

Statins may treat blood vessel disorder that can lead to fatal strokes

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In a finding that could save thousands of lives a year, University of Utah School of Medicine researchers have shown that a blood vessel disorder leading to unpredictable, sometimes fatal, hemorrhagic strokes, seizures, paralysis or other problems is treatable with the same statin drugs that millions of people take to control high cholesterol.

If the results of a study in mice are confirmed in a pilot trial with people, statins could provide a safe, inexpensive treatment for cerebral cavernous malformation (CCM), a disorder with no known drug therapy, according to U of U cardiologist Dean Y. Li, M.D., Ph.D., director of the Molecular Medicine Program and corresponding author of a study published Jan. 18 in *Nature Medicine* online.

"Brain surgery or radiation treatment has been the only option for CCM patients. But because of the risks in those operations, neurosurgeons are reluctant to perform them unless the patient is in immediate danger," Li said. "Our study proposes a potential strategy for a simple drug therapy that could cost only a few dollars a month at a pharmacy. However, our animal studies must first be evaluated in a pilot clinical trial being initiated."

Kevin J. Whitehead, M.D., also a cardiologist, assistant professor of internal medicine, and first author of the study, now is recruiting 50 to 100 people diagnosed with CCM to join a pilot trial of statins.

CCM is a disorder in which blood vessels in the brain become dilated

and weakened, and leak blood, causing strokes, headaches, seizures or other problems. Diagnosing CCM can be problematic. Some people are diagnosed after experiencing symptoms and undergoing an MRI; others find out they have CCM during an MRI for an unrelated problem. An estimated 25 percent of people with CCM experience no symptoms and never know they have it. In worst-case scenarios, "people don't know they have CCMs until they suffer from an acute brain attack," Li said.

According to Connie Lee of the Angioma Alliance, "Cavernous angioma or cerebral cavernous malformation is a common but little known illness that can strike with devastating consequences for individuals in any stage of life. The disease has affected the strongest among us, including prominent athletes such as the Olympic superstar, Florence Griffith Joyner, and the Tour De France champion, Alberto Contador. In its hereditary form, it is especially prevalent in members of the original Hispanic families that settled the American Southwest."

Although the precise number of people with CCM is not known, it's estimated up to 0.5 percent of the U.S. population or about 1.5 million people may have some form of CCM, according to Whitehead. "Statin therapy, particularly, could benefit people who are genetically predisposed to CCM," he said. "Of vital importance is the impact this research might have on the large number of our Hispanic population in the Southwest and Rocky Mountain West who carry a gene mutation, passed from common ancestors, that predisposes them to CCM."

Whitehead and Li suspect statins, such as Zocor, Lipitor, and similar drugs, treat CCM by stabilizing blood vessels so they don't leak.

CCM can be inherited genetically or occur sporadically. Three known genes have been associated with genetic-related CCM, but the role of those genes, Ccm1, Ccm2, and Ccm3, has been unclear. Whitehead and Li demonstrated that without Ccm2, the endothelium, a thin, inner lining

of cells that forms a blood vessel's tubular passage for blood flow, does not form properly. When that happens, blood vessels can become weak and dilated, allowing them to leak.

In mice with two distinct mutations of *Ccm2*, meaning the gene's function was knocked out, the researchers observed increased activity in Rho, an enzyme that regulates endothelium formation. Li and Whitehead theorized that increased Rho activity in endothelial cells might lead to the blood vessel defects seen in CCM patients. They tested their hypothesis by administering simvastatin, which is known to inhibit Rho activity, to mouse models with the *Ccm2* mutations and saw that the drugs strengthened the damaged blood vessels in the mice."

Eugene Golanov, M.D., Ph.D., a program director at the National Institute of Neurological Disorders and Stroke, part of the National Institutes of Health, said Li's and Whitehead's study is an important work. "By attacking this disease from many angles - including genetic, biochemical and pharmacological approaches - Dr. Li's team has shed new light on the mechanism of the disease and a potential drug therapy," Golanov said. "Their success illustrates the importance of encouraging teams of scientists and physicians across institutions and disciplines to target familial stroke diseases such as cerebral cavernous malformations."

Source: University of Utah Health Sciences

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