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2008

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citation for published version (APA)

Bouwman, F. H. (2008). *CSF biomarkers in dementia: Longitudinal aspects and combination with MRI*. [PhD-Thesis - Research and graduation internal, Vrije Universiteit Amsterdam].

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Summary

The general objective of this thesis was to explore longitudinal aspects of CSF biomarkers and post mortem changes of these CSF biomarkers. In addition the value of CSF and MRI was compared for discriminating (incipient) AD in memory clinic patients. First, we found a higher variability of baseline and follow-up $A\beta_{1-42}$ levels when assessed in different assays compared to assessment in the same assay. Therefore, in case of repeated spinal taps, determination of $A\beta_{1-42}$ levels should be performed in the same assay. Subsequently we described that the natural course of changes in CSF $A\beta_{1-42}$, total tau and ptau-181 levels over time was comparable in patients with subjective complaints, MCI and AD patients. The cross-sectional difference between groups, however, exceeded by far the longitudinal changes within groups. Thus, repeated assessment of these biomarkers is not useful in a clinical setting, as they are insensitive to disease progression. Second, we found that young and old AD patients have similar CSF biomarker levels, while elderly controls have lower $A\beta_{1-42}$ and higher (p)tau compared to young controls. This may suggest preclinical AD pathology in older controls, which should be borne in mind when using CSF biomarkers in clinical practice. In addition, although young and old AD patients may have similar levels in absolute terms, compared to their control group, the young AD patients *relatively* have more pathological levels, suggesting differences in AD pathology between young and old patients. Third, we concluded that determination of $A\beta_{1-42}$, total tau and ptau-181 levels in post mortem CSF is not useful as (p)tau levels were extremely high and $A\beta_{1-42}$ levels extremely low without differences between AD and LBD patients and controls. Fourth, combining CSF and MRI, we found hardly any association within diagnostic groups for CSF biomarker levels and whole-brain atrophy rate across controls, MCI and AD patients, although there are modest correlations of baseline CSF levels and whole-brain atrophy rate. Whole-brain atrophy rate was associated with clinical progression, measured by change in MMSE score, but

longitudinal changes in the CSF biomarker levels were not. In addition we showed that abnormal levels of CSF $A\beta_{1-42}$ and tau and an abnormal MTA-score are associated with a higher risk of progression to AD in MCI patients. The predictive values of CSF biomarkers exceeded that of the MTA-score. MCI patients with both abnormal CSF profile and an abnormal MTA-score, were at an even higher risk to progress to AD. This corresponds with what we found applying the newly proposed research criteria for AD: the combination of both abnormal CSF profile and abnormal MTA score in addition to an abnormal memory score yielded a specificity of 100% (sensitivity 43%), while abnormal VAT score with either abnormal MTA score or abnormal CSF profile yielded a specificity of 96% (sensitivity 86%). We conclude that MRI and CSF biomarkers appear to reflect different aspects of AD: atrophy measures on MRI appear to be linked to the clinical progression of the disease, whereas CSF biomarkers seem to reflect disease state rather than rate of progression.