Vascular factors in dementia: prevention and pathology
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Citation for published version (APA):
Chapter 8

General Discussion
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Although the two parts of this thesis describe different lines of research, both clearly focus on vascular aspects of dementia. The first objective of this thesis was to investigate whether intensive vascular care could slow down disease progression in early Alzheimer’s disease (AD). The second objective was to gain more insight in pathological changes in and around the capillary network in cerebral amyloid angiopathy and Alzheimer’s disease. In this chapter the findings as reported in this thesis will be summarized and commented upon, and directions for future research are discussed.

Vascular risk factors and dementia

There is strong epidemiological evidence that hypertension, hypercholesterolemia, obesity and diabetes mellitus in midlife impose an increased risk of dementia in late life, and the same trend is seen for lack of physical exercise, smoking and clustering of vascular risk factors known as the ‘metabolic syndrome’. In addition, it has been shown in several large cohort studies that treatment of vascular risk factors is associated with a decreased incidence of dementia and even a slowing of dementia progression in Alzheimer patients. However, epidemiological data are not sufficient to conclude that interventions aimed at vascular risk factors could slow down or prevent cognitive decline. In part one we describe the EVA-study, which puts this large assembly of purely observational data for the first time to the ultimate test of a randomized controlled trial. The results of this study show that in spite of the strong epidemiological evidence of the relationship between vascular risk factors and dementia, no effect on cognition, behaviour or activities of daily living was observed after two years of treatment of AD patients harboring vascular lesions on MRI, but suffering from mild dementia only. The radiological outcome of the EVA-trial, as described in chapter 3, does however support the principle that progression of vascular lesions, in this case white matter lesions, can be slowed by the use of intensive vascular care in early AD patients. Perhaps the assumption that the association of vascular risk factors with cognitive decline is through white matter lesions and (lacunar) infarcts is oversimplified, and other pathways such as blood-brain barrier disturbance plays a role in this process.

The fact that vascular lesions contribute to dementia severity and that an estimated 20% of the total risk of old-age dementia is attributable to vascular lesions, make it plausible that preventing additional cerebrovascular lesions can potentially contribute to the prevention of clinical deterioration. Therefore an important question is why the slowing of white matter lesions in the EVA-study did not result in a clinically relevant effect. Perhaps prevention of white matter lesion progression and maybe prevention of occurrence of new lacunes in a different spectrum of patients could result in a clinically measurable effect. Adequate treatment of hypertension and use of aspirin in stroke patients reduces the risk of future cerebral infarcts, therefore it was expected that our intervention would have an effect on the occurrence of new lacunar...
infarcts, even though this is of course a different group of patients with a different indication for treatment. The lack of effect on the occurrence of new lacunes could very well be due to the relatively small sample size; the study was not powered to find such a difference. Despite the fact that the severity of dementia could be labelled as mild in most EVA patients from a clinical perspective, possibly the neuropathological changes including plaques and tangles and hippocampal atrophy were already too advanced for the intervention to lead to a clinically detectable effect. Both hypertension and high body mass index (BMI) impose an increased risk of future dementia in mid-life, but are associated with a decreased risk of dementia in late life.11;12 A decline in blood pressure can be seen years before dementia onset and in old age low blood pressure has been reported to be associated with an increased dementia risk. In the EVA-study such a decline in blood pressure was indeed seen in the control group, where the systolic blood pressure decreased with an average of 15 mmHg over the two years follow-up. The decreased risk of dementia in subjects with a high BMI, possibly reflects the catabolic state in which subjects with dementia are, rather than being a causal relationship.

The greatest effect of intensive vascular care could probably be expected when initiated early, ideally probably in mid-life. Due to the low incidence of dementia in younger patients, this would require an unrealistic sample-size and follow-up period. In chapter four the outline of the preDIVA-trial is discussed, aimed at preventing dementia by intensive vascular care, in non-demented elderly. From a pragmatic and realistic point of view the subjects included are at an advanced age, in order to have a sufficiently high incidence of dementia over the planned follow-up of six years. This follow-up of six years is unprecedented in an intervention trial. The large sample-size, cluster-randomization and execution in 115 different general practices make this a complicated trial, and the competing risk of death due to other causes than dementia will be an important factor in the final analysis. It is expected that the intervention will also lead to a reduction of stroke, myocardial infarction and peripheral vascular disease. It is expected that all these incidents will influence the second primary outcome, handicap. The generic nature and the linearity of the AMC Linear Disability Scale make this a very suitable instrument to document the functional sequelae independent from their specific cause.

At least one other, somewhat smaller, trial investigating a multi-component intervention including several treatments aimed at vascular risk factors and encouraging a healthy lifestyle is ongoing and other trials worldwide are being planned.13 Hopefully at completion of preDIVA, in 2015, it will be clear whether such large scale community-based interventions as investigated in the preDIVA-trial can indeed prevent cognitive decline and dementia.

Pathological changes in the capillary network in dementia

The clinical relevance of cerebral amyloid angiopathy (CAA) has still not been elucidated. The fact that it is such a common finding in Alzheimer’s disease, and that
the culprit is amyloid-β (Aβ), the same as in the extracellular plaques, suggests a strong relationship. However, with increasing age it is also found in non-demented elderly subjects, and it imposes an increased risk of intracerebral haemorrhage in both the familial form as the sporadic form.

Three possible mechanisms could lead to an accumulation of Aβ: an increased production, a decreased degradation, or a decreased clearance. An increased production is likely to play an important role in early-onset autosomal dominant inherited forms of AD, when a mutation in the APP, PS-1 or PS-2 gene is present. In (capillaryCAA) capCAA the degradation or clearance of Aβ is probably failing. Several authors have suggested already that faulty clearance of Aβ across the BBB could play a major role in the pathogenesis of AD.\textsuperscript{14,15} It could be hypothesized that in capCAA the transport of intraneuronally produced Aβ towards the circulation is failing, and leads to the accumulation in and around the capillaries. The possibility of clearance of Aβ from the parenchyma via the cerebral microvasculature is supported by in vivo studies with Aβ-vaccination in Alzheimer patients. In some deceased vaccinated patients remarkably few plaques were found, as opposed to an enormous amount of CAA, suggesting that the vaccination lead to a mobilisation of Aβ from the plaques towards the vasculature.

At the capillary level, receptor-mediated transport across the BBB is needed for the Aβ to be cleared via the bloodstream. One important receptor to do this is the Low density Lipoprotein receptor-related protein 1 (LRP-1). Malfunction of this LRP-1 could potentially lead to clogging of this vascular elimination route and consequent accumulation of Aβ as dyschoric capCAA. In contrast with larger vessel CAA an inflammatory response with activated microglia is seen, as well as depositions of tau and ubiquitin. This suggests that capCAA, especially when involving dyschoric changes with Aβ-depositions in the surrounding neuropil, is indeed a process distinct from larger vessel CAA. The changes found around the capCAA affected vessels are remarkably similar to the changes around plaques. Possibly the parenchymal Aβ around the capillaries triggers the occurrence of an inflammatory response. It is plausible that such dramatic changes in the parenchyma could play a role in the pathogenesis of neurodegeneration and contribute to cognitive decline.

In spite of these severe parenchymal changes surrounding the capCAA, no specific clinical correlate of these changes could be delineated. Perhaps capCAA, just like CAA, is a pathological phenomenon not contributing to a specific clinical symptom, such as cognitive decline.

The subjects described in chapter 6 had rapidly progressive dementia which could not be readily explained, but they all had severe tau-pathology, and incidental cases of rapidly progressive Alzheimer’s disease have been reported before. Therefore it can not be concluded that the rapid deterioration was the direct consequence of the capCAA. The subjects described in chapter 5 confirm this doubt, because they had a wide range of symptoms compatible with their main clinical and pathological diagnosis (Alzheimer,
Parkinson), and some subjects were even cognitively intact despite the widespread capCAA. On the other hand, some subjects with severe Alzheimer encephalopathy with extensive plaques and tangles can be cognitively intact. It is conceivable that a certain amount of (combined) cerebral pathology is needed to cross the threshold of cognitive decline. Whether capCAA can contribute to cognitive decline can not be ruled out with the studies described in this thesis.

With the study on capillary density in Alzheimer patients the previous conflicting reports in the literature about capillary density in dementia are dealt with. The methodological shortcomings in previous publications on the subject have been evaded in this study, and with the use of stereological techniques it was shown that capillary density is not altered in AD. However, structural changes to the capillary bed do occur, and an increase in degraded capillaries (string-vessels) was observed. Whether these changes occur as a primary event or as a consequence of neuronal loss and less nutritional demand is still matter of debate.

**Future directions**

The most important achievement of medical science in the field of vascular risk management would be to achieve a mentality change in the population, i.e. before subjects become patients. For decades it is known that all previously discussed risk factors lead to an increased risk of cardiac disease, peripheral vascular disease and cerebrovascular disease, with major disability and loss of quality of life as a result, yet the number of people with an unhealthy lifestyle still increases. This clearly illustrates a lack of awareness in the population. The current worldwide epidemic of obesity shows we are moving in the wrong direction. The results of chapter 4 clearly illustrate that many risk factors are not sufficiently treated in elderly subjects, so here lays a major task for both clinicians and policy makers.

Possibly a population-based approach as described in chapter 4 will ultimately turn out not to be the most efficient way to evaluate the effect of intensive vascular care. One other possibility would be to select subjects with a high risk of dementia, based for instance on previously described dementia risk scores.\textsuperscript{16} This would require a smaller number of subjects to prove an effect since the incidence in this group would be higher. If intensive vascular care can indeed reduce the risk of dementia in these high-risk individuals, larger population-based studies could investigate if a similar result could be achieved in low-risk individuals. On the other hand, a small effect on a large population with a lower risk could still have a major effect at the population level. And it is conceivable that an intervention in subjects with the highest risk will actually not be efficacious, when an unfavourable vascular risk profile has been present for very long, and much of the damage has already been done.
The Alzheimer research community currently seems to miss the point of attention. Most research has a clear focus on amyloid-β, whereas in the majority of the Alzheimer patients, who are over 75 years of age, other factors such as the vascular component are probably at least as important. Since the predicted increase of dementia patients is completely in this high-age group, it is clear that a shift of attention towards the cause of dementia in old age is urgently needed. Remarkable in this context is the lack of prospective intervention trials and the continuation of publications about already well-known associations.

Pathological studies on CAA and capCAA are very interesting from a pathophysiological point of view. What is the relationship with parenchymal senile plaques? Why do some AD patients have abundant CAA and others don’t? And why do some subjects have extensive dyschoric capCAA and what is the relationship with AD pathology? As with the plaques in AD, the lack of clinical relevance is intriguing. Apparently in old age all these changes are not necessarily pathogenic. It is important to acknowledge that AD at old age is not the same as AD at young age. All the Aβ-related research will probably reveal results interesting for a small minority of very young patients with a variant of one of the Aβ-metabolism disorders. If this will finally result in the development of a treatment aimed at Aβ, it will most likely be beneficial only for a specific and small subgroup of patients, with a clear genetically determined form of Alzheimer’s disease.

Continuation of the described research lines

PreDIVA is ongoing and in early 2010 more than 2000 subjects have made a 2-year follow-up visit. The first interim analysis will take place when 4 years of treatment and follow up is completed in all patients (to be expected in the course of 2013). Several sub-studies within the main study are planned. Comparison of the approach and the results of preDIVA to other multi-component intervention studies that are ongoing or planned will hopefully lead to an increase of knowledge about the best population to target and about which interventions to use.

The next step in capCAA research would be to look at Aβ-transport mechanisms across the blood-brain barrier. This could give more insight in why such an extraordinary Aβ deposition in and around the capillaries in some subjects take place. Using the described sample of over 20 subjects with severe capCAA, this could result in an innovative project that is not easily initiated elsewhere, due to the unique set of subjects. Understanding what leads to the accumulation of Aβ in and around the capillary wall and which processes at the blood-brain barrier are involved, could possibly help understanding more of the dynamics of Aβ-metabolism in Alzheimer’s disease.


