An ID for Alzheimer's?

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(PhysOrg.com) -- Every aging baby boomer listens for the footsteps of Alzheimer's, and for good reason: It's estimated that 10 million American boomers will develop the disease. The need to develop preventative strategies, ideally long before Alzheimer's destructive, clinical symptoms appear, is critical.

In furthering the steps toward that goal, UCLA associate professor of neurology John Ringman and his colleagues confirm in the current issue of the journal *Neurology* that during Alzheimer's earliest stages, levels of specific proteins in the blood and spinal fluid begin to drop as the disease progresses, making them potentially useful as biomarkers to identify and track progression long before symptoms appear.

Identifying patients at the clinically "silent" stage is a prerequisite for advancing the strategies needed to prevent the symptoms from appearing. The hope is that one day, screening for such biomarkers could take its place beside such routine tests as colonoscopies and mammograms as another common tool of preventive medicine.

Familial Alzheimer's and sporadic Alzheimer's are two of the basic types of the disease. The majority of Alzheimer's cases are sporadic and late-onset, developing after the age of 65; the causes of this disease type are not completely understood. Familial Alzheimer's (FAD) is a rare form of the disease caused by certain gene mutations that affects less than 2 percent of Alzheimer's patients. FAD is early-onset, meaning the disease develops before age 65, and it is inherited; all offspring in the same generation have a 50-50 chance of developing FAD if one of their

parents had it. The markers the researchers tracked came from people with the FAD mutations.

"Since we knew that 50 percent of first-degree relatives will inherit the same rare mutations, we were able to study the biochemical changes occurring in the cerebrospinal fluid and blood as long as 30 years before the subjects were likely to develop the disease themselves," said Ringman, who is the assistant director of the Mary S. Easton Center for Alzheimer's Disease Research at UCLA. "This allowed us to identify markers that might be used to diagnose the disease prior to the development of overt symptoms, and also tells us a lot about the chain of events that cause the disease."

The study looked at several proteins that exist in the cerebrospinal fluid and plasma in 21 FAD mutation carriers and compared them to noncarriers. Knowing that the extracellular plaques characteristic of Alzheimer's that form in the brain consist largely of a fibrous beta-amyloid protein called AB42, the researchers looked at that protein and found that it was elevated in the plasma of FAD mutation carriers, appearing long before the development of obvious dementia. The level then appears to drop as the disease progresses. In addition, the researchers showed that the ratio of AB42 to another protein, AB40, was reduced in the cerebrospinal fluid of FAD mutation carriers and, further, that the levels of two other proteins, called t-tau and p-tau181, were elevated prior to overt symptoms.

"These results are worth highlighting because of the implications for Alzheimer's prevention research," Ringman said. "The presence of cerebrospinal fluid biomarkers of Alzheimer's disease prior to any clinical symptoms suggests the pathology of Alzheimer's precedes the clinical symptoms and further demonstrates that it may be possible to detect those changes prior to the appearance of cognitive dysfunction."

The use of subjects at risk for autosomal dominant Alzheimer's disease is both a strength and a weakness of the study, Ringman said. Using research subjects that are known to have a predisposition to Alzheimer's calls for caution. On the one hand, he said, "this population can be genetically defined so we can predict whether they will or will not develop the disease in the future with a high degree of certainty. However, these mutations are very rare, and some findings in this rare form of Alzheimer's disease may not generalize to more typical late-onset Alzheimer's disease."

Nevertheless, he said, since the pathology of FAD is essentially identical to that of sporadic Alzheimer's, it is plausible that the preclinical changes in these proteins are common to all forms of the disease and bear more scrutiny.

Provided by UCLA