Genetic variation may reduce Alzheimer's risk

January 8 2007

Dr. William D. Hill, neuroscientist at the Medical College of Georgia and Veterans Affairs Medical Center in Augusta.

Adults with a genetic variation enabling them to express higher levels of fetal hemoglobin may have a reduced risk of Alzheimer's disease, researchers say.

A study of 209 families with at least two siblings with Alzheimer's and one unaffected sibling showed that those with this genetic variation are less likely to have the disease, researchers say in Neurobiology of Aging.

An estimated 25 percent of the population has the XmnI polymorphism.

The study, available online but not yet scheduled for print, also showed that beta amyloid peptide, a major culprit in Alzheimer's, has an affinity for adult hemoglobin, says Dr. William D. Hill, neuroscientist at the Medical College of Georgia and Veterans Affairs Medical Center in Augusta and a corresponding author.

The hemoglobin attraction was discovered by using phage display technology to screen thousands of molecules in the human brain to find those that interact with beta amyloid peptide. This approach uses a virus to infect a bacterium so the bacterium will copy the virus.

The result looks like a microscopic cigar with the proteins of interest as whiskers on one end, says Dr. Hill. In this case, a library of brain molecules was inserted into the virus' whiskers to find proteins that would stick to beta amyloid.

Hemoglobin, found in red blood cells and responsible for carrying oxygen in the body, was among those that stuck.

Surprised that hemoglobin was even present, Dr. Hill suspected it was an artifact of preparing brain tissue for the library. But once he saw the attraction, he could not ignore it.

His lab actually first found an attraction for fetal hemoglobin, another surprise since most adults have little of this substance that snatches oxygen from the placenta and holds onto it tightly for the fetus. Looking further, his lab found adult hemoglobin was binding as well, so Dr. Hill and MCG hemoglobin experts Drs. Abdullah and Ferdane Kutlar decided to look at the XmnI polymorphism, which can significantly increase fetal hemoglobin expression in adults.

They turned to colleagues at the University of Alabama at Birmingham, one of three sites that contributed families to the National Institute of Mental Health Alzheimer's databank.

At the UAB databank, headed by Dr. Rodney C.P. Go, researchers found more surprises. "We wanted to look at people who had Alzheimer's and family members who don't to see who expressed the polymorphism the most," says Dr. Hill. They expected it would be the Alzheimer's patients and found just the opposite.

In what they suspect to be a horrific vicious cycle, beta amyloid could injure red blood cells, allowing more of them than usual to break open and spill their contents, including oxygen-carrying hemoglobin, into the bloodstream. Free hemoglobin is toxic; it can easily lose its iron group, causing cell-damaging oxidative stress. Now it appears freed hemoglobin may also bind to beta amyloid, which may enhance that protein's ability to wreak havoc in the brain.

Red blood cells break down every day and the body has molecules that bind free hemoglobin and iron and take them to the liver for elimination. "Part of our hypothesis is that it may be free-radical injury of our red blood cells by the beta amyloid that releases excessive hemoglobin which overwhelms our body's natural system for protecting us from free hemoglobin," Dr. Hill says.

Work in the late 1990s showed fragments of beta amyloid could actually attack red blood cell membranes and cause them to destruct, says Dr. Hill. "And, there is some evidence that red blood cells of Alzheimer's patients have been damaged so we think red blood cells are more fragile in some Alzheimer's patients allowing them to be more likely to break open.

Although the XmnI polymorphism's protection mechanism is not clear,

the researchers found in certain circumstances, adult hemoglobin bound better to beta amyloid, so if there are higher levels of fetal hemoglobin, there may not be as much interaction and subsequent injury, Dr. Hill says.

To determine the impact of the genetic mutation on Alzheimer's risk, studies need to be done on more Alzheimer's patients and their families, including taking blood levels of fetal hemoglobin, says Dr. Rodney T. Perry, UAB molecular geneticist and a study corresponding author.

"More studies are needed to confirm the physiologic basis of the interaction," says Dr. Perry who already is working with Dr. Hill to submit a grant to pursue more answers. If they document higher fetal hemoglobin levels in healthy family members with the XmnI polymorphism, the hypothesis that it is providing some sort of protective measure is more likely, says Dr. Perry. Also the amount of disease protection has yet to be determined, he notes. "It may be a small protection."

Either way, the role needs pursuing, Dr. Perry says. "It helps in trying to fill in the pieces of the puzzle of what is going on in the pathogenesis and different etiologies of the disease, how it may come about."

If they are right, the findings could open the doors to treatment approaches that increase fetal hemoglobin levels, Dr. Hill says. One such drug, hydroxyurea, already is used to treat sickle cells patients because fetal hemoglobin will not sickle.

Source: Medical College of Georgia