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Study helps explain why multiple sclerosis is more common in women

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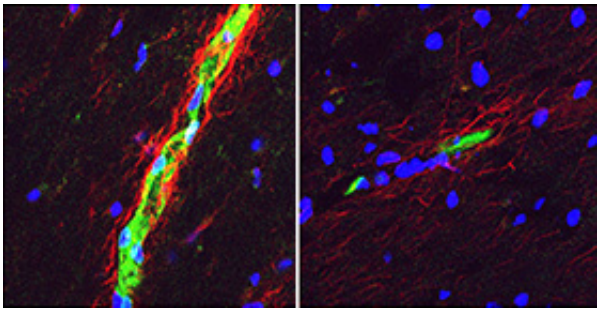

An image of tissue from a female brain (left) affected by multiple sclerosis (MS) shows that the brain has much higher levels of a blood vessel receptor (shown in red) than a male brain affected by MS (right). The difference could help explain why so many more women get MS. Credit: Robyn Klein

A newly identified difference between the brains of women and men with multiple sclerosis (MS) may help explain why so many more women than men get the disease, researchers at Washington University School of Medicine in St. Louis report.

In recent years, the diagnosis of MS has increased more rapidly among women, who get the disorder nearly four times more than men. The reasons are unclear, but the new study is the first to associate a sex difference in the brain with MS.

The findings appear May 8 in *The Journal of Clinical Investigation*.

Studying mice and people, the researchers found that females susceptible to MS produce higher levels of a blood vessel receptor protein, S1PR2, than males and that the protein is present at even higher levels in the brain areas that MS typically damages.

"It was a 'Bingo!' moment – our genetic studies led us right to this receptor," said senior author Robyn Klein, MD, PhD. "When we looked at its function in mice, we found that it can determine whether immune cells cross blood vessels into the brain. These cells cause the inflammation that leads to MS."

An investigational MS drug currently in clinical trials blocks other receptors in the same protein family but does not affect S1PR2. Klein recommended that researchers work to develop a drug that disables S1PR2.

MS is highly unpredictable, flaring and fading at irregular intervals and producing a hodgepodge of symptoms that includes problems with mobility, vision, strength and balance. More than 2 million people worldwide have the condition.

In MS, inflammation caused by misdirected immune cells damages a protective coating that surrounds the branches of nerve cells in the brain and spinal column. This leads the branches to malfunction and sometimes causes them to wither away, disrupting nerve cell communication necessary for normal brain functions like movement and coordination.

For the new research, Klein studied a mouse model of MS in which the females get the disease more often than the males. The scientists compared levels of gene activity in male and female brains. They also looked at gene activity in the regions of the female brain that MS damages and in other regions the disorder typically does not harm.

They identified 20 genes that were active at different levels in vulnerable female brain regions. Scientists don't know what 16 of these genes do. Among the remaining genes, the increased activity of S1PR2 stood out because researchers knew from previous studies that the protein regulates how easy it is for cells and molecules to pass through the walls of blood vessels.

Additional experiments showed that S1PR2 opens up the blood-brain barrier, a structure in the brain's blood vessels that tightly regulates the materials that cross into the brain and spinal fluid. This barrier normally blocks potentially harmful substances from entering the brain. Opening it up likely allows the inflammatory cells that cause MS to get into the central nervous system.

When the researchers tested brain tissue samples obtained from 20 patients after death, they found more S1PR2 in MS patients' brains than in people without the disorder. Brain tissue from females also had higher levels of S1PR2 than male brain tissue. The highest levels of S1PR2 were found in the brains of two female patients whose symptoms flared and faded irregularly, a pattern scientists call relapsing and remitting MS.

Klein is collaborating with chemists to design a tracer that will allow scientists to monitor S1PR2 levels in the brains of people while they are living. She hopes this will lead to a fuller understanding of how S1PR2 contributes to MS.

"This is an exciting first step in resolving the mystery of why MS rates are dramatically higher in women and in finding better ways to reduce the incidence of this disorder and control symptoms," said Klein, associate professor of medicine. Klein also is an associate professor of pathology and immunology and of neurobiology and anatomy.

More information: Cruz-Orengo L, Daniels BP, Dorsey D, Basak SA, Grajales-Reyes JG, McCandless EE, Piccio L, Schmidt RE, Cross AH, Crosby SD, Klein RS. Sexually S1PR2 expression enhances susceptibility to CNS autoimmunity. The *Journal of Clinical Investigation*, online May 8, 2014.

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