Chapter 1

General introduction

Alzheimer's disease

Alzheimer's disease (AD) is the most common form of dementia and its prevalence is increasing rapidly. It is estimated that 25 to 30 million people worldwide suffer from AD and this number will triple by 2040 as age is the most important risk factor for AD and life expectancy is increasing [1]. The diagnosis is based on criteria from the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) and the National Institute of Neurologic, Communicative Disorders and Stroke-AD and Related Disorders Association (NINCDS-ADRDA) which dictate that a patient, in order to fulfil the criteria for AD, has to have dementia, progressive dysfunction in memory and one other cognitive domain, normal consciousness, onset between 40-90 years of age and no other physical or neurological disease which can explain the symptoms. Magnetic resonance imaging (MRI) or computed tomography (CT) is used to rule out other causes of the symptoms such as a tumor or evidence of a stroke [1,2]. Recently, it has been proposed to use biomarkers based on cerebrospinal fluid analysis, structural MRI and amyloid imaging using Positron Emission Tomography (PET), as supporting diagnostic criteria in research settings since a definite diagnosis in vivo is still not feasible [3].

AD is characterized by a long pre-clinical phase in which neuropathological changes in the brain build up without any signs or symptoms of the disease [3,4]. In the pre-clinical phase of AD, some patients experience memory complaints. This state of subjective cognitive impairment (SCI) is common in the elderly and refers to a subjectively decline from previous levels of cognitive functioning, which cannot be confirmed by neuropsychological evaluation [5]. Longitudinal population-based studies have reported an association between SCI on the one hand and future cognitive decline [6] and dementia [7] on the other. Moreover, neuroimaging studies have shown that, in subjects with SCI, brain changes can be observed that are also found in AD patients [8-13]. This suggests that elderly with SCI may be at risk for developing AD, and therefore this group of subjects is frequently used to study AD in the pre-clinical stage. Alternatively, cognitive complaints may be caused by other factors such as depression, anxiety and quality of life [14-17]. The second pre-clinical phase of AD is characterized by memory deficits without deficits in other cognitive domains and without significant impairment in social or occupational functioning. This stage is generally referred to as amnestic mild cognitive impairment (aMCI). About 50% of subjects with aMCI develop AD within 3 years and therefore these subjects are frequently studied to assess abnormalities in the early stages of AD [18].

Although increasing age is the main risk factor for the development of AD, the disease also develops in younger patients. Early onset AD (EOAD) refers to patients before the age of 65 years, whereas late onset AD (LOAD) is defined with an onset age above 65 years. Although EOAD and LOAD patients share most of the same characteristics of the disease, previous research has shown differences in pattern and severity of cognitive decline, atrophy and neuropathology [19-21].

MRI markers in Alzheimer's disease

MRI in AD typically reveals atrophy of the brain in areas that are known to be affected by neurofibrillary tangle deposition and that are functionally associated with neuropsychological deficits. In AD, atrophy starts in the hippocampus and the enthorinal cortex and extends to the temporal, parietal and frontal neocortices during the disease progression [22]. Using volume measurements of the brain, AD patients can be distinguished from healthy elderly with a sensitivity and specificity of approximately 80% [1]. Unfortunately, atrophy of these structures is not sufficiently accurate to serve as a diagnostic criterion for the clinical diagnosis of AD in the earlier stages of the disease (MCI). The AD diagnosis based on MRI markers is often complicated by co-existing cerebral pathology. Besides atrophy, MRI in AD patients often reveals signs of small vessel disease (SVD) such as white matter hyperintensities, lacunar infarcts and microbleeds (MBs). Patients with such abnormalities suffer from a mixed pathology of AD and cerebrovascular disease [22].

Sporadic cerebral amyloid angiopathy and HCHWA-D.

Sporadic cerebral amyloid angiopathy (sCAA) is a common cerebrovascular disease of the elderly which is also found with a particularly high prevalence in AD patients. The clinical picture of sCAA is dominated by stroke and dementia. A group of CAA patients in whom a genetic basis for the disease has been identified are those with hereditary cerebral hemorrhage with amyloidosis-Dutch type (HCHWA-D). HCHWA-D is an autosomal dominant disease caused by a single base mutation at codon 693 of the amyloid precursor protein gene on chromosome 21, and occurs in a limited number of families in the villages of Katwijk and Scheveningen in the Netherlands [23]. HCHWA-D is characterized by the same symptoms as sCAA (recurrent strokes and cognitive impairment) [24], however the onset age is much earlier: these patients suffer from their first stroke at an average age of 50 years [25].

MRI markers in sporadic CAA and HCHWA-D

The most common radiological manifestations of both sporadic CAA and HCHWA-D are MBs and large intracerebral hemorrhages (ICH) with a lobar distribution, caused by amyloid-β deposition leading to fragility and rupture of the vessel wall. More recently, superficial siderosis (SS) has been recognized as a radiologically-visible manifestation of CAA [26,27]. Apart from these hemorrhagic manifestations, CAA and HCHWA-D are characterized by white matter hyperintensities [28-30], and in a subset of patients CAA-related vascular inflammation has been reported [31].

Pathology of AD and CAA/HCHWA-D

Deposition of amyloid-β (Aβ) in the brain is the common denominator of AD and CAA. In AD, Aβ accumulates extracellularly as plaques in brain parenchyma, whereas Aβ accumulates in the wall of cerebral arterioles and capillaries in CAA. Plaques are classified as senile/neuritic plaques or diffuse plaques. The former, together with neurofibrillary tangles, are the pathologic hallmark of AD and contain Aβ in the form of fibrils, i.e. amyloid. In CAA and HCHWA-D, Aβ is also deposited as fibrils, but in the vessel wall instead of the parenchyma [32-34]. Although AD and CAA are perceived as different disease entities, these conditions often coexist: at autopsy 40% of sporadic CAA patients have AD pathology and in 90% of AD patients CAA pathology is observed [35].

Diagnosis of AD and CAA: what's the problem?

AD is still a disease that can only be diagnosed with certainty at autopsy, based on the observation of the histological detection of senile plaques which contain fibrillary amyloid-β (Aβ), and neurofibrillary tangles. Currently, due to the absence of validated sensitive and specific tests, the clinical diagnosis of AD can only be made at a late stage of disease progression and with a considerable degree of uncertainty, "probable AD" at best, which is based on criteria from the DSM-IV and the NINCDS-ADRDA criteria. Nevertheless, the histological hallmarks of AD pathology are known to occur up to 10 to 20 years before the objective detection of cognitive decline [4].

Sporadic CAA can also not be diagnosed with certainty in vivo. Again, the major problem is the absence of reliable, non-invasive diagnostic tests. Currently, the only certain diagnosis is based on histological examination of brain tissue, and consequently the diagnosis is made post-mortem. The so-called 'Boston criteria' represented an effort to estimate the likelihood of the presence

of CAA during life, with categories of *probable* and *possible* CAA, mainly based on the presence and pattern of hemorrhagic lesions on neuroimaging studies. According to these criteria, lobar, cortical, and corticosubcortical hemorrhages are suggestive of the presence of CAA. The presence of a single hemorrhage in these areas gives rise to the diagnosis *possible* CAA, whereas the presence of multiple hemorrhages in these areas is a requirement for *probable* CAA. Hemorrhages in the basal ganglia, thalamus, or brainstem, brain regions typically spared by CAA, are exclusions to the diagnosis of probable CAA [36,37].

Detecting cerebral amyloid deposition in vivo using Pittsburgh compound (PiB), a contrast agent with a high affinity for amyloid, and PET is a promising diagnostic tool for cerebral amyloidoses [38-40]. However, this method has limitations: it is a costly procedure, requiring the presence of a cyclotron; it does not provide information on the presence of other types of pathology in the brain than the accumulation of amyloid; and it is not clear whether it can differentiate between parenchymal and vascular amyloid.

Ultra-high field MRI

MRI has three major advantages compared to PET-PiB: 1) less expensive, 2) no need of ionizing radiation, and 3) the possibility to generate image contrasts corresponding to multiple disease characteristics instead of a single one. The introduction of human MRI systems operating at a field strength of 7 Tesla (T), which is more than twice as high as the existing 1.5T and 3T MR systems, may offer new opportunities for detecting cerebral amyloidoses in vivo. The advantages of 7T MRI over the standard field strengths include an increase in spatial resolution, signal to noise ratio and contrast to noise ratio and, more interestingly, a much increased sensitivity to tissue susceptibility [41]. The size of amyloid plaques typically range from 16 to 150 μm in diameter, and most plaques are smaller than 25 μm, which is far lower than the anatomical resolution of most MRI systems. However, amyloid deposits contain iron, which gives rise to susceptibility effects in an area that is much larger than a plaque on T_2^*-weighted images [42-47]. At lower field strengths (3T) such changes have not been observed, which is probably due to insufficient resolution and sensitivity for the susceptibility effects that are induced by amyloid. 7T MRI might help overcoming these limitations and enable detection of amyloid deposition in vivo.

Aim of this thesis

The general aim of this thesis is to explore the possibility to detect changes related to amyloid deposition in vivo using ultra-high field MRI.

To achieve this goal we started in chapter 2 with exploring the ability of a human 7T MRI system to detect changes in the cerebral cortex related to amyloid deposition using *post-mortem* human brain specimens. In chapter 3, 4 and 5 we assessed whether amyloid-related changes can be observed *in vivo* using a human 7T MRI system and exploiting T_2^*-weighted phase information. In chapter 6 we reported on an in-vivo study on the prevalence and number of cortical microinfarcts (a manifestation of small vessel disease) in patients with AD and we determined the independent association of cortical microinfarcts with cognitive dysfunction. In chapter 7, the diagnostic value of two recently discovered MRI manifestations of sCAA, MBs and SS, was assessed in patients with HCHWA-D.

References

1. Minati L, Edginton T, Bruzzone MG et al. Current concepts in Alzheimer's disease: a multidisciplinary review. Am J Alzheimers Dis Other Demen. 2009;24:95-121.
2. Thies W, Bleiler L. 2013 Alzheimer's disease facts and figures. Alzheimers Dement. 2013;9:208-245.
3. Jack CR, Jr., Knopman DS, Jagust WJ et al. Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. Lancet Neurol. 2010;9:119-128.
4. Nelson PT, Braak H, Markesbery WR. Neuropathology and cognitive impairment in Alzheimer disease: a complex but coherent relationship. J Neuropathol Exp Neurol. 2009;68:1-14.
5. Jessen F, Amariglio RE, van BM et al. A conceptual framework for research on subjective cognitive decline in preclinical Alzheimer's disease. Alzheimers Dement. 2014.
6. Dik MG, Jonker C, Comijs HC et al. Memory complaints and APOE-epsilon4 accelerate cognitive decline in cognitively normal elderly. Neurology. 2001;57:2217-2222.
7. Jessen F, Wiese B, Bachmann C et al. Prediction of dementia by subjective memory impairment: effects of severity and temporal association with cognitive impairment. Arch Gen Psychiatry. 2010;67:414-422.
8. van der Flier WM, van Buchem MA, Weverling-Rijnsburger AW et al. Memory complaints in patients with normal cognition are associated with smaller hippocampal volumes. J Neurol. 2004;251:671-675.
9. Striepens N, Scheef L, Wind A et al. Volume loss of the medial temporal lobe structures in subjective memory impairment. Dement Geriatr Cogn Disord. 2010;29:75-81.
10. Saykin AJ, Wishart HA, Rabin LA et al. Older adults with cognitive complaints show brain atrophy similar to that of amnestic MCI. Neurology. 2006;67:834-842.
11. Stewart R, Godin O, Crivello F et al. Longitudinal neuroimaging correlates of subjective memory impairment: 4-year prospective community study. Br J Psychiatry. 2011;198:199-205.
12. Jessen F, Feyen L, Freymann K et al. Volume reduction of the entorhinal cortex in subjective memory impairment. Neurobiol Aging. 2006;27:1751-1756.
13. Stewart R, Dufouil C, Godin O et al. Neuroimaging correlates of subjective memory deficits in a community population. Neurology. 2008;70:1601-1607.
14. Eramudugolla R, Cherbuin N, Easteal S et al. Self-reported cognitive decline on the informant questionnaire on cognitive decline in the elderly is associated with dementia, instrumental activities of daily living and depression but not longitudinal cognitive change. Dement Geriatr Cogn Disord. 2012;34:282-291.

15. Montejo P, Montenegro M, Fernandez MA et al. Subjective memory complaints in the elderly: Prevalence and influence of temporal orientation, depression and quality of life in a population-based study in the city of Madrid. Aging Ment Health. 2011;15:85-96.
16. Jorm AF, Christensen H, Korten AE et al. Memory complaints as a precursor of memory impairment in older people: a longitudinal analysis over 7-8 years. Psychol Med. 2001;31:441-449.
17. Knopman DS. Subjective cognitive impairment: fickle but fateful. Neurology. 2012;79:1308-1309.
18. Albert MS, DeKosky ST, Dickson D et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. 2011;7:270-279.
19. Smits LL, Pijnenburg YA, Koedam EL et al. Early onset Alzheimer's disease is associated with a distinct neuropsychological profile. J Alzheimers Dis. 2012;30:101-108.
20. Moller C, Vrenken H, Jiskoot L et al. Different patterns of gray matter atrophy in early- and late-onset Alzheimer's disease. Neurobiol Aging. 2013;34:2014-2022.
21. Marshall GA, Fairbanks LA, Tekin S et al. Early-onset Alzheimer's disease is associated with greater pathologic burden. J Geriatr Psychiatry Neurol. 2007;20:29-33.
22. Frisoni GB, Fox NC, Jack CR, Jr. et al. The clinical use of structural MRI in Alzheimer disease. Nat Rev Neurol. 2010;6:67-77.
23. Levy E, Carman MD, Fernandez-Madrid IJ et al. Mutation of the Alzheimer's disease amyloid gene in hereditary cerebral hemorrhage, Dutch type. Science. 1990;248:1124-1126.
24. Bornebroek M, van Buchem MA, Haan J et al. Hereditary cerebral hemorrhage with amyloidosis-Dutch type: better correlation of cognitive deterioration with advancing age than with number of focal lesions or white matter hyperintensities. Alzheimer Dis Assoc Disord. 1996;10:224-231.
25. Wattendorff AR, Frangione B, Luyendijk W et al. Hereditary cerebral haemorrhage with amyloidosis, Dutch type (HCHWA-D): clinicopathological studies. J Neurol Neurosurg Psychiatry. 1995;58:699-705.
26. Linn J, Herms J, Dichgans M et al. Subarachnoid hemosiderosis and superficial cortical hemosiderosis in cerebral amyloid angiopathy. AJNR Am J Neuroradiol. 2008;29:184-186.
27. Feldman HH, Maia LF, Mackenzie IR et al. Superficial siderosis: a potential diagnostic marker of cerebral amyloid angiopathy in Alzheimer disease. Stroke. 2008;39:2894-2897.
28. Chen YW, Gurol ME, Rosand J et al. Progression of white matter lesions and hemorrhages in cerebral amyloid angiopathy. Neurology. 2006;67:83-87.
29. Rosand J, Muzikansky A, Kumar A et al. Spatial clustering of hemorrhages in probable cerebral amyloid angiopathy. Ann Neurol. 2005;58:459-462.

30. Haan J, Algra PR, Roos RA. Hereditary cerebral hemorrhage with amyloidosis-Dutch type. Clinical and computed tomographic analysis of 24 cases. Arch Neurol. 1990;47:649-653.
31. Kinnecom C, Lev MH, Wendell L et al. Course of cerebral amyloid angiopathy-related inflammation. Neurology. 2007;68:1411-1416.
32. Arnold SE. Part III. Neuropathology of Alzheimer's disease. Dis Mon. 2000;46:687-705.
33. Glenner GG, Murphy MA. Amyloidosis of the nervous system. J Neurol Sci. 1989;94:1-28.
34. Yamaguchi H, Maat-Schieman ML, van Duinen SG et al. Amyloid beta protein (Abeta) starts to deposit as plasma membrane-bound form in diffuse plaques of brains from hereditary cerebral hemorrhage with amyloidosis-Dutch type, Alzheimer disease and nondemented aged subjects. J Neuropathol Exp Neurol. 2000;59:723-732.
35. Vinters HV. Cerebral amyloid angiopathy. A critical review. Stroke. 1987;18:311-324.
36. Greenberg SM, Briggs ME, Hyman BT et al. Apolipoprotein E epsilon 4 is associated with the presence and earlier onset of hemorrhage in cerebral amyloid angiopathy. Stroke. 1996;27:1333-1337.
37. Greenberg SM. Cerebral amyloid angiopathy: prospects for clinical diagnosis and treatment. Neurology. 1998;51:690-694.
38. Johnson KA, Gregas M, Becker JA et al. Imaging of amyloid burden and distribution in cerebral amyloid angiopathy. Ann Neurol. 2007;62:229-234.
39. Lockhart A, Lamb JR, Osredkar T et al. PIB is a non-specific imaging marker of amyloid-beta (Abeta) peptide-related cerebral amyloidosis. Brain. 2007;130:2607-2615.
40. Ikonomovic MD, Klunk WE, Abrahamson EE et al. Post-mortem correlates of in vivo PiB-PET amyloid imaging in a typical case of Alzheimer's disease. Brain. 2008;131:1630-1645.
41. Duyn JH. The future of ultra-high field MRI and fMRI for study of the human brain. Neuroimage. 2012;62:1241-1248.
42. Vanhoutte G, Dewachter I, Borghgraef P et al. Noninvasive in vivo MRI detection of neuritic plaques associated with iron in APP[V717I] transgenic mice, a model for Alzheimer's disease. Magn Reson Med. 2005;53:607-613.
43. Falangola MF, Lee SP, Nixon RA et al. Histological co-localization of iron in Abeta plaques of PS/APP transgenic mice. Neurochem Res. 2005;30:201-205.
44. Grundke-Iqbal I, Fleming J, Tung YC et al. Ferritin is a component of the neuritic (senile) plaque in Alzheimer dementia. Acta Neuropathol. 1990;81:105-110.
45. El Tannir El Tayara N, Delatour B, Le Cudennec C et al. Age-related evolution of amyloid burden, iron load, and MR relaxation times in a transgenic mouse model of Alzheimer's disease. Neurobiol Dis. 2006;22:199-208.

46. Exley C. Aluminium and iron, but neither copper nor zinc, are key to the precipitation of beta-sheets of Abeta_{42} in senile plaque cores in Alzheimer's disease. J Alzheimers Dis. 2006;10:173-177.
47. Lovell MA, Robertson JD, Teesdale WJ et al. Copper, iron and zinc in Alzheimer's disease senile plaques. J Neurol Sci. 1998;158:47-52.