Multiple sclerosis appears to protect against Alzheimer's disease

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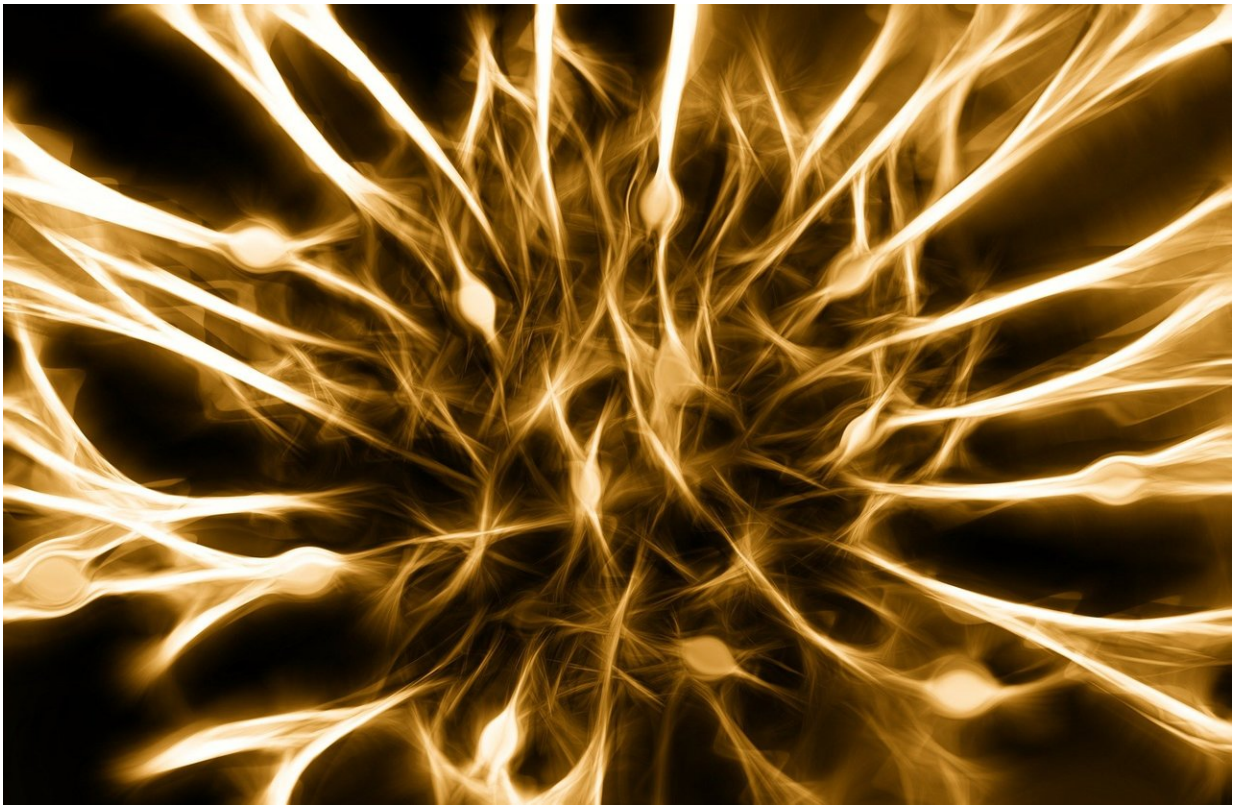

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People with multiple sclerosis (MS) are far less likely than those without the condition to have the molecular hallmarks of Alzheimer's disease, according to new research from Washington University School of Medicine in St. Louis.

The discovery suggests a new avenue of research through which to seek Alzheimer's treatments, said Matthew Brier, MD Ph.D., an assistant professor of neurology and of radiology and the study's first author.

"Our findings imply that some component of the biology of multiple sclerosis, or the genetics of MS patients, is protective against Alzheimer's disease," Brier said. "If we could identify what aspect is protective and apply it in a controlled way, that could inform therapeutic strategies for Alzheimer's disease."

The study, an example of clinical observations directly impacting research, was published in the *Annals of Neurology*.

A collaboration between WashU Medicine experts in Alzheimer's and MS, the investigation was prompted by a suspicion Brier's mentor and collaborator, Anne Cross, MD, had developed over decades of treating patients with MS, an immune-mediated disease that attacks the central nervous system. Although her patients were living long enough to be at risk of Alzheimer's or had a family history of the neurodegenerative disease, they weren't developing the disease.

"I noticed that I couldn't find a single MS patient of mine who had typical Alzheimer's disease," said Cross, the Manny and Rosalyn Rosenthal and Dr. John Trotter MS Center Chair in Neuroimmunology.

"If they had cognitive problems, I would send them to the memory and aging specialists here at WashU Medicine for an Alzheimer's assessment, and those doctors would always come back and tell me, 'No, this is not due to Alzheimer's disease.'"

Cognitive impairment caused by MS can be confused with symptoms of Alzheimer's disease; Alzheimer's can be confirmed with blood and other biological tests.

To confirm Cross' observation, the research team used a new, FDA-approved blood test that was developed by WashU Medicine researchers. Known as PrecivityAD2, the blood test is highly effective at predicting the presence of amyloid plaques in the brain. Such plaques are an indicator of Alzheimer's disease and previously only could be verified with brain scans or spinal taps.

Brier, Cross and their colleagues recruited 100 patients with MS to take the blood test, 11 of whom also underwent PET scans at WashU Medicine's Mallinckrodt Institute of Radiology. Their results were compared with the results from a control group of 300 individuals who did not have MS but were similar to those with MS in age, genetic risk for Alzheimer's, and cognitive decline.

"We found that 50% fewer MS patients had amyloid pathology compared to their matched peers, based on this blood test," Brier said. This finding supported Cross' observation that Alzheimer's appeared to be less likely to develop among those with MS.

It is not clear how amyloid accumulation is linked to the cognitive impairment typical of Alzheimer's, but the accumulation of plaques is generally understood to be the first event in the biological cascade that leads to cognitive decline.

The researchers also found that the more typical the patient's MS history was, in terms of age of onset, severity and overall disease progression, the less likely they were to have amyloid plaque accumulation in that patient's brain compared with those with atypical presentations of MS. This suggests there is something about the nature of MS itself that is protective against Alzheimer's disease, which Brier and Cross are planning to investigate.

MS patients generally have multiple flare-ups of the illness over the

course of their lifetimes. During these flare-ups, the immune system attacks the central nervous system, including within the brain. It's possible that this immune activity also reduces amyloid plaques, the researchers said.

"Perhaps when the Alzheimer's disease amyloid pathology was developing, the patients with MS had some degree of inflammation in their brains that was spurred by their immune responses," Brier said. Referring to work by co-author David M. Holtzman, MD, the Barbara Burton and Reuben M. Morriss III Distinguished Professor of Neurology, Brier noted that activated microglia, which are part of the brain's immune response in MS, have been shown to clear amyloid from the brain in animal models.

Brier and Cross have begun the next steps of this research, both to tease out the possible human genetics involved, as well as to test amyloid plaque development in animal models representing MS.

More information: Matthew R. Brier et al, Unexpected Low Rate of Amyloid-β Pathology in Multiple Sclerosis Patients, *Annals of Neurology* (2024). DOI: 10.1002/ana.27027

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