Editorial

Where do we stand on the relationship between tau biomarkers and mild cognitive impairment?

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Abstract: We present an editorial on a recent publication by Amlien *et al.* [2013] in which diffusion tensor imaging (DTI) was used to quantify longitudinal decreases in fractional anisotropy (FA) and increased radial diffusivity (D_R) in patients with mild cognitive impairment (MCI). These longitudinal alterations were found to be greater in MCI patients with high cerebrospinal fluid (CSF) tau levels at baseline and greater than healthy controls. Amlien *et al.* concluded that tau levels were an important early biomarker for predicting rate of disease progression and outcome. The results of this study are an interesting finding for possible predictive use of tau levels in MCI. However, in our assessment, the methodology does not support the conclusion that CSF total tau levels are predictive of MCI progression towards a disease state such as Alzheimer's disease (AD). Further longitudinal study is needed, that includes follow-up neuropsychological assessment and conversion of subjects in the study to AD, to conclude that CSF total tau levels represent a predictive biomarker of MCI progression towards AD.

Key Words: Mild cognitive impairment (MCI); diffusion tensor imaging (DTI); Alzheimer's disease; amyloid beta; tau protein

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Introduction

Amlien *et al.* (1) recently reported a potentially important finding—that high tau levels in cerebrospinal fluid (CSF) for patients diagnosed with mild cognitive impairment (MCI) were correlated with longitudinal diffusion tensor imaging (DTI) measures of decreases in fractional anisotropy (FA) and increases in radial diffusivity (D_R) relative to age-matched controls. Both of these results are consistent with a longitudinal loss of white matter integrity for patients diagnosed with MCI that have high CSF tau levels relative to controls, although the FA measure did not show significant differences between the high- and low-level tau groups diagnosed with MCI. These authors stated that: "The findings support the CSF total tau level as an important early biomarker for predicting rate of disease progress and outcome" [p. 300 (1)]. We agree that Amlien *et al.* have observed an interesting finding that longitudinal differences in FA and D_R are greater in patients diagnosed with MCI, although we have concerns with the conclusion that these data support that CSF total tau levels represent a predictive biomarker of MCI progression towards a disease state [e.g., Alzheimer's disease (2,3)].

MCI: syndrome and subtypes

We begin our discussion of Amlien *et al.* with a brief discussion of MCI and Alzheimer's disease (AD). MCI is defined as a relatively mild disruption of cognitive function in one or more domains, even though global cognitive function and activities of daily living are relatively unaffected (4,5). Alzheimer's disease is defined by an increased density of plaques and neurofibrillary tangles

in the brain (6). The plaques consist largely of amyloid-beta and the neurofibrillary tangles consist largely of hyperphosphorylated tau (7). It is unclear what causes the over-production of amyloid-beta and tau in AD patients, and also it is unclear which is more important—although one possibility is that increased amyloid-beta production helps trigger the tau cascade (7).

MCI is considered to be a preclinical stage of dementia in many individuals—particularly for Alzheimer's disease (5,8). Approximately 50 percent of individuals diagnosed with MCI convert to AD within five years (5,9). However, this means that approximately 50% of individuals diagnosed with MCI do not convert to dementia. Another important issue related to MCI is the existence of different subtypes. Petersen *et al.* (4) suggested amnestic and non-amnestic subtypes, and that individuals could be diagnosed with single-domain (typically just amnestic) MCI or multi-domain MCI (typically amnestic and another domain—such as executive dysfunction). Amnestic MCI has the highest conversion rate to AD, although executive dysfunction MCI may convert to other types of dementia [e.g., frontotemporal dementia (4)].

Amlien *et al.* and MCI participants: did they convert to AD?

Perhaps the greatest concern with the Amlien *et al.* study is that none of the MCI patients in the study converted to AD. Because a large number of individuals diagnosed with MCI never convert to AD or any other form of dementia (5,9), it is not clear to us how one can use the Amlien *et al.* results to predict the progression of MCI toward a disease state. In the ideal situation, all the high-tau participants would have converted to AD and all of the low-tau participants would not. However, we do not know whether any of the high-tau participants will ever convert to AD (or the conversion status of the low-tau participants). Without this important conversion status data, it is impossible to determine whether CSF-based tau biomarkers predict whether patients will convert to AD or some other form of dementia.

Getting back to the issue of different subtypes in MCI, we also do not know the composition of different subtypes in the Amlien *et al.* study. It would have been optimal if all of the high-and low-tau participants were diagnosed with amnestic MCI because this subtype has a higher probability of converting to AD than do the other subtypes (5). It may be possible that the high-tau group was predominantly of the amnestic subtype, but that the low-tau group was of another subtype (e.g., single-domain executive dysfunction). Such a scenario might have resulted in an artifact in which it appeared that a tau biomarker predicted longitudinal loss of white-matter integrity (FA and D_R), but in this case, tau levels would be confounded with MCI subtype.

Comparisons between high-tau and low-tau groups

Another concern with the Amlien *et al.* study was that while MCI patients did show significantly lower FA levels than did controls in the cross-sectional results, there were no overall group differences in FA rate of change between the MCI patients and controls. If this is to be clinically significant, it is not enough for there to be differences across groups—the rate of change must be greater for the MCI individuals to convert to AD. Furthermore, the MCI high-tau group did not differ significantly from the low-tau group in either FA or D_R longitudinal measures of white-matter integrity. It is the case, though, the high-tau group showed significantly larger FA and D_R longitudinal changes than did the controls, but this comparison does not directly assess the utility of tau biomarkers in MCI patients. A stronger case for the efficacy of a tau biomarker to predict the course and conversion of MCI to AD would be to demonstrate that a high-tau MCI group showed more longitudinal change in FA and D_R measures of white-matter integrity than did a low-tau group. This evidence for a tau biomarker would be further enhanced if it could also be shown that the positive correlation between high-tau and loss of white-matter integrity was positively correlated with poorer neuropsychological assessment performance after AD conversion.

Is it tau or amyloid?

In the Amlien *et al.* study, they reported amyloid-beta (Aβ42 level) measures, but did not use this information as a covariate. The amyloid-beta levels were slightly higher in the low-tau group than in the high-tau group, and this may have actually masked some of the tau effect. Some researchers have hypothesized that the amyloid cascade in AD begins before the tau cascade, and even though CSF tau levels correlate better with conversion from MCI to AD than do CSF amyloid levels, there is good reason to believe that amyloid changes may begin the process that ends in AD (e.g., Karran *et al.*, 2011). Consequently, in future research, we suggest that amyloid levels be added as covariates to tau

studies. Research does support that Amlien *et al.* did pick the stronger biomarker (tau over amyloid), but it still makes good sense to control for amyloid levels in tau studies.

ROIs and their functional significance

In the DTI analyses reported by Amlien *et al.*, they observed that three fiber tracts (regions of interest, or ROIs) showed significant interactions between group and time for the D_R measure of white-matter integrity (no fiber tracts showed significant changes in FA). The three significant fiber tracts were the hippocampal area of the cingulum, the right inferior longitudinal fasciculus, and the right superior longitudinal fasciculus. While these three fiber tracts do have important functional relationships with cognitive processes that are known to be affected in AD [e.g., the hippocampus is known to be related to indexing for episodic memory (10), and episodic memory deficits are a critical symptom of AD], Amlien *et al.* did not make this link. Consequently, we recommend that research on tau biomarkers and white-matter integrity in the future describe this functional link between significant white-matter loss (derived from DTI measures) and known cognitive and/or affective symptoms associated with AD.

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