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Blood test takes step toward predicting Alzheimer's risk, Stanford researchers find

STANFORD, Calif. - One of the most distressing aspects of Alzheimer's disease is the difficulty in determining whether mild memory problems are the beginning of an inevitable mental decline. Researchers at the Stanford University School of Medicine have developed a blood test that is a step toward giving people an answer two to six years in advance of the onset of the disease.

The test identifies changes in a handful of proteins in blood plasma that cells use to convey messages to one another. The research team discovered a connection between shifts in the cells' dialog and the changes in the brain accompanying Alzheimer's. They found that the blood test could indicate who had Alzheimer's with 90 percent agreement with clinical diagnoses, and could predict the onset of Alzheimer's two to six years before symptoms appeared.

"Just as a psychiatrist can conclude a lot of things by listening to the words of a patient, so by 'listening' to different proteins we are measuring whether something is going wrong in the cells," said Tony Wyss-Coray, PhD, associate professor of neurology and neurological sciences and senior author of the study.

"It's not that the cells are using new words when something goes wrong," said Wyss-Coray. "It's just that some words are much stronger and some are much weaker; the chatter has a different tone."

The study will appear in the Oct. 15 advance online edition of Nature Medicine.

"I really think it has enormous potential," said Lennart Mucke, MD, director and senior investigator of the Gladstone Institute of Neurological Disease at the University of California-San Francisco, who did not participate in the study. "Most researchers in this field agree that there is an urgent need for better lab tests for Alzheimer's disease, and this study has addressed this need admirably."

Listening to cells' messages may not only lead to the first noninvasive diagnostic test for Alzheimer's; it could also lead to similar discoveries about other disorders by focusing on what cells use to talk to each other, said Wyss-Coray, who is part of the Geriatric Research, Education and Clinical Center at the Veterans Affairs Palo Alto Health Care System.

Currently, the clinical diagnosis for Alzheimer's is one of exclusion - by testing for other causes of memory loss and cognitive declines, such as stroke, tumors and alcoholism. If those conditions are eliminated as causes of memory loss, what remains is Alzheimer's, which is the most common cause of dementia. Even the clinical diagnosis is imperfect, and the only definitive diagnosis is by brain autopsy after a person has died.

According to the Alzheimer's Association, more than 5 million Americans are afflicted with the disease, which robs patients of memory, thinking and the ability to communicate.

The blood-test concept began when Wyss-Coray and Sandip Ray, one of the two first authors of the paper, collaborated to measure levels of 120 different proteins used by cells to communicate to see if any of them could be indicators for Alzheimer's.

At the time the work was done, Ray was an employee of Satoris Inc., a company co-founded by Ray, Wyss-Coray and Yuen So, MD, PhD, professor of neurology and neurological sciences. Wyss-Coray is a consultant for Satoris Inc.

Ray used blood samples from five people diagnosed with Alzheimer's, and compared those to samples from five people who didn't have the disease. He found a number of proteins used for communication that demonstrated striking differences between the two groups.

Markus Britschgi, PhD, a postdoctoral scholar in Wyss-Coray's lab, became intrigued with the idea that proteins used by cells to communicate could be measured in the blood to indicate what is going on in the body - including the brain.

"This study made me realize that we should get away from this image of a brain isolated from the body," said Britschgi, who is also a first author of the paper. "The brain is part of the body and so it's connected in one huge network."

Reaching out to clinics in the United States, as well as Sweden, Poland and Italy, Britschgi obtained a total of 259 archived blood samples from individuals who had symptoms ranging from nothing abnormal to mild cognitive impairment to advanced Alzheimer's. Starting with 120 communication proteins, the team developed an analysis procedure to recognize if there

was a pattern seen in Alzheimer's that could be compared with that of people without the condition. They discovered that as few as 18 proteins were sufficient to identify an Alzheimer's-specific pattern.

Among blood samples from 92 individuals who ranged from no symptoms to full dementia, the protein analysis matched the clinical diagnosis 90 percent of the time.

They then asked if they could predict the development of Alzheimer's among 47 people with mild cognitive impairment who had been followed from two to six years. The test - done on blood samples taken several years earlier - flagged 91 percent of the patients who developed Alzheimer's by the end of the follow-up time, as diagnosed by conventional methods.

"Already we have people approaching us at meetings asking if they can give us a vial of their grandfather's blood for testing," said Britschgi. Their findings show that it is possible to use factors in the blood to diagnose and even predict the disease, but, the authors emphasized, it must now be confirmed in other labs.

According to Satoris Inc, the company will develop a commercial Alzheimer's blood test, initially for use in research labs and, if confirmed as reliable, eventually as a clinical diagnostic test upon regulatory approval.

Britschgi and Wyss-Coray are interested in finding out why the cell communication pathways are altered in Alzheimer's. In their study, they determined that the 18 proteins that indicate Alzheimer's are also involved in the production of new blood cells, immune processes and apoptosis, the process of programmed cell death when a cell is no longer needed.

"Our hypothesis is that there is something wrong with the production of certain blood cells, which may be needed to clear that stuff that accumulates in the brain in Alzheimer's disease," said Wyss-Coray. "That makes a lot of sense, and it is very exciting to think of immune cells and molecules interacting with the brain."

Mucke, the director of Gladstone, added, "It will be interesting to find out in clinical trials if the identified disease markers are also useful for monitoring the response of individual patients to therapeutic interventions. That would be tremendous."

Of the 25 authors included on this paper, six other contributors from Stanford are included. They are: Yoshiko Takeda-Uchimura, a research associate in Wyss-Coray's laboratory; Leah Friedman, PhD, senior research scholar in psychiatry and behavioral sciences; William Robinson,

MD, PhD, assistant professor of medicine; Jared Tinklenberg, MD, professor of psychiatry and behavioral sciences; Jerome Yesavage, MD, professor of psychiatry and behavioral sciences; and Robert Tibshirani, PhD, professor of health research and policy and of statistics. Tibshirani is also a consultant for Satoris Inc.

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