Study details source of mental problems associated with multiple sclerosis

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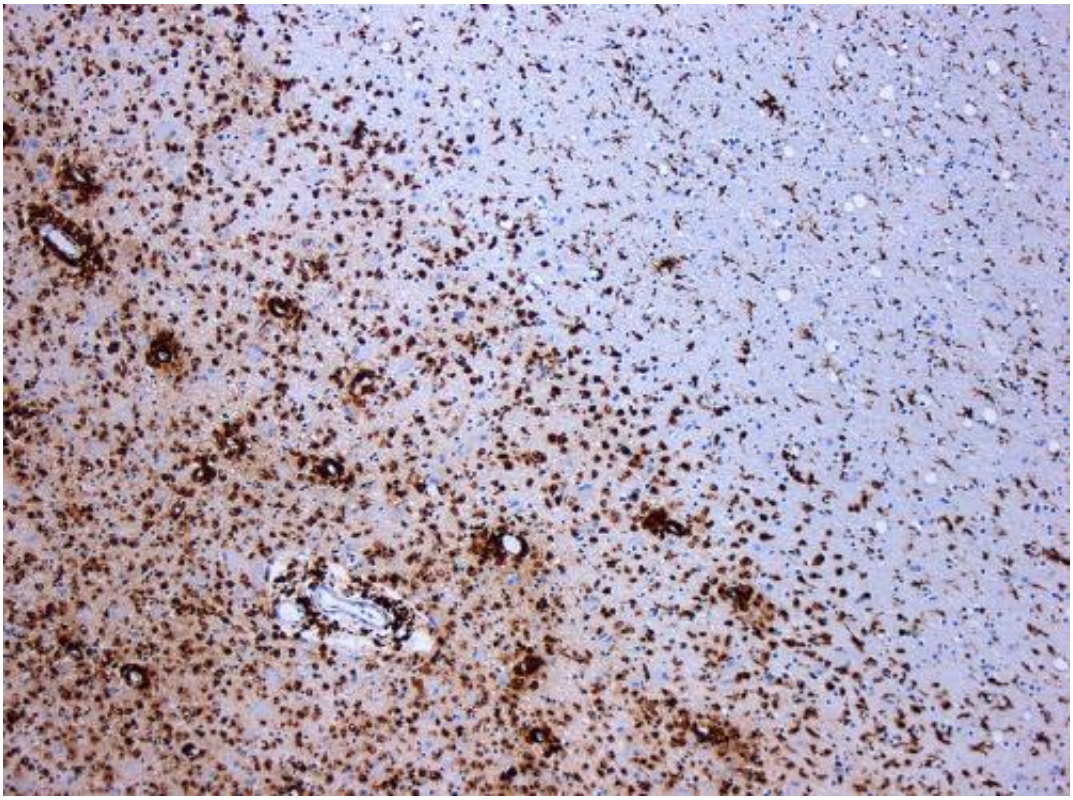

Demyelination by MS. The CD68 colored tissue shows several macrophages in the area of the lesion. Original scale 1:100. Credit: CC BY-SA 3.0 Marvin 101/Wikipedia

A study out today sheds new light on multiple sclerosis (MS), specifically damage in the brain caused by the disease that may explain the slow and continuous cognitive decline that many patients experience.

The findings, which appear in the *Journal of Neuroscience*, show that the brain's immune system is responsible for disrupting communication between nerve cells, even in parts of the brain that are not normally considered to be primary targets of the disease.

"This study identifies for the first time a new disease mechanism in MS which causes damage to neurons independent of the loss of white matter and demyelination that is the hallmark of the disease," said the lead author, neurologist Matthew Bellizzi, M.D., Ph.D., with the Center for Neural Development and Disease at the University of Rochester Medical Center (URMC). "This damage represents another component of the disease and one that is not prevented by the current immunosuppressive drugs employed to treat MS."

Multiple sclerosis is a disease of the central nervous system that affects an estimated one million people worldwide. While the precise cause of MS is unknown, it has long been understood that the immune system in individuals with MS attacks myelin, a fatty white matter tissue in the central nervous system that wraps the fibers—or axons—that connect nerve cells. When myelin is lost or damaged, a process called demyelination, signals between nerve cells can be delayed, disrupted, or even blocked.

Most people associate MS with motor and sensory symptoms like muscle weakness, numbness or tingling in arms and legs, difficulty with coordination, walking, and balance, blurred vision, and slurred speech. However, up to 70 percent of people with MS will also go on to develop cognitive problems later in life, such as difficulty processing information, concentrating, finding the right word when speaking, and memory loss.

"For too long, MS has been characterized as a disease that impairs people's mobility, speech, or vision," said Harris Gelbard, M.D, Ph.D.

the director of the URMC Center for Neural Development and Disease and senior author of the study. "However, the aspect of the disease that many patients complain has the greatest impact on their quality of life is the loss of cognitive independence."

While physicians currently have at their disposal several frontline drugs that are effective in suppressing the immune system attacks that can lead to myelin damage, these therapies do not prevent the progressive cognitive problems. This has led the researchers to speculate that there could be additional damage occurring in the central nervous system during MS that has not been fully understood or appreciated. Previous studies have hinted that neurons that lie outside areas of the brain affected by myelin loss could also be casualties of the autoimmune response in MS patients.

The URMC team conducted a series of experiments in mouse models of MS which showed that neurons in the hippocampus, an area of the brain not associated with motor control, were being damaged at the synapse—the point of connection where one neuron's axon meets its neighbor and allows the two cells to communicate with each other through the transmission of chemical signals.

One of the culprits appears to be a cell in the central nervous system's defenses called microglia. Microglia serve as the brain's "first responders" and are activated to help fight infection or other assaults on the nervous system and clean up the debris from damaged cells.

One of the functions of microglia is to maintain the health of the synapse so that it can function normally to help the hippocampus with learning and memory.H owever, when the immune system is over-activated during MS, distress signals are sent throughout the brain causing the microglia to switch from their normal nurturing role and take up an aggressive pro-inflammatory response.

The microglia release a molecule called platelet-activating factor (PAF) that affects the excitatory signaling that neurons use to activate one another and encode new memories. High levels of PAF can lead to an over-activation of these signals that, like a power surge, destroys the receiving end of the synapse. This, in turn, causes more microglia and other immune cells to rush to the site of injury, triggering a chronic and self-perpetuating cycle of destruction.

"The cumulative effect is like trying to put out a fire with gasoline," said Gelbard.

The researchers believe that this phenomenon is ultimately responsible for much of the cognitive impairment and progressive decline that many individuals with the disease experience.

While the activation of microglia and resulting damage to the synapse is not impacted by the drugs currently used to treat MS, the researchers are now focused on potential drug candidates known to suppress the signaling pathways that cause the nerve cells and microglia to become overactive, including a drug that is being investigated to treat HIV-associated neurological disorders.

Provided by University of Rochester Medical Center