Published in final edited form as:

Neurology. 2008 February 19; 70(8): 586–587. doi:10.1212/01.wnl.0000299905.05595.68.

Toward a plasma marker for Alzheimer disease: Some progress, but still a long way to go

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Progress in neurology frequently lags 10 to 20 years behind that of cardiology. Early data correlating cardiovascular disease and serum levels of total and low-density lipoprotein cholesterol have led to treatments (exercise, weight loss, and statins) which have decreased age-adjusted cardiovascular mortality rates by 40%. In this regard, serum cholesterol levels have transitioned from a biomarker to a risk factor as treatment aimed at lowering serum levels have conferred clinical benefits. For 25 years, neurologists have been trying to apply this model to Alzheimer disease (AD) with little success. In the current issue of *Neurology*,[®] Ertekin-Taner et al.¹ add to the growing literature that plasma A β 42 levels are a potential biomarker for AD.^{2–6} Because A β 42 was elevated in plasma in asymptomatic first-degree relatives of patients with presenilin 1, presenilin2, and amyloid precursor protein mutations who had early onset AD (EOAD), they reasoned that A β 42 levels might also be elevated in asymptomatic first-degree relatives of patients with late onset AD (LOAD).

The Jacksonville Mayo group compared plasma A β 42 levels between two cohorts of relatives of patients with AD and two groups of controls. The first cohort consisted of 103 first-degree relatives of patients with LOAD and 106 unrelated controls, the second of 109 subjects from 25 multigenerational LOAD families and 50 married-in spouses. In both cohorts, the relatives were between 20 and 65 years of age and cognitively normal. In both cohorts, small but significant differences between relatives and controls were found. However, there are several important caveats. First, the absolute magnitude of the differences was small. Second, measurements of A β 42 required substantial normalization, and comparisons of absolute values across different assay batches were not possible. Indeed, the absolute value in family members in one study was virtually the same as that of controls in a second study. Third, although the Mayo group showed only modest variation in A β 42 levels on a time scale of hours or days, substantial increases occur with normal aging after the age of 65. In terms of predictive value in individual family members, the utility of A β 42 remains to be demonstrated.

Among patients with dementia and clinical Alzheimer disease, plasma A β 42 levels are lower than normal, suggesting that plasma levels gradually decline from elevated levels through normal levels to low level as patients transition from cognitively normal with increased genetic risk through MCI and into clinical dementia. Thus to be clinically useful, clinicians would need to do long term tracking of A β 42 levels.

Their study also adds indirect evidence concerning the heritability of LOAD. Genetic studies of EOAD where many cases are autosomal dominant quickly led to finding of mutations in the amyloid precursor protein, presenilin I, and presenilin II genes. These findings were strongest support for the amyloid cascade hypothesis as each mutation led to increased synthesis of A β 42. However, EOAD—arbitrarily defined as onset before age 65—accounts for less than 5% of all cases of AD. What are the genetic contributions to LOAD?

In 1993, Corder et al.⁷ reported that apolipoprotein ϵ 4 was associated with increased risk of AD and earlier age at onset. The apolipoprotein ϵ 4 allele was not fully penetrant—subjects homozygous for the allele have lived into their 100s and never develop AD. Only 40% of all patients with LOAD have even one apolipoprotein ϵ 4 allele, yet to date no other LOAD gene has been conclusively proven and some have doubted whether “another apoE” where a common polymorphism contributes to a significant share of LOAD cases will be found.⁸ The current work of Ertekin-Taner et al. demonstrates that the inheritability of elevated plasma A β was $31.9 \pm 13.8\%$ (p as shown < 0.007) using a conservative analysis model. This group had previously shown that genetic mutations that cause EOFAD increase plasma A β 42, so the variants responsible for the heritability of A β would be expected to contribute to the heritability of LOAD, but the precise relationship between the inheritability of LOAD and plasma A β remains to be determined.

In contrast to biomarkers in blood, CSF biomarkers are already used by some in the diagnosis of AD and are certainly closer than blood markers to being of genuine clinical usefulness. CSF levels of hyperphosphorylated tau and A β 1–42 have been predictive of conversion from MCI to AD.⁹ At first one might think that lumbar puncture is too invasive to gain widespread acceptance as a screening test in patients whose only risk for AD is advancing age. Yet lumbar puncture may be no more invasive than colonoscopy, which is the standard of care as a screening test for colon cancer in adults over age 50. Nonetheless, the utility of a marker in plasma or serum that can be obtained repeatedly is self-evident.

The report by Ertekin-Taner et al.¹ adds yet another small set of data supporting the “amyloid cascade hypothesis.” Longitudinal studies testing whether cognitively normal first-degree relatives with elevated A β 42 levels truly do develop AD more frequently than cognitively normal first-degree relatives with normal A β 42 levels have not been completed. Until such studies are completed and replicated, plasma A β 42 levels must remain one of many potential biomarkers. In the meantime, plasma A β 42 has proven to be a surrogate quantitative phenotype for AD that is useful in identifying candidate genes associated with AD.

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