INTRODUCTION

Alzheimer’s disease (AD) is a major health problem, estimated to affect over 25 million people worldwide. Despite all efforts, an effective therapy is still lacking. As AD pathology is already present years before cognitive symptoms appear, diagnosing AD before the dementia stage might improve therapeutic options. Biomarkers for AD have now become available and can detect AD pathology in non-demented subjects. In this thesis we investigate the use of biomarkers in clinical practice for the diagnosis and prognostication of subjects with mild cognitive impairment (MCI). In addition we assess the use of biomarkers for the selection of MCI subjects for clinical trials that aim to prevent progression from MCI to AD-type dementia.

Mild cognitive impairment

Mild cognitive impairment (MCI) can be seen as a clinical status in between cognitively healthy and dementia. Subjects with mild cognitive impairment experience a decline in cognitive functioning which can be determined by neuropsychological examination, but does not cause problems in activities of daily living. Amnestic MCI, in which memory impairment is the predominating complaint, is the most common type of MCI. It is distinguished from non-amnestic MCI, where there is deterioration in other cognitive functions while memory is spared. AD is an important cause of MCI. In memory clinic settings up to 10% of the MCI subjects progress to AD-type dementia per year. However, other conditions such as psychiatric, somatic or other neurodegenerative diseases can also cause MCI.

Clinical features of AD

AD has a prevalence strongly increasing with age, from less than 1% before the age of 60 to around 20% in subjects older than 80 years. Memory impairment is the most frequent presenting complaint, but disturbances in other cognitive domains as language, executive functioning, praxis or visuospatial performance also occur. Especially in younger subjects, AD can also manifest with symptoms other than memory impairment. Cognitive impairment usually starts with subtle changes and progresses slowly over the years. If impairment is present in at least two cognitive domains and causes problems in a patient’s daily functioning a diagnosis of AD-type dementia is made.

Pathology of AD

Neuropathologically, AD is characterized by extracellular deposits of amyloid (“senile plaques”) and intracellular accumulation of tau (“neurofibrillary tangles”) in the brain, first described by Alois Alzheimer in 1907. Although much research has been done since then, the exact pathophysiological mechanism of AD remains to be unraveled. According to the widely accepted amyloid cascade hypothesis, amyloid plaques occur first, followed by neurofibrillary tangles and eventually leading to neuronal loss, specifically of the hippocampus, a brain structure essential for memory performance (figure 1). In most cases the cause of AD pathology is not clear. Three genes, presenilin 1, presenilin 2 and amyloid precursor protein, all affecting amyloid metabolism, have been identified that cause AD-type dementia by an autosomal dominant inheritance, but altogether they are responsible for only a small minority of the AD patients. Most patients have a sporadic form of the disease. Although genetic factors
are less clear in sporadic AD, they do seem to be important as illustrated in a study finding almost 80% heritability for AD in twins.\textsuperscript{19} The strongest and most studied genetic risk factor for sporadic AD is the APOE-\(\varepsilon\)-4 genotype.\textsuperscript{20,21} The presence of one APOE-\(\varepsilon\)-4 allele increases the risk for AD-type dementia about three times, while subjects with two APOE-\(\varepsilon\)-4 alleles have a more than ten times increased risk.\textsuperscript{22} In addition, factors as vascular impairment, oxidative stress, inflammation and lipid metabolism also seem to be involved in the pathophysiology of AD, but the exact mechanism is not clear.

**Biomarkers for AD**

Biomarkers that reflect the pathological changes seen in AD and can be measured in vivo (figure 1). In this thesis we examined biomarkers in blood and cerebrospinal fluid (CSF) and using magnetic resonance imaging (MRI). For practical reasons a blood based biomarker would be preferable, but so far no reliable blood biomarker is available for AD. In CSF, that can be obtained by lumbar puncture, AD pathology can be found. The presence of amyloid plaques in the brain correlates with a decreased level of amyloid beta 1-42 (A\(\beta\)1-42) in the CSF, while the presence of neurofibrillary tangles in the brain is reflected by increased levels of CSF total tau (t-tau) and tau phosphorylated at threonine 181 (p-tau).\textsuperscript{23} Using MRI, a non-invasive technique for visualizing brain structure, the volume of the hippocampus can be assessed. These biomarkers in CSF and on MRI cannot only distinguish subjects with AD-type dementia from healthy control subjects, but can also predict progression to AD-type dementia in subjects with MCI.\textsuperscript{24-28}

**Diagnostic criteria for AD**

For decades the diagnosis of probable Alzheimer’s disease has been a pure clinical diagnosis that could only be made in demented subjects.\textsuperscript{29} Recently, new criteria have been developed, which enable the use of biomarkers to support the diagnosis in demented subjects.\textsuperscript{30} Moreover, in research settings AD can now be diagnosed in subjects with MCI and biomarker evidence of AD.

![Figure 1. Schematic overview of pathological cascade and associated biomarkers in Alzheimer’s disease](image-url)
The possibility to diagnose AD in a predementia stage of the disease is a major step forward in AD research and could improve opportunities for new disease modifying strategies.

Challenges in diagnosing AD in subjects with MCI

As AD is an important but not the only cause of MCI, one of the main challenges is to distinguish those subjects with MCI due to AD from subjects with MCI due to other causes. Various blood, CSF and imaging biomarkers have been tested as predictors for progression to AD-type dementia in subjects with MCI, with varying degrees of success. CSF and imaging biomarkers that have been shown to predict progression from MCI to AD-type dementia with high accuracy can now be used to diagnose AD in subjects with MCI. However, as these diagnostic criteria have not yet been validated, prognosis of subjects fulfilling these criteria is still largely unknown. Although the criteria aim to enable selection of MCI subjects with AD pathology for clinical trials, at this moment it is unknown which biomarkers would be most suitable for this purpose. In addition, it is uncertain whether predictive accuracy of the biomarkers is similar for all MCI subjects. For example predictive accuracy may be lower in older subjects, as amyloid pathology is frequently found in cognitively healthy elderly. Also predictive accuracy may be different for subjects with amnestic and non-amnestic MCI, as memory impairment is the most frequent presenting complaint in AD. Furthermore, the criteria lack a hierarchic order of the biomarkers, although the respective biomarkers may have different diagnostic and prognostic value considering their place in the amyloid cascade.

THESIS OUTLINE

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. First we will investigate biomarkers as predictors for AD-type dementia in subjects with MCI. Second we will assess biomarkers as predictors of cognitive decline in subjects with MCI due to AD.

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

In this part we will answer the following questions.

- What are the best predictors in blood and CSF for progression to AD-type dementia in subjects with MCI?
- What is the best combination of established biomarkers in CSF and MRI to predict progression from MCI to AD-type dementia?
- Are biomarkers useful for the selection of MCI subjects for clinical trials that aim to slow down progression from AD-type dementia?
- Is the predictive accuracy of CSF Aβ1-42 and tau similar for younger and older MCI subjects?
- Is the predictive accuracy of CSF Aβ1-42 and tau and hippocampal atrophy similar for subjects with amnestic and non-amnestic MCI?

First, in chapter 2.1 we performed a meta-analysis of studies that investigated biomarkers in blood and CSF as predictors for AD-type dementia in subjects with MCI. Using the data from this
meta-analysis we assessed how the use of CSF biomarkers for selection of subjects would affect sample size and costs in a (fictive) trial with medication that aims to slow down progression from MCI to AD-type dementia. In **chapter 2.2** we compared the use of a 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.

In **chapter 3** we compared the predictive accuracy of biomarkers in CSF and MRI for different MCI subgroups. In **chapter 3.1** we compared the predictive accuracy of CSF Aβ1-42 and t-tau for younger and older subjects and performed subanalyses for APOE-ε4 negative and positive subjects separately. In addition, in **chapter 3.2**, we compared predictive accuracy of CSF and MRI biomarkers in subjects with amnestic and non-amnestic MCI.

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

The second part of this thesis is dedicated to the question whether biomarkers can also be used as prognostic markers of further cognitive decline in subjects with MCI due to AD.

In **chapter 4** we focused on predictors of rapid progression from MCI due to AD to AD-type dementia. 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. In **chapter 4.2** we selected subjects with MCI and evidence of amyloid pathology and assessed whether CSF t-tau and hippocampal atrophy could predict progression to AD-type dementia and rapid cognitive decline.

In the last chapter of this thesis we give a summary of our main findings and answer the questions described above. We discuss methodological issues and provide recommendations for future research.

**REFERENCES**

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