General discussion and conclusion
The general aim of this thesis was to expand the knowledge of early-onset dementia and its two most common causes, Alzheimer’s disease (AD) and Frontotemporal Dementia (the behavioural variant, bvFTD).

In this thesis we show that early-onset dementia has a much higher impact on mortality compared to late-onset dementia. Secondly, we show that early-onset AD and bvFTD are both heterogeneous diseases, with wide variability in clinical presentation and imaging characteristics. Our findings are important for the differential diagnosis of early-onset dementia, as due to clinical heterogeneity, early-onset AD and bvFTD are not always easy to discriminate.

The main findings of this thesis are summarized and discussed in this section.

**Early-onset dementia**

Dementia is considered a disease of the elderly and the prevalence increases rapidly with increasing age. It is known that increasing age is the most important risk-factor for dementia, which, combined with the increased aging of the population, most likely accounts for the observed increase over the years of late onset dementia. However, it is increasingly recognized that dementia can occur at a younger age (arbitrarily defined as < 65 years) and it is known that there seems to be a strong age dependency for early-onset dementia as well, with a duplication of prevalence numbers with a 5 year increase in age.

Increasing age is not only the most important risk factor for dementia but also for death. Moreover, dementia by itself is considered an important risk for death. However, it is unclear whether age modifies the risk of death in demented patients. Some studies did not find an effect of age on the mortality risk in demented patients. Other studies showed that patients with an earlier onset had a lower mortality risk compared to older patients, but had a higher mortality risk compared to the general population. Finally, an increased mortality risk in younger patients has been described. We found that early-onset dementia has a much higher impact on mortality than late-onset dementia. Our results adds to the growing body of evidence that dementia with an early onset often follows a more aggressive course. From the different dementia types, AD had the lowest mortality risk and seemed to follow a more benign course. Earlier studies on mortality focussed on AD and FTLD and suggested that especially FTLD has a malignant course and limited life expectancy. We could not fully replicate these results, although the mortality risk we found for bvFTD was higher than those found for AD, but lower than those for Dementia with Lewy bodies (DLB) and other dementias. Unfortunately, data on causes of death were not available. Our findings are important to keep in mind when establishing a prognosis for patients with early-onset dementia and their caregivers and for management of the care they need.
Early-onset Alzheimer’s disease
It is increasingly recognized that atypical presentations can occur especially in young patients with AD. Several studies have reported apraxia, visual or visuospatial dysfunction, language impairment or executive dysfunction as presenting symptoms in patient with AD. We compared the prevalence of atypical presentations between early- and late-onset AD and found a five time higher occurrence of atypical presentations in young AD patients (chapter 3.1). In the group with a non-memory phenotype, apraxia / visuospatial dysfunction was the most frequently reported presenting symptom, followed by language impairment and an aphasic-apraxic-agnosic syndrome, whereas only a minority presented with executive dysfunction or visual impairment. Not much is known about the causes of these atypical presentations and why they seem to occur more often in younger patients. It has been suggested that different clinical phenotypes reflect different underlying genotypes and it has already been found that patients with a memory phenotype had a higher proportion of ApoE-ε4 alleles compared to patients with a non-memory phenotype. Unfortunately, pathological confirmation was only available in a minority of patients from this study. We therefore cannot fully exclude other underlying pathology or mixed pathology. However, we believe that this study gives a good representation of atypical phenotypes in AD and we emphasize that atypical presentations of AD should be considered in the differential diagnosis of early-onset dementia.

In early-onset AD patients the characteristic medial temporal lobe atrophy (MTA) is often lacking, whereas a posterior atrophy pattern, including the posterior cingulate gyrus, the precuneus and the cortex of the parietal lobes, is found. However, in contrast to the widely established visual rating scale for MTA, up till now there is no rating scale available to measure posterior atrophy. We developed and validated a visual rating scale for posterior atrophy (chapter 3.2). This scale showed good to excellent intra- and inter-rater agreement even between raters with different degrees of experience. Visual assessment of posterior atrophy was able to discriminate AD patients not only from controls but also from patients with other dementias, whereas MTA failed to discriminate between AD and other dementias. Furthermore, we found that a large proportion of the patients had prominent posterior atrophy (28%) and minimal MTA, whereas only 15% had prominent MTA and mild posterior atrophy. Although this posterior atrophy pattern is most often seen in early-onset AD, we could not find a direct relation between age and posterior atrophy. However, we found that the proportion of patients with predominant PA was higher in early-onset AD compared to late-onset AD (34% versus 20%). Moreover, patients with only prominent PA were younger than patients with only prominent MTA, although this difference did not reach statistical significance. In contrast, MTA was associated with increasing age.
Both MTA and posterior atrophy were associated with lower MMSE scores, but further research is essential to analyse relations between posterior atrophy and cognition. The findings of this study underline the importance of evaluating posterior atrophy in a clinical setting.

Both the current clinical criteria and the newly proposed research criteria for AD have always put an emphasis on the presence of memory impairment. Furthermore, the presence of hippocampal atrophy is always considered an important supportive feature for the diagnosis of AD and in the newly proposed criteria the presence of memory impairment and hippocampal atrophy is already sufficient for the diagnosis of prodromal AD. We however not only showed a wide variability in clinical symptoms, with a large proportion of patients presenting without the characteristic memory impairment, but also showed that patients with AD often show prominent posterior atrophy on MRI, with relative sparing of the hippocampus. Both findings argue against the emphasis put on memory impairment and hippocampal atrophy in AD and suggest further refinement of the diagnostic criteria in order to cover the more atypical presentations as well \(^{39,40}\). Recently such new diagnostic criteria for AD have been proposed. For the diagnosis of probable AD these criteria emphasize the presence of atypical (non-memory) presentations versus the most common amnestic presentation. Furthermore, they add an increased level of certainty when there is evidence for AD dementia biomarkers (positive PET amyloid imaging, low CSF Aβ\(_{1-42}\), elevated CSF tau and p-tau, decreased fluorodeoxyglucose (FDG) uptake on PET imaging in the temporoparietal cortex and disproportional atrophy on MRI in the temporal or parietal lobe)\(^{82}\). The findings in this thesis are in line with these newly proposed criteria.

Further clinico-pathological research is vital to determine if and where AD pathology is present in patients with atypical presentations and could give us more information about the correlation between affected area and presenting symptoms. The question remains if a hippocampal atrophy pattern is characteristic for ‘typical AD patients’ and a posterior atrophy pattern for ‘atypical AD patients’.

It has been suggested that young AD patients show a faster cognitive decline than older AD patients \(^{21,23}\). However, studies on the difference in cognitive decline between early-onset AD patients and late-onset AD patients are limited and results conflicting \(^{41,42}\). Our study showed a clear effect of age at onset on the rate of cognitive decline in a large sample of AD patients (chapter 3.3). Furthermore, we showed that the effect of age at onset is attributable to ApoE ε4 non-carriers. In non-carriers, patients with an early onset showed a double rate of cognitive decline compared to late-onset patients and seem to have a more aggressive disease course. However, young and older ApoE ε4 carriers showed a similar rate of decline.
Previous studies have shown conflicting results with regard to the relation between ApoE genotype and rate of cognitive decline in AD patients, which could be explained by our results, since these previous studies did not take age at onset into account. Although ApoE ε4 is a known risk factor in AD, our data suggest that, especially in early-onset AD, the presence of APOE ε4 protects patients, once they actually have the disease.

**Frontotemporal dementia: the behavioural variant**

The presence of frontal and/or temporal lobar atrophy on neuroimaging is only a supportive feature for the diagnosis bvFTD and although this atrophy pattern is frequently present in patients with bvFTD, there is a wide variability in the extent of the atrophy and asymmetry is often seen. Moreover, a substantial proportion of patients with bvFTD may have a normal MRI at presentation and may develop the specific atrophy pattern on MRI over time. We studied a group of bvFTD patients with well documented demographical, behavioural and cognitive features and found that patients with bvFTD have a heterogeneous aspect on MRI at presentation, varying from a normal aspect to diffuse cortical atrophy and frontal and/or temporal atrophy. (chapter 4.1). We did not find major differences in demographical, clinical and cognitive characteristics between the groups, which is in line with the supportive role of neuroimaging in the current criteria for diagnosing bvFTD. However, we agree with the newly proposed addition of neuroimaging findings to the clinical diagnostic criteria of bvFTD to increase the degree of certainty. These criteria further emphasize the heterogeneity in clinical picture, with varying degrees of behavioural change with or without cognitive deficits. Although executive dysfunction is still the most common cognitive deficit in patients with bvFTD, the presence of memory or visuospatial impairment is no longer an exclusion criterion.

It has been reported that patients without atrophy on MRI have a much slower cognitive decline and seem to follow a more benign course compared to patients with atrophy on MRI (defined as ‘benign-variant FTD’) 54,57. Our study was in line with these previous findings, as we found that these patients seemed less severely demented and had less severe language impairment. On the one hand a normal MRI could be a reflection of early stage bvFTD, with the development of the specific atrophy pattern over time. However, this seems not to hold true for all patients as we did not find differences in disease duration between the groups with and without atrophy on MRI and additional imaging (FDG-PET and SPECT) showed typical bvFTD characteristic in only half of the patients with a normal MRI on baseline. However, additional neuroimaging is certainly indicated in those patients with normal MRI, as it can add a degree of certainty to the clinical diagnosis. On the other hand patients with a normal scan appearance might represent the ‘benign-variant’ or have an alternative underlying substrate causing these changes in behaviour for example a psychiatric disorder.
Further research is essential to make clear to what extent the normal MRIs at presentation represent early ‘classic’ bvFTD and which proportion represents the ‘benign’ subtype. Whether there are differences in clinical picture, cognitive functioning and underlying pathology between the ‘classic’ bvFTD and the ‘benign’ variant bvFTD remain intriguing and important aspects for further research. Is the benign variant of bvFTD a real subtype of bvFTD and can it be considered as a neurodegenerative disorder? Or are we looking at another disease? It is important to make this distinction, not only when treatment becomes available.

bvFTD is not only a heterogeneous disease with respect to atrophy seen on MRI, but also in values of cerebrospinal fluid (CSF) biomarkers. A wide range of CSF tau concentrations have been found in bvFTD, whereas CSF amyloid beta (Aβ1-42) varies between normal and low values. The wide variability in levels of CSF biomarkers remains largely unexplained, but might be related to the heterogeneity of underlying pathology or to varying neurodegenerative stages, particularly while it is known that disease duration in bvFTD varies between 2 until 20 years.

Assuming a relationship of cognitive decline with the stage of neurodegeneration and a relation between CSF biomarkers and neurodegeneration, one would expect a relationship between CSF biomarker levels and cognition or behaviour in patients with dementia. Several studies have investigated relations between CSF biomarkers and cognition or behaviour change in bvFTD, with only limited results. In our study we found no correlations between CSF biomarkers and behaviour in patients with bvFTD, but found that high values of tau and low values of Aβ1-42 were correlated with more impairment of cognition. The latter was a surprising finding, as amyloid deposition is not a pathological hallmark of bvFTD. However, soluble Aβ42 and Aβ40 have been found to be increased in FTLD with tau mutations, suggesting Aβ peptides are associated with tau pathology. There is also limited evidence from other studies that pathological processing of Aβ might indirectly be linked to FTD pathology. We could support this suggestion even more, as we still found independent relations between CSF Aβ1-42 and CSF tau and cognition when we entered both CSF biomarkers in the same model. It seems that both Aβ1-42 and tau play a role in bvFTD, although the exact underlying pathophysiological mechanism in bvFTD remains unknown.

It could be argued that patients with low CSF Aβ1-42 and high CSF tau might have underlying AD pathology. Unfortunately, pathological confirmation was not present for these patients and we therefore cannot fully excluded misdiagnosis, however, omitting patients with such an AD-like CSF profile from analysis, did not essentially change the correlations between CSF Aβ1-42 and cognition. We therefore deem it unlikely that misdiagnosis accounts for all our results. It could be hypothesized that more neurodegeneration leads to more CSF abnormalities, and therefore CSF biomarker levels particularly correlate with the amount of cognitive decline in neurodegenerative diseases.
However, caution must be taken with the interpretation of our results. Pathologically bvFTD is characterized by either tau positive inclusions or tau-negative ubiquitin-positive inclusions (FTLD-U) and it is not yet known if the routine CSF biomarkers truly reflect both these underlying pathologies. Our results could very well be representative for just a subgroup of bvFTD patients. Further clinico-pathological research is essential, not only to shed more light on the exact role of amyloid beta in bvFTD but also to determine whether specific CSF biomarkers profiles reflect specific underlying pathology in bvFTD.

Finally, another important aspect of heterogeneity in bvFTD is found in the clinical presentation. Characteristically bvFTD patients presents with a profound change in behaviour and personality, characterized by apathy and loss of initiative or social disinhibition and distractibility. Cognitive deficits, if present, consist of impairment in abstraction, planning and problem solving (dysexecutive syndrome), whereas memory, language and spatial functions are relatively preserved. However, prominent memory impairment has been described in patients with pathologically confirmed bvFTD. Furthermore, bvFTD patients have been found to perform worse on verbal abilities compared to AD patients and finally some bvFTD patients present with only mild behavioural change and normal performance on neuropsychological tests.

To illustrate the heterogeneity of FTD, in chapter 4.3 we describe two siblings with a clinical phenotype of slowly progressive episodic memory loss with profound hippocampal atrophy, suggestive for AD, which was indeed the clinical diagnosis. Additional investigation (CSF analysis and [11C]PIB Positron Emission Topography (PET)) suggested the absence of underlying amyloid pathology, which was confirmed by the identification of the R406W tau mutation, leading to a genetically based diagnosis of FTD. This case illustrates the heterogeneity of bvFTD and underlines that the presence of memory impairment does not exclude a diagnosis of bvFTD.

**Conclusion**

This thesis highlights the importance of awareness for and recognition of early-onset dementia. Although less common than late-onset dementia, it is an important problem and should be recognized as such. Early-onset dementia has a high impact on mortality and is associated with faster cognitive decline. An early and accurate diagnosis is of great value for patient, caregiver and health professionals. Moreover, the upcoming amount of disease modifying drugs, clinical trials and specialized support, makes an early and accurate diagnosis essential. Unfortunately, many clinicians are still unaware of the existence and the clinical symptoms of a dementing illness at an earlier age. The overlap between the main causes of early-onset dementia, AD and bvFTD, plays an important role in the difficulties of making an early and accurate diagnosis. A good discrimination between diseases is only possible, when there is a sufficient knowledge about the characteristics of the diseases.
With this thesis we provide additional information about both diseases, which hopefully helps to a better understanding and therefore a better discrimination between these diseases.

**Future perspectives**

Further extensive research is essential to gain as much knowledge as possible about dementia at an early age. Prevalence and incidence studies are one of the important aspects for further research since these estimates are important to for planning social and health services for patients and their caregivers. Recent data on prevalence of dementia at a younger age are limited and vary widely \(^{15,77-81}\). Unfortunately, we did not have enough data resources to conduct a proper prevalence and incidence study of early-onset dementia and its subtypes. It therefore remains the question whether prevalence numbers of early-onset dementia will show an increase over the years as is seen in late-onset dementia. Whether such an increase represents an actual increase or an increasing awareness and better coverage of young patients with dementia, is another important question.

Furthermore, we already showed that early-onset dementia has a more malignant course compared to late-onset dementia. From all subtypes, early-onset AD seemed to follow the most benign course. Whereas other studies have already shown that FTLD often follows a more malignant course. We however, could not confirm these results. Further research to determine the causes of death in both AD and FTLD, could lead to a better understanding why FTLD often has a more malignant course then AD. However, this suggestion does not count for all FTLD subtypes, as it has been shown by several studies that a group of bvFTD patients seem to have a much slower decline and follow a more benign course \(^ {54,57}\). Extensive research into mortality risks and exact causes of death in AD and (the subgroups of) FTLD, are essential to early point out patients at risk, which could lead to earlier intervention and treatment.

Finally, although we have shown that there is a broad variability in clinical presentation and imaging characteristics in early-onset AD and bvFTD, further research is essential. It remains the question what the causes are of these differences in clinical presentation and imaging characteristics. Further research into underlying pathology, disease progression over time and clinico-pathological correlations are important and may lead to a better understanding of both diseases. This is essential not only to better differentiate between the diseases, but also to better inform patients and their caregivers about the course of the disease and for the development of specific disease modifying drugs.
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