Vascular factors in dementia: prevention and pathology
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Summary
The first part of this thesis describes two clinical trials on the treatment of vascular risk factors to slow down cognitive decline in patients with Alzheimer's disease and to prevent dementia in community-dwelling elderly subjects. The EVA-study (Evaluation of Vascular Care in Alzheimer's disease) is a randomized controlled clinical trial comparing standard care to intensive vascular care in patients with early Alzheimer's disease with cerebrovascular lesions on MRI. The vascular care consisted of a combination of life-style interventions and medication. The results of the EVA-study show that after two years of follow-up the progression of white matter lesions in the intervention group is less than in the control group. This radiological effect is not accompanied by a clinical benefit of this intervention, since no effect could be detected on cognitive decline, behavioral problems or activities of daily living.

The preDIVA study (Prevention of Dementia by Intensive Vascular care) is an ongoing large cluster-randomized clinical trial among over 3534 cognitively intact elderly subjects, executed in primary practice with a follow-up of six years. The practices, rather than the subjects, are randomized to standard care or intensive vascular care, delivered by a practice nurse. Like in the EVA-study, the intervention consists of a combination of life-style interventions and medication. The baseline data show that as many as 87% of the subjects have at least one vascular risk factor amenable to treatment, and that 76% has a systolic blood pressure over 140 mmHG, illustrating the large window of opportunity for improvement of vascular risk management. The cluster-randomized design has methodological implications that should be taken into account when analyzing the data of this study.

The second part of this thesis describes the neuropathological characteristics of capillary cerebral amyloid angiopathy (capCAA), and morphological changes of the capillary network in Alzheimer's disease. CapCAA is frequently accompanied by so-called dyshoric changes, referring to the spread of amyloid-β (Aβ) in the surrounding neuropil. The distribution of different isoforms of Aβ in capCAA is different from the distribution in larger vessel CAA and follows a distinct pattern. The dyshoric changes are accompanied by microglial activation and depositions of tau and ubiquitin, resembling the changes that are seen around Aβ plaques in Alzheimer's disease. A remarkable high number of subjects with capCAA have one or two APOE-ε4 alleles. CapCAA can occur in patients suffering from Alzheimer’s disease, but also in patients with Parkinson’s disease, and occasionally even in cognitively intact subjects. A small series of six subjects with capCAA is described, who were clinically suspected of Creutzfeldt-Jakob disease, because of rapidly progressive dementia with sometimes EEG- and CSF-changes compatible with this diagnosis, but severe Alzheimer changes at autopsy.

Morphological changes of the capillary network in Alzheimer's disease occur, consisting mainly of an increase in degenerated capillaries (‘string vessels’). The cortical capillary density was measured in thick tissue sections using stereology software and the ‘space balls method’. No evidence was found that the actual capillary density in Alzheimer's disease is different from that in age-matched controls.