Study details source of mental problems associated with MS

Rochester, NY, USA (January 26, 2016) - A study out today sheds new light on multiple sclerosis (MS), specifically damage in the brain caused by the disease that may explain the link and previously unexpected finding that some patients experience. The finding, which appears in the Journal of Neurology, says that the brain's immune system is responsible for disrupting communication between nerve cells, even in parts of the brain that were not previously 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 disease process that affects the nerve myelin sheath," said Harris A. Kopolovic, Ph.D., a research professor of neurology and neuroscience at the University of Rochester Medical Center (URMC). "This damage represents another component of the disease process 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. It's the leading cause of disability in young adults, with those diagnosed in their 20's and 30's making up 70% of patients. MS is an autoimmune disease in which the immune system attacks the-myelin- a protective sheath that surrounds the long, thin nerve fibers in the brain and the spinal cord. When myelin is lost or damaged, the signals to and from the brain are disrupted, leading to muscle weakness, sensory problems, or severe cognitive impairment.

Most people associate MS with motor and sensory symptoms like muscle weakness, numbness or tingling in arms and legs, but research shows that many patients also suffer from severe cognitive symptoms, including difficulty concentrating and memory loss. For too long, MS has been characterized as a disease that impairs people's mobility, speech, or vision. Other forms of MS, such as demyelinating disease, can cause problems with memory, attention, and executive function that can be as disabling as the effects on mobility. Understanding the cause of these cognitive symptoms could improve the quality of life of people with MS.

"Difficulties with memory and attention due to multiple sclerosis are among the most common and severe problems patients report. These difficulties have a significant impact on patients' quality of life, work performance and daily function. As a result, many patients complain has the greatest impact on their quality of life is the loss of cognitive independence," said Kopolovic.

While physicians currently have at their disposal several frontline drugs that are effective in suppressing the immune response, these drugs do not prevent the cognitive problems associated with MS. Most of these patients say that the treatments they are taking are not working for them. 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 that plays a key role in forming memories, can be damaged even in areas that are not normally considered to be primary targets of the disease. The hippocampus is a part of the brain that provides a significant contribution to cognitive function, but its exact role in cognitive impairment related to MS is not fully understood.

Microglia, which are immune cells that help fight infection, are activated to help fight infection or other insults to 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 neuron communicate with other cells in the brain. Microglia are normally quiet, with few signs of inflammation, but when activated they become more like macrophages, white blood cells that fight infection.

One of the culprits appears to be in the natural immune system's defenses against the brain's immune cells' switch from their normal nurturing role and take up an aggressive pro-inflammatory role. Microglia are activated to help fight infection or other insults to the nervous system and clean up the debris from damaged cells.

The URMC team conducted a series of experiments in mouse models of MS that showed that microglia in the hippocampus, as well as those in other areas of the brain, are activated and become pro-inflammatory when they are activated. This leads to increased inflammation, which can damage the synapse, leading to impaired communication between neurons in the brain. The result of these experiments was that the hippocampus, a part of the brain that provides a significant contribution to cognitive function, can be damaged even in areas that are not normally considered to be primary targets of the disease.

"The damage to microglia due to MS involves the immune system's reaction to a disease that can cause damage in the brain even in areas that are not normally considered to be primary targets of the disease," said Kopolovic. "This damage represents another component of the disease process that is not prevented by the current immunosuppressive drugs employed to treat MS."
The microglia release a molecule called platelet-activating factor (PAF) that affects the excitatory signaling that occurs at 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 hope to develop new medications that can stop the cycle of destruction that occurs for both people with normal or damaged synapses, including a group that is being investigated in their new MS clinical developmental therapies.

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Additional co-authors of the study include Jasmine Geathers and Kevin Allan with URMC. The research was supported with grants from the National Multiple Sclerosis Society and the National Institute of Mental Health.

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