Clinical and magnetic resonance observations in cerebral small-vessel disease
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Summary
The study reported in this thesis tried to address the following questions:

1. Is it possible to detect genetic factors and vascular risk factors that are specifically associated with the development of small- or large-vessel disease?

2. Are the different clinical and MRI manifestations, that are attributed to small-vessel disease, like lacunar infarcts, white matter lesions and intracerebral hemorrhages, mutually related? Do the various results of small-vessel disease occur in one patient? Are there clinical and MRI manifestations of small-vessel disease that have been unnoticed until now?

3. What differences exist in the evolution of early clinical signs and symptoms between cerebral infarcts caused by small- or large-vessel disease?

Chapter 1 gave a brief overview of cerebral small-vessel disease and its manifestations. In a historical perspective the controversies around the concept of small-vessel disease are reviewed.

In chapter 2 we studied the differences in genetic and vascular risk factors between patients with cerebral small-vessel disease and patients with large-artery atherosclerosis. Hypertension and the apolipoprotein E (apoE) ε2/ε3 genotype have been associated with cerebral small-vessel disease (SVD). However, the relation with hypertension remains controversial. Patients with cerebral SVD often have concomitant large-vessel disease (LVD), which may obscure possible differences in etiology and risk factors between SVD and LVD. Specific risk factors for SVD have not yet been studied in patients with cerebral SVD only, i.e. without signs or symptoms of LVD. We identified signs of cerebral SVD on MRI in a cohort of patients with symptomatic atherosclerotic disease. We compared vascular risk factors and apolipoprotein E polymorphism in patients with and without these MRI lesions. In addition, we compared patients with signs of cerebral SVD only (without any signs or symptoms of LVD) to patients with combined SVD and LVD. Hundred-thirty-two patients fulfilled our MRI-criteria of cerebral SVD. In a multivariate analysis, age
(OR 1.1, 95%CI 1.1-1.1), the absence of apoE ε2 (OR 5.4, 95%CI 2.0-14.5) or ε4 alleles (OR 2.1, 95%CI 1.0-4.2) were associated with cerebral SVD. Among the 132 patients with cerebral SVD, 27 patients had “pure” SVD (without manifestations of LVD). Hypertension (OR 2.6, 95% CI 1.1-6.2) was independently associated with patients with “pure” SVD. Our findings suggest an interaction between age, apoE genotypes and hypertension for the development of either cerebral SVD or LVD. One hypothesis is that certain patients with vascular risk factors, such as smoking, may develop large-vessel atherosclerosis at a relatively early age, promoted by hypertension and genetic factors. Others may be relatively protected against environmental factors, but develop cerebral small-vessel arteriopathy at a more advanced age, mainly as a consequence of hypertension.

In chapter 3 we examined the frequency of pontine hyperintense lesions (PHL) on T2- and proton density-weighted images of MRI in patients with symptomatic atherosclerosis and the factors, that are associated with these lesions. Histopathological findings in 2 patients have been reported previously by others. PHL resemble periventricular white matter lesions (WML), and a vascular etiology has been suggested. We studied 229 patients: 31% presented with ischemic stroke, 31% with myocardial infarction and 38% with peripheral arterial disease. PHL were found in 23% of these patients. Patients with PHL are significantly older and more often have lacunar infarcts and periventricular WML, compared with patients without PHL. In a logistic regression model the presence of WML (odds ratio (OR) 2.7, 95% confidence interval (CI) 1.4-5.3) and lacunar infarcts (OR 2.0, 95%CI 1.01-4.0) were independently associated with PHL. PHL were more common in patients with ischemic stroke (39%) than in patients with myocardial infarction (11%) or peripheral arterial disease (19%) (p <0.004). We conclude, that PHL occur often in patients with symptomatic atherosclerosis. The association with periventricular WML and lacunar infarcts suggests that PHL is a form of small-vessel disease, with possibly the same pathogenesis.

In chapter 4 we examined the clinical relevance of isolated pontine...
hyperintense lesion on MRI in patients with atherosclerosis. Seventeen atherosclerotic patients with isolated PHL on MRI (without other white matter lesions) were compared with 17 patients without PHL (or other WML), matched for age, sex and initial manifestation of atherosclerosis. Subjects and observer were blinded to the MRI findings. We assessed symptoms, impairment and disability with a protocolized interview and neurological examination, and disability scales. On all items patients with PHL scored worse than their controls. We found the largest differences in the frequencies of disequilibrium, difficulties with speech or swallowing, the Timed Walking Test and the body care and movement subscale of the Sickness Impact Profile. Except for disequilibrium (p = 0.04), these differences did not reach statistical significance. Abnormal tandem-walking tests were more frequent in patients than in controls. Pyramidal signs were equally distributed. We propose PHL as a cause of symptoms of disequilibrium in patients with atherosclerosis. Symptoms are probably elicited by dysfunction of the corticopontine fibers, the pontocerebellar fibers or the pontine nuclei.

In chapter 5 we compared the frequencies of signs of old intracerebral hemorrhages (hemosiderin deposits) on brain MRI’s in 66 patients with ischemic stroke, 69 with myocardial infarction and 86 with peripheral arterial disease (total 221 patients). MRI’s were independently assessed by two investigators without knowledge of clinical or laboratory data. In 31 patients (14%) we found signals consistent with local cerebral hemosiderin deposits on gradient echo MRI. In 24 patients they were clinically silent. Hemosiderin deposits were significantly more frequent in patients with ischemic stroke (26%) than in patients with myocardial infarction (4%) or peripheral arterial disease (13%) (p = 0.002). Hemosiderin deposits were associated with the presence of cerebral white matter lesions (odds ratio 5.3, 95% CI 2.5-12.4) and the association was stronger in patients with severe cerebral white matter lesions. Our findings support the hypothesis that cerebral vessels of patients with ischemic stroke are more prone to rupture than those of patients with other manifestations of atherosclerotic disease, which may explain the higher incidence of intracerebral hemorrhages when these patients are treated with oral
anticoagulants. The association of microhemorrhages with cerebral white matter lesions suggests, that they are another manifestation of cerebral small-vessel disease.

In chapter 6 we studied the frequency and the pattern of progression of symptoms in a prospective study of patients with large-artery atherosclerotic strokes or small-vessel occlusive strokes presented within 24 hours. Accurate data on stroke progression in different stroke types may shed light on the mechanisms involved and may guide therapeutic interventions. We used data collected during the FISS-bis trial. Of the 767 patients 225 (29%) had a large-artery atherosclerotic stroke and 205 (27%) a small-vessel occlusive stroke. We excluded 5 patients from whom the Unified Neurological Stroke Scale (UNSS) scores on the 10th day were missing. Progression of symptoms was defined as a decrease in the UNSS score of 1 or more points on the 10th day as compared to the first day, or death within 10 days. In addition, the physicians noted a daily impression of the clinical status in terms of improvement, no change or deterioration compared to the previous day. After 10 days 78 (18%) patients had deteriorated and 14 (3%) died, making a total of 92 (22%) patients. These patients were significantly older, more often had large-artery stroke, extracerebral complications and mass effects on CT-scans of both day 1 and day 10, and worse initial UNSS scores than patients without progression. In a multivariate model, large-artery disease (odds ratio (OR) 3.7, 95% confidence interval (CI) 2.1 - 6.5), the occurrence of an extra-cerebral complication (OR 2.2, 95%CI 1.2 - 4.0), diabetes mellitus (OR 1.9, 95%CI 1.1 - 3.2), and female sex (OR 1.7, 95%CI 1.0 - 2.8) were independently associated with progression of symptoms. In 365 patients, of whom a CT-scan of day 10 was present, mass effect on day 10 (OR 6.3, 95%CI 3.1 - 12.8) was also associated with progression of symptoms. Our findings suggest that neuroprotective treatment may be more valuable in large-artery strokes and provide indirect evidence that early treatment of extra-cerebral complications may prevent symptom progression. Maximum effort should be devoted to stabilize the general condition of patients by early and rigorous treatment of extra-cerebral complications.