Vascular factors in dementia: prevention and pathology
Richard, E.

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Chapter 1

Introduction
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1. Historical overview of Alzheimer's disease

The most common form of dementia in the elderly is Alzheimer’s disease, accounting for approximately 70% of all dementia cases, followed by vascular dementia, accounting for 15% of the cases. This information about prevalence can be read in most neurological textbooks, and sometimes it seems as if old-age dementia is considered almost synonymous with Alzheimer’s disease. This has certainly not been the case over the past 100 years, since Aloys Alzheimer described the first case of the disease that would later be called after him. The patient Alzheimer described in 1906 in his paper in ‘Algemeine Zeitschrift fuer Psychiatrie’, entitled ‘Ueber eine eigenartige Erkrankung der Hirnrinde’, was only 51 years of age when Alzheimer first saw her.1 He described the neuropathological changes, now known as plaques and tangles. Before this, at the end of the 19th century, Alzheimer considered pre-senile dementia to be caused by ‘atheromatosis’ of cerebral vessels. After his description, it took until 1910 until Ernst Kraepelin, who had been his mentor, coined the described condition ‘Alzheimer’s disease’. For decades after this Alzheimer’s disease was considered as a rare form of pre-senile dementia, as opposed to old-age dementia which was generally thought to be caused by atherosclerotic disease of the brain, a condition already recognised as a cause for dementia long before Alzheimer saw his patient. In the 1970’s the strict distinction between Alzheimer’s disease and old age dementia faded again when quantitative measures of cognitive functioning were correlated with pathological changes in the brain. At the end of the1970’s and early 1980’s the cholinergic hypothesis emerged. According to this hypothesis the degeneration of cholinergic cells in the nucleus basalis of Meynert led to a lack of acetylcholine in the brain with cognitive decline as the ultimate result.

At the end of the 20th and early 21st century the plaques and tangles that Alzheimer already saw through his microscope received most attention again. The molecular structure and the main components of plaques (beta-amyloid) and tangles (hyperphosphorylated tau protein) were extensively studied, and most attention in the field of dementia research went to these pathological changes in the brain.

Over the last two decades, vascular disease as an important contributor to old-age dementia has received more and more attention again, and the insights about the causes of Alzheimer’s disease are shifting once more, but this time more nuances are added and researchers are not looking for a single explanation for this complicated and possibly heterogeneous disease anymore. With the progress in clinical medicine, with better neuro-imaging techniques and more sophisticated neuropathological techniques, the strict division between Alzheimer’s disease and vascular dementia is once again fading.
2. Vascular risk factors and the risk of dementia

Researchers as long as 60 years ago realized that in order to gain insight in the pathophysiology of diseases which slowly develop over long time, large groups of people would have to be followed over many years. The famous ‘Framingham study’ was the first such study and several other large prospective cohort studies have followed.\(^2\) The relationship between vascular risk factors and dementia was repeatedly reported. It was found that atherosclerosis and hypertension are significant risk factors for the development of dementia later in life.\(^3,4\) This association was later found for other vascular risk factors including diabetes mellitus, hypercholesterolemia and overweight as well.\(^5-7\) Several other large prospective studies found associations between these risk factors and dementia as well, and in some studies lack of physical exercise and smoking were also found to be associated with an increased risk of dementia.\(^8,9\)

In addition to these observational cohort studies, some intervention studies, mainly in cardiology, used cognitive decline and dementia as secondary outcome parameter. These studies found that the treatment of especially hypertension can possibly prevent cognitive decline and incident dementia.\(^10\)

No studies specifically aimed at prevention of cognitive decline or dementia by targeting vascular risk factors have been performed thus far.

The importance of a vascular component of Alzheimer’s disease is further supported by findings on neuro-imaging and at autopsy. Cerebrovascular lesions as found on MRI are very common in clinically diagnosed Alzheimer patients and contribute to dementia severity.\(^11\) At autopsy, often cerebrovascular lesions are found, in addition to plaques and tangles. These cerebrovascular lesions contribute to dementia severity, and especially in older subjects the presence of plaques and tangles does not correlate very well with cognitive functioning, suggesting other factors, such as vascular lesions, might play an important role.\(^12\)

3. Cerebral capillary abnormalities

Cerebral amyloid angiopathy (CAA) is characterized by depositions of amyloid-β (Aβ) mainly in the menigeal and cortical arteries and arterioles. In rare cases it is familial, but the vast majority of CAA-cases are sporadic and the presence of CAA is strongly correlated with age. It is a common finding in the elderly and a very common finding in patients with Alzheimer’s disease (70-100%).\(^13\) The correlation with dementia severity is very weak, and sporadic CAA is, like familial CAA, mostly associated with intracerebral haemorrhages.

In addition to meningeal and cortical arteries and arterioles, in a small proportion of the subjects with CAA a remarkable involvement of the capillaries can be found, referred to as capillary CAA, or capCAA. The presence of capCAA occurs in any severity stage of CAA, making it unlikely to be just a severe form of CAA. Sporadic CAA can be divided into type 1, involving capillaries, and type 2, without capillary involvement.\(^14\) The two types of CAA are closely related, yet certain characteristics justify this division into two
different types. CapCAA is correlated to the severity of Alzheimer changes (i.e. plaques and tangles), whereas larger vessel CAA is not. The correlation between dementia and capCAA is weak, whereas there is no correlation between dementia and larger vessel CAA. The apolipoprotein E-ε4 allele, one of the strongest susceptibility genes for Alzheimer’s disease, is far more common in capCAA than in larger vessel CAA. Another remarkable feature of capCAA is the sometimes extensive spread of amyloid-β depositions into the neuropil surrounding the capillaries. These depositions were coined ‘angiopathie dyshorique’ in the sixties of the 20th century by the French neuropathologist Surbek, and this phenomenon is currently referred to as dyshoric angiopathy. These dyshoric changes are hardly seen around the larger CAA-affected vessels, and are a relatively rare phenomenon, of which the clinical significance is unclear.

4. Capillary morphology

The involvement of the vascularisation of the brain in the development of dementia and Alzheimer’s disease in particular has inspired small groups of researchers for decades. In spite of the fact that most attention in dementia research recently went to Aβ and tau metabolism, some researchers kept studying the role of the capillary network and blood-brain barrier dysfunction in the pathogenesis of dementia. Morphological changes to the capillary network including looping of arterioles, increased tortuosity of the capillaries, occurrence of so-called string-vessels (remnants of capillaries), and capillary density were studied, albeit not very intensively.

Recent research has focussed more on the function of the blood-brain barrier, rather than on morphological changes. The ‘neurovascular unit’, consisting of a capillary, the surrounding cellular components (astrocytes and their endfeet, pericytes, neurons), and the actual blood-brain barrier with its tight junctions are intensively studied by several research groups in the world, hypothesizing that faulty amyloid-β transport across it can be a major culprit in the accumulation of amyloid-β in the brain. Remarkably little studies have been done on the gross morphological changes of the capillary network in Alzheimer’s disease. Vascular lesions as seen from a clinical point of view (cerebral infarcts and white matter lesions) can probably not sufficiently explain the association of Alzheimer’s disease with the presence of vascular risk factors, since these lesions are not found in all patients.

5. Aims and outlines of this thesis

Part 1 of this thesis is on clinical studies aiming at modifying cardiovascular risk factors in order to slow down cognitive decline or prevent dementia in the elderly. This part starts with the results of the EVA-study including 123 Alzheimer patients with cerebrovascular lesions on MRI who were randomized to either standard care or intensive vascular care aiming at several vascular risk factors including hypertension, diabetes mellitus, hypercholesterolemia and overweight. The clinical outcomes of this
study are described in **chapter 2**. Serial MRI scans were made in a subset of these patients, and the progression of cerebrovascular lesions over a two-year follow-up period is described in **chapter 3**. Progression of white matter lesions, as well as lacunar infarcts, hippocampal atrophy and global cortical atrophy are described. Following this relatively small study in Alzheimer patients, a new study was designed, in which the effect of intensive treatment aimed at vascular risk factors in elderly non-demented subjects is evaluated. This *preDIVA*-study is a large cluster-randomized clinical trial, including more than 3500 subjects and has started in 2006. The rationale and outline of the study, as well as methodological issues and some baseline data, are discussed in **chapter 4**.

**Part 2** of this thesis reports neuropathological studies on capillary changes in dementia. In **chapter 5** a rare form of cerebral amyloid angiopathy is described. Twenty-two subjects with extensive capillary cerebral amyloid angiopathy with dyschoric changes were studied for their clinical and pathological characteristics. With immunohistochemical techniques the changes in and around the capillaries are visualized and the clinical data of the patients were retrospectively collected and studied. Some subjects with a rapidly progressive dementia, clinically suspected of Creutzfeldt-Jakob disease, also turned out to have extensive capillary cerebral amyloid angiopathy with dyschoric changes. In **chapter 6** the clinical characteristics, including cerebrospinal fluid abnormalities, EEG-findings and MRI-findings of these patients are described. The reasons why these 6 cases were wrongly suspected of having Creutzfeldt-Jakob disease are discussed. **Chapter 7** is a neuropathological study on the morphology of the capillary network in Alzheimer’s disease and controls. Stereological techniques were used to measure the capillary density in the cerebral cortex of these patients and then compared to controls.

In **chapter 8**, the general discussion, the findings of this thesis are summarized. Future directions for clinical studies on vascular risk factors and dementia are discussed. Pathophysiological mechanisms for the contribution of vascular risk factors in dementia are discussed.
References


