Best treatment for MS may depend on disease subtype

July 1 2008

Animal studies by University of Michigan scientists suggest that people who experience the same clinical signs of multiple sclerosis (MS) may have different forms of the disease that require different kinds of treatment.

The results, if borne out in further studies, point to a time when doctors will be able to target specific inflammatory processes in the body and more effectively help MS patients, using available drugs and new ones in the pipeline.

Since the 1990s, the treatment picture has brightened for people with multiple sclerosis in its most common form, relapsing-remitting MS. Beta interferon drugs and glatiramer acetate (marketed as Copaxone) have proved effective at decreasing the attack rate and suppressing inflammatory plaque development in many patients with MS. Yet why the drugs help some patients, but not others, has remained a mystery.

The U-M research team conducted the studies in mice that have a disease similar to MS: experimental autoimmune encephalomyelitis or EAE. The team found that different inflammatory chemicals, whose activity is linked to two different types of immune system T cells, could bring on the same paralysis and other MS-like signs. They also showed that drugs that block one of the inflammation pathways were not effective at blocking the other. The results, published online ahead of print, will appear in the July 7 issue of the *Journal of Experimental Medicine*.

"These two forms of disease differ in the specific anti-inflammatory agents that they are responsive to," says Benjamin Segal, M.D., the study's senior author and the director of the Multiple Sclerosis Center at the U-M Health System.

"We already know that some people respond better to the drugs beta interferon or Copaxone than others. Now we've shown proof that you can cause MS-like syndrome in mice due to qualitatively different types of inflammatory damage. As a result, these two kinds of inflammation likely require different approaches to treatment," says Segal. He directs the Holtom-Garrett Program in Neuroimmunology and is the Holtom-Garrett Family Professor of Neurology at the U-M Medical School.

Context:

In 85 percent of MS cases, patients begin with what is called a relapsing-remitting form of the disease. Initially, they have attacks in which they experience symptoms for a time, return to normal, then have attacks again. In the last 15 years, several beta interferon drugs and Copaxone have been effective in many patients at limiting the number of attacks. These drugs also can also decrease damage in the brain as visualized on MRI scans.

Research details:

Both groups of mice developed similarly severe and rapid paralysis. But the researchers found clear differences in the inflammatory agents involved, called cytokines and chemokines, and in the resulting damage to the central nervous system.

Mice injected with Th1 cells showed a pattern of central nervous system inflammation that resembled that of common MS, with lesions filled with macrophages, a type of immune system defender cell. Mice

injected with Th17 cells, however, had lesions filled with another immune cell type, neutrophils. In these mice, inflammation reached deep in central nervous system tissues and in the optic nerve.

In both groups of mice, the scientists tested the effects of neutralizing antibody drugs similar to drugs being developed against autoimmune diseases in humans. Some of the drugs inhibited disease in the Th17 mice, but not in the mice receiving Th1 cells. Other drugs were effective against both types of disease.

"That's our proof that these really are different mechanisms of disease," says Mark Kroenke, the study's first author and a Ph.D. student in immunology at U-M.

Implications:

"We speculate at some point being able to identify and measure active inflammatory agents in patients, and to develop customized profiles that would help predict what treatments will be effective," Segal says.

In addition, Segal says, the findings may aid the search for effective drugs for two difficult-to-treat diseases closely related to MS: neuromyelitis optica, which affects the optic nerve and spinal cord, and opticospinal MS, most common in Asia. The pattern of inflammation the team saw in the Th17-injected mice resembled the pattern in these variants of MS.

Source: University of Michigan