Biomarkers in the differential diagnosis of dementia

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Chapter 1: Introduction

Dementia is one of the major health challenges and one of the most prevalent diseases affecting elderly. The proportion of older people in the world, especially in the Western world, increases as life expectancy increases. Currently, 40 million people live with dementia worldwide, but the burden of dementia grows with agedness and is estimated to increase to 131.5 million by 2050.

More than hundred years ago, neuropathologist and psychiatrist Alois Alzheimer published his important work about dementia in „Histologische und histopathologische Arbeiten über die Grosshirnrinde“. In the past 3 decades the molecular events that initiate dementia have become clarified, with a central role of protein aggregation in the pathogenesis. Further determination of the histopathologic process is a key to the development of potentially disease modifying treatments. At present there is still no cure for dementia. However, when such treatments will develop, they will be based on the specific underlying pathophysiology. This may be achieved with in vivo biomarkers for dementia as they can be assumed to improve the diagnostic accuracy, which could become an essential prerequisite in staging, tracking, and providing a more quantitative categorization of the disease, as well as for documenting the effect of potential therapeutics. This thesis aims to explore the value of cerebrospinal fluid and Positron Emission Tomography (PET) biomarkers in the differential diagnosis of dementia.

Dementia is clinically characterised by cognitive deterioration, with behavioural and affective changes, and a negative impact in daily life functioning. Alzheimer’s disease (AD) is the most common cause of dementia, accounting for 60-80% of the affected cases. In AD cases with young onset, i.e. between 30 and 60 years, the cause is often genetic, with a strong Mendelian inheritance pattern and monogenetic hereditary forms such as for example presenilin-1 and amyloid precursor protein. Apart from genetic risk factors, cerebrovascular risk factors, environmental factors and lifestyle plays a role in the development and the progression of dementia.

AD typically presents itself with episodic memory decline, accompanied by interferences in other cognitive domains, i.e. executive functioning, orientation in time and space, or language. Atypical presentations of AD have a different sequence in time, with late memory decline and may present themselves by difficulties in language, visuospatial cognition, or executive functioning at an early stage. Approximately 30% of early-onset AD patients have an atypical course with late memory deficits. The clinical stage of AD has an insidious onset and is mild in the earliest phase of the disease. If patients suffer from subjective cognitive complaints, their cognitive decline can initially not be objectified by (neuropsychological) examination. When cognitive complaints become objectively verifiable but do not yet affect the performance of activities of daily living, the patient has reached the stage of mild cognitive impairment (MCI). By gradually worsening of the symptoms, restraining activities of daily living and affecting multiple cognitive domains, the patient has reached the dementia stage of AD. About 10-15 % of
MCI patients annually progress to AD. This gradual decline is described as the continuum of AD, which includes a preclinical stage, subjective cognitive decline, MCI, and dementia due to AD (Figure 1).

**Figure 1** The disease continuum of AD.

Abb: CH, cognitively healthy; SCD, subjective cognitive decline; MCI, mild cognitive impairment.

In early dementia, behavioural and psychiatric symptoms frequently occur, such as depression, sleep disturbances, anxiety and apathy. It is important to exclude other causes of cerebral dysfunction, which can also present themselves with the above mentioned symptoms, such as cerebrovascular disease, metabolic disturbance, psychiatric disease, brain tumour or central nervous system infections. Brain imaging, preferably magnetic resonance imaging (MRI) as well as blood and cerebrospinal fluid (CSF) tests can be performed to investigate and exclude alternative diagnosis. Neuropsychological examination can objectivate cognitive function and quantify affected cognitive domains and evaluate whether the patient also suffers from depression or other behavioural symptoms. This can be extended by psychiatric evaluation. In memory clinics these diagnostic investigations are often provided in a ‘one–day work–up’.

Until recently, the diagnosis of AD was based only on clinical symptoms and the definite diagnosis was provided by AD neuropathology at post-mortem examination. Histopathological hallmarks of AD are deposits of extracellular amyloid-β (Aβ) protein and intracellular neurofibrillary pathology consisting of neuritic plaques, neurofibrillary tangles (NFT) and neuropil threads (Figure 2).
Figure 2 Immunohistochemical staining of amyloid plaques (‘Plaque’) and neurofibrillary tangles (‘Tangle’).

The presence of Aβ protein conducted in the ‘amyloid cascade’ hypothesis, which states that AD initiates from an imbalance between production and clearance of the Aβ protein\(^{21}\). The excess of Aβ leads to the formation of Aβ oligomers and fibrils, which eventually become insoluble and deposit into extracellular amyloid plaques\(^{22}\). Amyloid oligomers and plaques, especially those of the 42-amino acids (Aβ\(_{1-42}\)) peptide, are toxic and impair neuronal function\(^{23}\). The toxic effects of Aβ induce activity changes of kinases and phosphatases, leading to hyperphosphorylation of Tau proteins, which further aggregates into intracellular neurofibrillary tangles\(^{24}\). Predominantly oligomeric tau has toxic effects on neurons, including synaptic dysfunction, mitochondrial and nuclear impairment, and microglial dysregulation\(^{25}\). Furthermore, misfolded tau can trigger the cascade of pathological tau spreading\(^{25}\). Eventually, the toxicity of Aβ and Tau will cause widespread neurodegeneration, many years before the onset of clinical symptoms\(^{26}\).

Core pathological in vivo biomarkers reflect the disease-specific pathophysiological processes and are included in the biomarker-based research criteria for AD\(^{13,27}\). Depending on the pathological process they represent, these biomarkers are divided into three categories: ‘A’, ‘T’ and ‘N’ biomarkers\(^{28}\). A’ biomarkers of amyloid deposition are decreased levels of Aβ\(_{1-42}\) in the CSF and increased ligand retention of amyloid-specific probes on positron emission tomography (PET). ‘T’ or Tau biomarkers of neurofibrillary tangles are increased levels of phosphorylated tau in CSF and increased ligand retention of tau-specific probes on PET. General neuronal degeneration ‘N’ biomarkers are increased CSF levels of total tau protein, decreased glucose metabolism on \(^{18}\)F]fluorodeoxyglucose (\(^{18}\)F]FDG) PET and brain atrophy on MRI\(^{29}\). The ‘N’ biomarkers are believed to be closely linked to disease progression and has therefore potential to measure outcome in clinical trials\(^{28}\). The ‘ATN’ biomarkers correlate to a specific AD-related protein and lead to different biomarker profiles (Figure 3)\(^{29}\); those
with normal AD biomarkers (no color), those with non-AD pathophysiology (dark grey), and those who are in the Alzheimer’s pathophysiologic continuum (light grey). “Alzheimer's pathophysiologic continuum” denotes either AD pathophysiology or clinically AD.

<table>
<thead>
<tr>
<th>AT(N) profiles</th>
<th>Biomarker category</th>
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<tbody>
<tr>
<td>A-T-(N)-</td>
<td>Normal AD biomarkers</td>
</tr>
<tr>
<td>A+T-(N)-</td>
<td>Alzheimer’s pathologic change</td>
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<tr>
<td>A+T+(N)-</td>
<td>Alzheimer’s disease</td>
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<tr>
<td>A+T+(N)+</td>
<td>Alzheimer’s disease</td>
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<tr>
<td>A+T-(N)+</td>
<td>Alzheimer’s and concomitant suspected non Alzheimer’s pathologic change</td>
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<tr>
<td>A-T+(N)-</td>
<td>Non-AD pathologic change</td>
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<tr>
<td>A-T-(N)+</td>
<td>Non-AD pathologic change</td>
</tr>
<tr>
<td>A-T+(N)+</td>
<td>Non-AD pathologic change</td>
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</tbody>
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Figure 3: AT(N) profiles. A: decreased levels of CSF Aβ, increased ligand retention of amyloid-specific probes on positron emission tomography (PET). T: increased CSF Tau/p-Tau/tau-specific probes on PET. N: increased CSF Tau, decreased glucose metabolism on [18F]fluorodeoxyglucose ([18F]FDG) PET, and brain atrophy on MRI.

Since the development of in vivo biomarkers, information about the pathophysiological process is becoming more important to diagnose AD. Valid diagnostic biomarkers are linked to neuropathology, be able to detect the disease early in its course and be able to distinguish it from other dementias, as well as being non-invasive and simple to use, inexpensive and not influenced by symptomatic drug treatment, with a sensitivity and specificity of more than 85%. Amyloid deposition or ‘A’ biomarkers are detectable at an earlier stage than biomarker changes of neurofibrillary pathology. However, in vivo biomarkers are less sensitive than histopathological assays after death. Therefore, the early detection of ‘A’ biomarkers does not necessarily imply that amyloid deposition actually happens prior to neurofibrillary pathology.

Other frequent causes of dementia are Lewy body disease (DLB) and Frontotemporal lobar degeneration (FTD). Lewy body dementia (DLB) is named after the neuropathologist Friedrich Lewy, who described in 1912 inclusions ("Lewy bodies") in patients with parkinsonism. Spillantini et al. (1997) discovered a 140 amino acid protein α-synuclein as a major component of Lewy bodies. α-Synuclein plays a pivotal role both in the development of the disease and the propagation of the pathology in Parkinson’s Disease (PD), Multiple system atrophy (MSA) and DLB, together referred to as 'α-synucleinopathies'. FTD is a major cause of young onset dementia, predominantly
affecting the frontal and temporal lobes and its heterogeneous neuropathological characteristics can roughly be divided into tauopathy, ubiquitin and TDP 43 pathology. Although DLB and FTD have characteristic symptoms and disease courses, these symptoms still show substantial overlap with AD. In these cases, biomarkers can improve the diagnostic accuracy for clinicians. For example, diagnostic work-up in specialised clinical centres achieve average sensitivity and specificity values of respectively 81% and 70% for a clinical diagnosis of probable AD.

The aim of this thesis is to improve the classification of dementia by the characterization and validation of CSF and molecular imaging biomarkers. In the current diagnostic memory clinic work-up, including MRI scan and lumbar puncture, PET diagnostic scans are becoming more widely available. The decision to perform diagnostic work-up and the extent to which this is performed, is based on an individual consideration of patient and care factors, i.e. work- and family concerns, peer support, genetic counseling or participation in clinical trials. Therefore, a correct anamnesis and hetero-anamnesis will always be a crucial part of the investigation.

In part 1, Cerebrospinal fluid (CSF) biomarkers are explored. In chapter 2 an update of Alzheimer’s disease CSF biomarkers and the role of α-Synuclein biomarkers are discussed. Chapter 3 describes CSF biomarkers in a large dementia cohort with different types of dementia, and whether the CSF ‘AD’ profile can differentiate between the different types of dementia. In a subgroup the concordance of CSF biomarkers with neuropathology is investigated. In chapter 4, the CSF biomarker α-Synuclein is explored to differentiate DLB, the second most common form of dementia, from AD. In addition, the association between CSF biomarkers (Aβ42, t-tau and p-tau) and cognitive performance in DLB and AD is investigated.

In part 2 the potential of PET biomarkers in different types of dementia is treated. Chapter 5 gives an overview of nuclear imaging in Frontotemporal dementia (FTD). Functional biomarkers and nuclear imaging techniques may be helpful to detect specific markers of pathology or deficits of different neurotransmitter systems and may thus provide valuable insight in the pathophysiology of FTD. In chapter 6, a 18F-FDG PET pattern of DLB is identified by a multivariate analysis. This multivariate method is based on a Scaled Subprofile Modelling/ Principal Component Analysis (SSM/PCA) approach and aims to determine a unique FDG PET covariance pattern for DLB. In chapter 7, PET imaging in a subgroup of AD patients with the biomarkers 18F-FDG PET and 11C-PiB PET are discussed. The phenomenon of Crossed Cerebellar Diaschisis is unilateral cerebellar hypometabolism as a remote effect of supratentorial dysfunction of the brain in the contralateral hemisphere. The clinical relevance, therapeutic implications and possible non-amyloid pathophysiological mechanisms of CCD in AD are discussed. In chapter 8, relative cerebral flow from dynamic PIB scans as an alternative for FDG scans in Alzheimer’s disease PET studies are investigated. Chapter 9 describes the preliminary results are described of the ‘Dual PET’ study, which was set up to investigate the
diagnostic value of combined $^{18}$F-FDG and $^{11}$C-PIB PET biomarkers in AD and other types of dementia’s.

Chapter 10 provides a **summary and general discussion** about the combination of different biomarkers in dementia.

References:


