General Introduction and aims of the thesis
Introduction

According to the DSM IV criteria dementia is defined as the presence of memory impairment with at least one other cognitive deficit, including aphasia, apraxia, agnosia and disturbances in executive functioning. The deficits must be severe enough to lead to social and functional impairment in daily living and must represent a decline from a previous higher level. Furthermore, the diagnosis cannot be made based on cognitive impairment in the presence of a delirium ¹.

Dementia is typically considered as a disorder of the elderly and the prevalence increases exponentially with age ²,³. With the increasing number of elderly people in our society, the number of patients with dementia in Europe is expected to increase up to 16 million in the following 50 years ⁴. However, dementia also occurs at a younger age (arbitrarily defined as < 65 years). Its prevalence in Europe, Japan and Israel, varies between 54/100.000 in the age category 30-64 and 67-98/100.000 in patients from 45-64 years of age, although it has been scarcely investigated ⁵-⁸. Studies into prevalence of dementia in the Netherlands in 2007 showed numbers varying between 0.01 - 4 per 1000 persons in age category 25-65 and from 3.0-72.5 per 1000 persons in the age category 65-85 ⁹,¹⁰. In patients with early-onset dementia as for patients with late-onset dementia, there seems to be a strong age dependency, with prevalence numbers duplicating with a 5 year increase in age ¹¹-¹³.

Furthermore, several studies found that the mortality risk in patients with dementia decreased with age, suggesting that dementia with an earlier onset has a more malignant course ¹⁴-¹⁷.

The differential diagnosis of early-onset dementia is wide and includes treatable-but also rare sporadic and hereditary diseases ⁵,¹⁸-²⁰. Alzheimer’s disease (AD) and Frontotemporal Dementia (FTD) are two of the most common neurodegenerative causes of dementia at a younger age.

Dementia with an early onset is more difficult to diagnose than late-onset dementia, not only because of lower prevalence rates and the wider range of aetiologies, but also because of the relatively more frequent occurring atypical presentations ¹⁸,²⁰. An early and accurate diagnosis is important for patients and their caregivers, to remove unwarranted uncertainty and plan future supportive measures, but also for healthcare professionals, while the various dementias differ in management and course. For example, the severe behavioural change, often seen in FTD, can have devastating psychological, social and financial consequences for patients and their families and often require a multidisciplinary approach. Furthermore, there is a fast approach of disease modifying drugs for AD, although unfortunately only symptomatic drugs are available for FTD.

This thesis focuses on early-onset dementia, especially on AD and FTD.
Alzheimer’s disease

In 1907 Alois Alzheimer published the results of his post-mortem studies of a 55 year old patient, Auguste D, who developed dementia at the age of 51. She became the first patient who suffered from what was later called Alzheimer’s disease. Her symptoms included severely impaired memory, aphasia, apraxia, agraphia, paranoia and auditory hallucinations. She deteriorated rapidly and died four years after the disease onset. Post-mortem examination revealed a diffuse atrophic brain without macroscopic focal degeneration. Specimens prepared with Bielschowsky’s silver impregnation staining technique showed changes of the neurofibrils and unusual deposits/plaques in the cortex. Nowadays, these features (neurofibrillary tau-containing tangles and amyloid plaques) are considered as typical for AD.

In 1910 Kraepelin stated that the case described by Alzheimer could not be classified as senile dementia and for many decades the diagnosis of AD was only given to those dementing before the age of 65 years, whereas elderly demented individuals were considered as having senile dementia. In 1978 British authors reported that plaques and neurofibrillary tangles were the main cause of what was then believed to be senile dementia, which made AD a central focus of attention and put an end to the belief that senile dementia and AD were two different diseases.

AD is the most common cause of dementia at both older and younger age. The most common and prominent presentation in AD is impairment in anterograde episodic memory, with inevitable progression gradually resulting in involvement of other cognitive domains. The diagnosis is currently made according to the criteria of the National Institute on Neurological and Communicative Diseases and Stroke-Alzheimer Disease and Related Disorders Association (NINCDS-ADRDA criteria, table 2). However, there is an increasing awareness that the clinical presentation of AD is not homogeneous and patients can present with predominant impairment in other domains beside memory, including visuospatial function and praxis, language and executive skills. These presentations appear to occur more often in younger patients and make the discrimination from other types of dementia more difficult. However, the exact prevalence of atypical presentations and whether they are strictly bound to age at onset remains unknown. When clinical symptoms are not fully consistent with a diagnosis of AD, additional features to support the diagnosis are essential. Imaging is a widely accepted additional investigation, which can give support to a clinical diagnosis of AD. Atrophy of the medial temporal lobe (MTA) is one of the most important diagnostic marker on magnetic resonance imaging (MRI) in patients with AD, although it has been suggested that especially in young AD patients other, more posterior areas may be affected besides the medial temporal lobe. It remains unclear how many patients present with this specific atrophy pattern and whether posterior atrophy is specific for AD alone.
**Table 2: NINCDS-ADRDA criteria for probable Alzheimer’s disease**

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<td>Dementia established by clinical examination and confirmed by neuropsychological tests</td>
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<td>Deficits in two or more areas of cognition, including memory impairment</td>
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<td>Progressive worsening of memory and other cognitive functions</td>
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<td>No disturbances of consciousness</td>
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<tr>
<td>Onset between 40 and 90 years of age</td>
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<tr>
<td>Absence of systemic disorders of other brain disease that in and of themselves could account for the progressive deficits in memory and cognition</td>
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**Frontotemporal dementia**

In 1892 Arnold Pick was the first to describe a patient with behavioural change and language disturbances, in which post-mortem examination revealed marked macroscopic left frontotemporal atrophy. Almost 20 years later, it was again Alois Alzheimer who not only reported the frontal and temporal atrophy, but also described the microscopic intraneuronal inclusions and called them Pick bodies, in honour of his colleague. The Dutch neurologist van Mansvelt was one of the first to describe clinic-anatomico-pathological correlations in Pick’s disease. He described the general breakdown of impulse control and speech disturbances and recognised three types of cerebral localisation: frontal, temporal and the mixed type. Almost a century after Arnold Pick’s first description, the Manchester and Lund group both collected samples of patients with a clinical picture suggestive of progressive selective damage to the frontal regions, with non-specific neuronal degeneration and without evidence for Alzheimer pathology. These patients were characterized by social breakdown, personality change and lack of insight and the term dementia of the frontal lobe type (DFT) was introduced. In 1998 the term frontotemporal lobar degeneration (FTLD) was proposed for the spectrum of clinical syndromes associated with degeneration of the frontal and/or temporal lobes and diagnostic, supportive and exclusion criteria were stated for the different clinical syndromes frontotemporal dementia (FTD), semantic dementia (SD) and progressive non fluent aphasia (PNFA). Up to now these criteria are used to diagnose these specific types of dementia, although there is an increasing awareness for the need of new clinical diagnostic criteria, because of the clinical and pathological complexity of this disorder.

FTD, the behavioural variant of FTLD (often abbreviated as bvFTD) is the most common form of FTLD and a common form of dementia at a younger age. According to the current criteria a patient must present with an insidious onset and gradual decline in social capacities, decline in regulation of personal conduct, early emotional blunting and early loss of insight. The presence of several other behavioural symptoms, like mental rigidity, loss of initiative, disinhibition and hyperorality are supportive for the diagnosis bvFTD. Other supportive features include language and speech impairment and physical signs like incontinence and rigidity.
Cognitive deficits consist of impairment in abstraction, planning and problem solving (executive disturbances), whereas memory and visuospatial function are relatively preserved.

Although bvFTD is associated with atrophy of the frontal and/or temporal lobes, it is only a supportive feature and not mandatory for the diagnosis bvFTD. A subgroup of patients may have a normal MRI at presentation and may develop the specific atrophy pattern on MRI in time. It has been suggested that patients with a normal scan have a more benign course, although findings have been limited. The clinical picture of bvFTD is variable and varies from the characteristic behavioural change and executive dysfunction to normal performance on neuropsychological testing or prominent memory impairment. In conclusion bvFTD is a clinically complex disorder and not always easy to distinguish from patients with other degenerative diseases such as AD or from behavioural change without underlying neurodegeneration.

**Difficulties in early-onset dementia: AD versus FTD**

According to the consensus criteria the clinical symptoms associated with AD and bvFTD are quite different. Whereas AD is characterized by prominent memory impairment, which is relatively rare in bvFTD, behavioural change is the core symptom in bvFTD, but relatively uncommon in the early stages of AD. However, with the increasing recognition of heterogeneity in the clinical picture of both AD and bvFTD, the discrimination between the two diseases is not always easy to make and both diseases are often simultaneously mentioned in the differential diagnosis of early-onset dementia.

**Aim and outline of the thesis**

This thesis aims to gain a better knowledge of early-onset dementia. We aimed to achieve a better knowledge about survival characteristics of early-onset dementia compared to late-onset dementia. Furthermore, by separately investigating AD and bvFTD, we intend to unravel their respective clinical phenotypes, which could lead to a better understanding of these important causes of early-onset dementia.

**Early-onset dementia**

In chapter 2 we investigate the impact of dementia on mortality and look at the difference in impact between patients with early-onset dementia and patients with late-onset dementia. We therefore compare both groups with age matched controls. Subsequently, we look at the impact on mortality of the different dementia types.

**Early-onset Alzheimer’s disease**

In chapter 3 we take a closer look at the most common cause of dementia, AD. Chapter 3.1 describes the frequency and clinical picture of atypical presentations, defined as prominent cognitive impairment in other domains beside memory, in a large cohort of AD patients from our memory clinic. We expect to find a larger number of patients with an atypical presentation among the younger AD patients.
In chapter 3.2 we describe and validate a newly developed visual rating scale to measure atrophy in the posterior brain regions on MRI and evaluate the differences in the degree of posterior atrophy between AD, other dementias and controls. We hypothesize that this specific atrophy pattern will occur more often in patients with AD. In chapter 3.3 we compare the differences of in the rate of cognitive decline between patients with early- and late-onset AD.

Frontotemporal dementia: the behavioural variant

We then shift our focus to the other common form of dementia at a younger age, bvFTD. Chapter 4.1 focuses on the differences in clinical symptoms between bvFTD patients with frontal and/or temporal atrophy on MRI and patients without this specific atrophy pattern, hypothesizing that especially patients with a normal MRI will be less severely demented. In chapter 4.2 we investigate the relations between levels of CSF biomarkers, tau and amyloid beta_1-42, and cognition. We hypothesize that especially levels of CSF tau either as a marker of the degree of intracerebral tau-pathology or as a non-specific marker of neurodegeneration would be related with cognition in bvFTD. Finally chapter 4.3 describes two siblings with a R406W tau mutation, presenting with a clinical presentation resembling AD, illustrating the clinical heterogeneity in bvFTD.

In chapter 5 the main findings of this thesis are summarised, followed by a discussion of the results and further future recommendations.

Reference list


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