AAD: A Skin-Based Test for Alzheimer's Disease?

Small study show high Tau protein levels in buccal swabs

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Action Points

ORLANDO -- Patients with Alzheimer's disease had significantly higher levels of the disease-associated protein phosphorylated Tau (P-tau) in buccal mucosal swabs as compared with a normal control group, a small preliminary study showed.

Swabs from 11 patients with Alzheimer's disease had median immunostaining for P-tau of 45% as compared with 18% for the healthy control patients. However, a comparative analysis of 10 cadaveric brains from patients with various neurodegenerative disorders failed to identify Tau protein in the brainstem of any specimens despite the presence of neurofibrillary tangles in the hippocampal area, reported Sami Saikaly, a medical student at the University of Central Florida College of Medicine in Orlando, and colleagues.

The findings added to previous evidence of p-Tau accumulation in epidermal cells, and investigators vowed to continue looking for a possible Tau pathology pathway between the brain and periphery, which might have diagnostic potential in Alzheimer's disease.

"This result supports the hypothesis that tau proteinopathy is not only expressed in neurons, but also in other cells of ectodermal origin," said Saikaly in a presentation at the American Academy of Dermatology annual meeting. "A potential pathway of tau pathology connecting the brain with the periphery requires further study. These results support the hypothesis that the skin reflects the changes that are occurring in the hippocampus."

Though intriguing, the results are too preliminary to speculate about a potential role for evaluating P-tau levels in peripheral tissues in the diagnosis or management of patients with Alzheimer's disease, according to neurologist David S. Knopman, MD, of the Mayo Clinic in Rochester, Minn. The poster presentation lacked information about the patient control group, and the cadaveric study included a single control, he noted.

Additionally, the report lacked specifics about the patients with Alzheimer's disease, such as whether they had pathologic disease associated with high Braak stage paired filament Tau.

"There really isn't enough information to evaluate the claim, but I hope that the authors pursue the idea further," Knopman, who was not involved in the study, wrote in an email to MedPage Today. "I am concerned about the specificity of the finding because most older people have some paired helical filament tau at least in their medial temporal lobes, so much more work with autopsy-proved or tau PET-proved cases will be necessary to establish the specificity and sensitivity of the finding."

The findings represented the latest work to realize a longstanding goal of senior author Robert Norman, DO, also of the University of Central Florida: Develop a simple, inexpensive, noninvasive test for Alzheimer's disease.

"At my practice in Tampa, we take care of hundreds of patients in nursing homes and along the way became more and more interested in the correlation between the skin and the brain," Norman told MedPage Today. "Prior to this time, we've only been able to do postmortem studies to check for dementia. The only alternative has been to do brain scans and extensive testing that can cost thousands of dollars. We're looking to develop a relatively inexpensive test that can substantiate the clinical diagnosis, the Mini-Mental State Exam (MMSE), and be part of the whole package to determine definitively whether someone has Alzheimer's disease."

"I have a tremendous amount of compassion for patients with dementia, and it's very frustrating not to be able to do more for them," he added. "I honestly believe that [dementia] is the pandemic of the 21st century, and if we don't get out ahead of it and become very aggressive, not only will a lot of patients suffer but the next generation of physicians who care for these patients are going to suffer, as well."

The presence of P-tau in the hippocampal region of the brain is diagnostic for Alzheimer's disease. Establishing a Tau pathway between the brain and peripheral tissues would be a necessary step toward developing a potential diagnostic test based on analysis of peripheral tissue.

Norman and colleagues previously found skin punch biopsies from patients with Alzheimer's disease exhibited significantly higher staining for P-tau as compared with dementia-free patients. That work led to collaborative studies with researchers in Mexico, demonstrating P-tau protein in skin cancer lesions, including squamous and basal-cell lesions.

The findings led to additional research into potential epidermal sources of tau, including the small study of patients with Alzheimer's disease. Recognizing the invasiveness of punch biopsies, investigators wanted to determine whether buccal swab specimens from patients with Alzheimer's disease might be used to detect P-tau.

The 11 patients included in the analysis all had clinical diagnoses of Alzheimer's disease confirmed by standard imaging and neuropsychologic testing, including the MMSE. For comparison, investigators recruited seven age-matched patients without dementia. Additionally, the investigators examined cadaveric brains from patients with neurodegenerative disorders (including Alzheimer's) to compare tau-associated pathology with findings from the buccal-swab study.

The results showed that buccal specimens from the patients with Alzheimer's disease had significantly higher levels of immunostaining for P-tau as compared with buccal samples from the control group (P=0.04).

The study of cadaveric brains yielded inconsistent results, as the investigators found neurofibrillary tangles, ghosts, and neuritic plaques in the hippocampus of some of the brains but no evidence of tau-associated pathology in any of the brainstems.

Norman said the research showed a tendency toward more intense staining in patients with lower MMSE scores (associated with more severe dementia). Future studies will focus on identifying more correlations between clinical and laboratory data and evaluating different types of monoclonal antibodies in an effort to improve results.