Biomarkers may help predict risk of Alzheimer's disease in patients with mild cognitive impairment

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Several cerebrospinal fluid (CSF) biomarkers showed good accuracy in identifying patients with mild cognitive impairment who progressed to Alzheimer disease, according to a study in the July 22/29 issue of *JAMA*.

Alzheimer disease (AD) is the most common cause of dementia, affecting more than 15 million individuals worldwide. Because of the type of progression of the disease, there is a need for methods enabling early diagnosis. "Treatments would need to be initiated very early in the disease process, before the neurodegenerative process is too severe. Much focus has thus been directed on patients with mild cognitive impairment (MCI), which is a syndrome characterized by cognitive impairment beyond the age-adjusted norm, but not severe enough to fulfill the criteria for dementia," the authors write.

Biochemical changes in the brain are reflected in the CSF, and intense research efforts have been made to develop biomarkers for the central pathogenic processes in AD that can be used as diagnostic tools. Some studies have shown that CSF biomarkers may be useful to identify incipient (beginning) AD in patients with MCI, but most of these studies have been small and conducted at single centers, according to background information in the article.

Niklas Mattsson, M.D., of the Sahlgrenska Academy at the University of Gothenburg, Mölndal, Sweden, and colleagues conducted a multicenter

study to assess the diagnostic accuracy of the CSF biomarkers β-amyloid1-42 (Aβ42), total tau protein (T-tau), and tau phosphorylated at position threonine 181 (P-tau) in identifying incipient AD in a large group of patients with MCI. The study had two parts: a cross-sectional study involving patients with AD and controls to identify biomarker cutoff levels, followed by a prospective cohort study involving patients with MCI, conducted 1990-2007. A total of 750 individuals with MCI, 529 with AD, and 304 controls were recruited by 12 centers in Europe and the United States. Individuals with MCI were followed for at least 2 years or until symptoms had progressed to clinical dementia.

During follow-up, 271 participants with MCI were diagnosed with AD and 59 with other dementias. The researchers found that the Aβ42 assay in particular had considerable intersite variability. Patients who developed AD had lower median (midpoint) Aβ42 and higher P-tau and T-tau levels than MCI patients who did not develop AD during follow-up. Cut-offs with sensitivity (the proportion of affected individuals who have a correct positive test result for the disease that the test is intended to reveal) set at 85 percent were defined in the AD and control groups and tested in the MCI group, where the combination of Aβ42/P-tau ratio and T-tau identified incipient AD with a sensitivity of 83 percent and specificity (the proportion of individuals with correct negative test results for the disease the test is intended to reveal) of 72 percent.

"We determined in a large multicenter study that the CSF biomarkers Aβ42, T-tau, and P-tau can be used to predict with good accuracy which MCI patients will develop AD, as previously found in smaller studies. This multicenter collaboration avoids several of the risks of biases associated with single-center studies by having included substantially more patients than previous studies. Cerebrospinal fluid biomarker changes were found to be significantly associated with incipient AD. However, the considerable intercenter variations in assays and patient assessments described point to a need for standardization of sample

handling as well as of clinical assessments. Although each memory clinic center followed up its cohorts prospectively and used established clinical criteria, a limitation of the present study is the lack of fully harmonized study protocols for all centers, which might account for some of the intercenter variations that we observed," the researchers write.

"Using CSF Aβ42, T-tau, and P-tau in memory clinics will result in some false-positive cases, as well as false-negative cases, and the biomarkers may therefore be useful primarily as screening tools, selecting individuals for a detailed further clinical follow-up. Furthermore, they may be useful in enriching study populations for clinical trials of future disease-modifying AD treatments. Until such treatments become available, however, these tests are not generally appropriate for routine clinical use because it is not currently possible to alter the development of AD."

More information: *JAMA*. 2009;302[4]:385-393.

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