Imaging Plus Biomarker Predicted Dementia in AD

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CHICAGO — A combination of specialized brain imaging and cerebrospinal amyloid β_{42} measurements powerfully predicts the presence—and absence—of Alzheimer's-type dementia.

For several years researchers have focused on $A\beta_{42}$ in cerebrospinal fluid (CSF) as a possible biomarker of Alzheimer's disease (AD): Higher levels indicate the protein is still soluble, whereas lower levels suggest that it might be building up in the brain as neuropathologic plaque. But an unpredictable overlap of CSF $A\beta_{42}$ among controls, Alzheimer's patients, and those with mild cognitive impairment has confounded any definitive conclusions, Anne Fagan, Ph.D., said at the International Conference on Alzheimer's Disease.

"Over the years, many people have looked at the level of this protein in CSF in nondemented and Alzheimer's subjects," said Dr. Fagan of Washington University, St. Louis. "Although the mean levels are different, there has always been a question over why there is this tremendous amount of overlap, with many controls showing $A\beta_{42}$ levels as low as those we see among Alzheimer's patients, and some Alzheimer's patients showing levels as high as those of normal controls."

The advent of Pittsburgh imaging compound B (PIB), an imaging agent that lights up amyloid plaques during positron emission tomography scanning, has allowed Dr. Fagan to more fully explore the associations of $A\beta_{42}$ in the brain and the CSF. She presented the results of a prospective study of 132 subjects, all of whom underwent PIB scanning and a lumbar puncture for CSF $A\beta_{42}$ levels within a 2-year period. These volunteers had a mean age of 66 years; 113 were cognitively normal, 14 had very mild Alzheimer's dementia, and 5 had mild Alzheimer's dementia.

Dr. Fagan and her colleagues found what she called "a striking inverse relationship between the levels of amyloid in the brain and levels of $A\beta_{42}$ in the CSF."

Of the 37 subjects whose PIB-PET scans showed high levels of brain amyloid, 36 (97%) had low CSF $A\beta_{42}$. Conversely, 80 of the 95 with low levels of brain amyloid (84%) had high CSF $A\beta_{42}$. These relationships were strong regardless of cognitive status at the time of testing. "Low CSF $A\beta_{42}$ appears to be an excellent marker for the presence of brain amyloid, regardless of whether people have dementia or not. The presence of low CSF $A\beta_{42}$ combined with PIB-positivity in the brain may be antecedent biomarkers of Alzheimer's disease, predicting who will develop future dementia."

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DR. FAGAN

Indeed, some independent clinical follow-up data on the cohort seem to confirm this, Dr. Fagan said. Three subjects who were cognitively normal at the time of testing, but were PIB-positive and had low CSF $A\beta_{42}$, have since developed a diagnosis of very mild Alzheimer's dementia.

Four who had a diagnosis of very mild Alzheimer's at the time of testing, but who were PIB-negative and had high CSF $A\beta_{42}$ have had their diagnoses changed to either "no dementia" or "non-Alzheimer's dementia." "This seems to say that high CSF $A\beta_{42}$ and cortical PIB-negativity may be useful for a differential diagnosis, identifying possible Alzheimer's misdiagnoses in the very early stages."

Finally, Dr. Fagan noted, four subjects who were cognitively normal at the time of testing and were PIB-negative but had low CSF $A\beta_{42}$ have since undergone additional PIB scans. "One subject is now PIB-positive, indicating the presence of cortical amyloid, and two others may have PIB-positivity in some select brain regions. Levels of CSF $A\beta_{42}$ may decrease prior to cortical amyloid becoming detectable by PIB, and thus may be a very sensitive biomarker for the earliest, preclinical stages of Alzheimer's."

The potential clinical impact of such an early diagnostic tool could be profound. "Our goal is to push the disease diagnosis back to a much earlier time, hopefully into this preclinical stage," Dr. Fagan said at the meeting sponsored by the Alzheimer's Association. ■