.

The dozen or so autoantibodies all stuck to a chemical pattern that resembled one found in common viruses, including Epstein-Barr Virus (EBV), which infects more than 85% of all people, yet has been flagged in previous studies as a contributing cause for MS.

Years before diagnosis, this subset of MS patients had other signs of an immune war in the brain. Ahmed Abdelhak, MD, co-author of the paper and a postdoctoral researcher in the UCSF laboratory of Ari Green, MD, found that patients with these autoantibodies had elevated levels of neurofilament light (Nfl), a protein that gets released as neurons break down.

Perhaps, the researchers speculated, the immune system was mistaking friendly human proteins for some viral foe, leading to a lifetime of MS.

"When we analyze healthy people using our technology, everybody looks unique, with their own fingerprint of immunological experience, like a snowflake," DeRisi said. "It's when the immunological signature of a person looks like someone else, and they stop looking like snowflakes that we begin to suspect something is wrong, and that's what we found in these MS patients."

A test to speed patients toward the right therapies

To confirm their findings, the team analyzed blood samples from patients in the UCSF ORIGINS study. These patients all had neurological symptoms and many, but not all, went on to be diagnosed with MS.

Once again, 10% of the patients in the ORIGINS study who were diagnosed with MS had the same autoantibody pattern. The pattern was 100% predictive of an MS diagnosis. Across both the Department of Defense group and the ORIGINS group, every patient with this autoantibody pattern had MS.

"Diagnosis is not always straightforward for MS, because we haven't had disease specific biomarkers," Wilson said. "We're excited to have anything that can give more diagnostic certainty earlier on, to have a concrete discussion about whether to start treatment for each patient."

Many questions remain about MS, ranging from what's instigating the immune response in some MS patients to how the [disease](#) develops in the other 90% of patients. But the researchers believe they now have a definitive sign that MS is brewing.

"Imagine if we could diagnose MS before some patients reach the clinic," said Stephen Hauser, MD, director of the UCSF Weill Institute for Neurosciences and a senior author of the paper. "It enhances our chances of moving from suppression to cure."

More information: Colin R. Zamecnik et al, An autoantibody signature predictive for multiple sclerosis, *Nature Medicine* (2024). DOI: 10.1038/s41591-024-02938-3 , www.nature.com/articles/s41591-024-02938-3

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