Diagnosis and prognosis of Alzheimer’s disease in subjects with mild cognitive impairment
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SUMMARY

Introduction

Biomarkers of AD pathology in CSF and on MRI are now available and can be used to diagnose subjects with ‘MCI due to AD’. However, as the criteria for MCI due to AD have not yet been validated, prognosis of subjects fulfilling these criteria is largely unknown. Aim of this thesis was to assess the use of AD biomarkers for the diagnosis and prognosis of subjects with MCI and for the selection of MCI subjects for clinical trials. The thesis has two main topics: I. Biomarkers as predictors for AD-type dementia in subjects with MCI, II. Biomarkers as predictors of cognitive decline in subjects with MCI due to AD.

Main findings

Biomarkers as predictors for AD-type dementia in subjects with MCI

In chapter 2 we assessed biomarkers in blood, CSF and MRI as predictor for progression from MCI to AD-type dementia and for the selection of MCI subjects for clinical trials.

In chapter 2.1 we performed a meta-analyses of biomarkers for progression from MCI to AD-type dementia in blood and CSF. In addition, we used these results to explore the use of CSF biomarkers for the selection of subjects for a fictive trial with a drug that aims to slow down progression from MCI to AD-type dementia. In blood only Aβ1-40, Aβ1-42 and homocystein have been tested in multiple studies, but none of them could predict progression from MCI to AD-type dementia. In CSF Aβ1-42, t-tau and p-tau all predicted progression from MCI to AD-type dementia. The combination or ratio of CSF Aβ1-42 and t-tau was the best predictor for progression to AD-type dementia, with a sensitivity of 0.87 and a specificity of 0.70. We found that the use of CSF Aβ1-42 and tau for the inclusion of MCI subjects in a clinical trial could substantially reduce trial costs.

In chapter 2.2 we assessed the combination of CSF and MRI biomarkers as predictors for progression from MCI to AD-type dementia and for the selection of subjects for clinical trials. We found that the ratio of Aβ1-42/t-tau in CSF and hippocampal atrophy on MRI independently predicted progression from MCI to AD-type dementia, but the overall predictive accuracy of CSF Aβ1-42/t-tau for AD-type dementia after two years was around twice as high as that of hippocampal atrophy. After analysis of CSF, additional MRI analyses had prognostic value when the Aβ1-42/t-tau ratio was normal, but not when the Aβ1-42/t-tau ratio was abnormal. Analysis of CSF Aβ1-42/t-tau ratio always improved predictive accuracy for AD-type dementia and cognitive decline, regardless of MRI results. The use of only CSF biomarkers for the selection of MCI subjects for a clinical trial had the best trade-off between sample size and number of subjects required for screening.

In chapter 3 we compared the predictive accuracy of biomarkers in CSF and MRI for different MCI subgroups.

In chapter 3.1 we found that the overall predictive accuracy of CSF Aβ1-42 and to a lesser extent CSF t-tau for AD-type dementia was lower in older than in younger MCI subjects. The lower overall predictive accuracy in older subjects was mainly caused by a higher prevalence of abnormal biomarkers in older subjects who did not progress to AD-type dementia (MCI-no
AD) for both CSF Aβ1-42 and t-tau. In addition, older who progressed to AD-type dementia had less abnormal levels of CSF Aβ1-42 than younger subjects, especially when they were APOE-ε4 negative. The use of age-optimized cut-points did not improve overall predictive accuracy. In chapter 3.2 we compared the predictive accuracy of CSF and MRI biomarkers in subjects with amnestic and non-amnestic MCI. Overall predictive accuracy for progression to AD-type dementia of both CSF and MRI measures was similar for subjects with amnestic MCI and subjects with non-amnestic MCI, but sensitivity was lower and specificity higher in subjects with non-amnestic MCI. Calculating optimized cut-points for both subgroups separately resulted in more lenient cut-points for subjects with non-amnestic MCI. Although using these cut-points did not change overall predictive accuracy, it increased sensitivity at the cost of a lower specificity in subjects with non-amnestic MCI, resulting in a sensitivity and specificity similar to those in subjects with amnestic MCI.

**Biomarkers as predictors of cognitive decline in subjects with MCI due to AD**

In chapter 4.1 we selected subjects with MCI who all progressed to AD-type dementia and compared CSF and MRI biomarkers as predictors for cognitive decline. We found that high levels of CSF t-tau and p-tau, medial temporal lobe atrophy and low MMSE score predicted more rapid progression to AD-type dementia, while CSF level of Aβ1-42 was not associated with time to dementia. In chapter 4.2 we selected subjects with MCI and abnormal CSF Aβ1-42 and assessed whether CSF t-tau and hippocampal atrophy could predict progression to AD-type dementia and rapid cognitive decline. During a mean follow up of 2.3 years, 57% of the subjects progressed to AD-type dementia. For subjects with only abnormal CSF Aβ1-42 but no abnormal injury markers (i.e. normal CSF tau and hippocampal volume) disease course was relatively benign, while almost all of the subjects who had also abnormal CSF t-tau and hippocampal atrophy progressed to AD-type dementia.

In chapter 5.2 we will discuss our main findings and answer the research questions described in the introduction. In addition we will address methodological issues of the studies described. We will conclude with recommendations for future research.