Alzheimer's Biomarkers Show Tantalizing Hint at Utility for Tracking Prevention

— Study points to biomarkers that predict amyloid plaque accumulation speed

by John Gever, Contributing Writer, MedPage Today, July 29, 2024

PHILADELPHIA -- Blood tests for Alzheimer's disease biomarkers may not only be useful for clinical diagnosis but could also make it possible to test preventive therapies in people not yet showing any signs of the condition, researchers said.

In a prospectively followed cohort of older people with normal cognition and low amyloid-β (Aβ) plaque burdens in their brains, baseline plasma levels of tau and Aβ protein species predicted the speed at which Aβ plaques accumulated over 5 years of follow-up, according to Oskar Hansson, MD, PhD, of Skåne University Hospital in Malmö, Sweden, and colleagues.

Specifically, participants with a low ratio of two Aβ amino acid forms (Aβ42/40) and high ratio of tau217 phosphorylation (i.e., tau with a phosphate molecule attached at the threonine-217 residue, %p-tau217) showed dramatically faster plaque accumulation, the researchers reported in *JAMA Neurology*. The study was also to be presented at the Alzheimer's Association International Conference (AAIC).

The report followed one from many of the same researchers, also presented at AAIC, indicating that a model based on this same pair of biomarkers outperformed human doctors in diagnosing Alzheimer's disease in people with cognitive deficits.

For people without such symptoms, or even with Aβ substantial plaque burdens, the findings could pave the way for "primary prevention" trials to identify drugs or other therapies that keep Aβ from accumulating in the brain. These would be targeted at individuals who, because of family history, genetic features, or other factors, are thought likely to develop Alzheimer's disease down the line.

Such trials, which necessarily must enroll people with no cognitive deficits and low plaque burdens, are currently not feasible. If participants were simply plucked randomly from the general population, either huge numbers or decades of follow-up would be needed to determine whether a particular therapy was effectively preventing plaque buildup and, hopefully, Alzheimer's disease.

But if a subpopulation likely to undergo rapid Aβ accumulation could be identified, then such trials could be shorter and wouldn't need so many participants to confirm an effect. That's where the Aβ42/40 and %p-tau217 blood test comes in.

The study drew primarily from the so-called BioFINDER-2 cohort study underway in Sweden, which enrolled cognitively normal older people from 2017 to 2022 and followed them with tests including periodic PET scans to evaluate brain Aβ plaque burden. Overall, the cohort included 495 people, among whom 384 had low plaque burdens (<40 centiloid). Median age in this latter group was 65 (IQR 54-76). An average of 2.7 years elapsed from the baseline PET scan to the last.

By far the most rapid plaque accumulation was seen in people with low (defined as below the median) Aβ42/40 and high (above the median) %p-tau217 at baseline, as opposed to the three other groups with different combinations of high versus low ratios. The low Aβ42/40, high %p-tau217 group also had the highest average plaque burden at baseline. This group then saw brain Aβ accumulation shoot up during 5 years of follow-up, whereas it didn't change dramatically in the other three groups. Participants with high baseline Aβ42/40 and low %p-tau217 showed no mean increase at all in brain plaque levels.

Hansson and colleagues also looked at baseline Aβ42/40 and %p-tau217 individually. As expected, participants with low Aβ42/40 showed faster plaque accumulation than those with high initial levels. The same was found for high versus low %p-tau217. In both cases, though, the rate of accumulation was lower than with the combination of low Aβ42/40 and high %p-tau217.

Put another way, correlating low baseline Aβ42/40 and high %p-tau217 with subsequent plaque accumulation produced an R^2 value of 0.48, signifying a very strong relationship.

To check on these findings, the researchers performed the same analyses on two other prospective cohorts: an earlier Swedish study now called BioFINDER-1 and another conducted at Washington University's Knight Alzheimer Disease Research Center in St. Louis. The same pattern of results was seen in these groups, comprising 205 and 283 initially cognitively normal individuals, respectively, Hansson's group reported.

Importantly, though, many participants -- close to half -- with low baseline Aβ42/40 and high %p-tau217 did not show particularly rapid plaque buildup. And a receiver-operating characteristic analysis failed to show a significant difference in predictive ability between the two-marker combination and %p-tau217 alone, although both were superior to Aβ42/40. That led the authors to express caution about immediately applying their results to prevention trial designs.

"Future studies in a larger sample and using highly precise approaches for quantitation of plasma p-tau217 and Aβ42/40 (such as for example, assays on fully automated platforms) are needed," they wrote.

John Gever was Managing Editor from 2014 to 2021; he is now a regular contributor.

Disclosures

Funding for the study came from a wide variety of sources, primarily U.S. and European government grants and nonprofit foundations. No pharmaceutical or diagnostic companies were involved.

Study authors reported extensive relationships with industry outside the reported work. Also, several reported intellectual property interests in Aβ and tau testing for diagnostic and prognostic purposes. One author was an employee of C2N Diagnostics.

Primary Source

JAMA Neurology

Source Reference: *Janelidze S, et al "Plasma phosphorylated tau 217 and Aβ42/40 to predict early brain Aβ accumulation in people without cognitive impairment" JAMA Neurol 2024; DOI: 10.1001/jamaneurol.2024.2619.*

0 Comments

Medical News From Around the Web

LOS ANGELES TIMES
California vs. Florida: The surprising answer to which handled COVID better

BECKER'S HOSPITAL REVIEW
Flu hospitalizations climb for 3rd week in a row: 7 notes

CBS NEWS
COVID variant BA.2.86 triples in new CDC estimates, now 8.8% of cases

Recommended For You

Neurology
New Extended-Release Parkinson's Drug Approved

Neurology
Omega-3 and Alzheimer's Gene; Parkinson's Microbiome Transplant; The Role of Reelin

Primary Care
Sugar Substitute and Blood Clots; Bacteria in Microwaves; Lives Saved by COVID Vax

Public Health & Policy
Mask Ban Approved; Magnesium and Sleep; Tenet Hospitals Sold

Pulmonology
David Lynch's Emphysema; Trump Losing His Train of Thought; Emergency Blood Shortage

AAIC
Intermittent Fasting May Improve Memory, Executive Function, Early Trial Suggests

Medical News From Around the Web

LOS ANGELES TIMES
California vs. Florida: The surprising answer to which handled COVID better

BECKER'S HOSPITAL REVIEW
Flu hospitalizations climb for 3rd week in a row: 7 notes

CBS NEWS
COVID variant BA.2.86 triples in new CDC estimates, now 8.8% of cases

VACCINE
Modeling COVID-19 vaccine booster-elicited antibody response and impact of infection history.

ANNALS OF FAMILY MEDICINE
Practice Facilitation to Support Family Physicians in Encouraging COVID-19 Vaccine Uptake: A Multimethod Process Evaluation.

NATURE MEDICINE
Financial incentives for COVID-19 vaccines in a rural low-resource setting: a cluster-randomized trial.