Through the looking glass: Risk factors, radiological hallmarks and cognitive function in cerebral small vessel disease
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SUMMARY

Cerebral small vessel disease is an illness of the small blood vessels in the brain, which can lead to a variety of symptoms, varying from cognitive dysfunction and dementia to motor dysfunction and stroke. As the blood vessels involved are very small, they cannot be readily visualized with current scanning techniques. Therefore, radiological abnormalities believed to be caused by cerebral small vessel disease are used as markers for cerebral small vessel disease. The most commonly used radiological markers are white matter hyperintensities (WMHs) and lacunar infarcts. These markers are highly prevalent in the population, as over 90% of patients over 80 years have some degree of white matter hyperintensities and around 25% of all strokes are lacunar infarcts. Several issues regarding the aetiology of cerebral small vessel disease remain unresolved. There is a clear need for identification of potentially modifiable risk factors, not only to identify those patients most at risk, but for future therapeutic interventions as well. Moreover, there is still much unknown about the clinical implications of WMHs and lacunar infarcts. For example, whether there are certain properties of those lesions, such as progression over time, that predict clinical outcome. Finally, WMHs and lacunar infarcts are generally seen as markers for the same disease, although evidence suggest that each marker could play a different role in the phenotype of cerebral small vessel disease. There are even indications that there is aetiological heterogeneity within the group WMHs and the group of lacunar infarcts. This thesis focuses on these unresolved questions regarding WMHs and lacunar infarcts as radiological markers for cerebral small vessel disease.

The first part of this thesis examines the role of homocysteine in the development of cerebral small vessel disease. In chapter 2, we examined the relationship between homocysteine levels and presence of WMHs and lacunar infarcts in 1232 patients (mean age 59±10 years) from the SMART-MR study and examined the relationship between homocysteine levels and cognitive function in a subsample of 763 patients. The results show that increasing homocysteine levels are associated with larger WMH volumes (B=0.01, 95% CI 0.002% to 0.02%) and increased risk of lacunar infarcts (OR=1.04, 95% CI 1.01 to 1.07, per 1 µmol). Moreover, hyperhomocysteinemia was associated with worse cognitive dysfunction (B=-0.12, 95% CI -0.22 to -0.01), although this association was independent of WMH volume, suggesting that homocysteine influences cognition through other factors than subcortical damage seen on MRI.

Therefore, in chapter 3, we examined the relation between elevated homocysteine levels and increase of brain atrophy and cognitive decline in 663 patients, of which there were
2 MRIs and/or 2 neuropsychological assessments (n=416) respectively. There were no significant associations between homocysteine levels and changes in global, cortical and subcortical atrophy nor cognitive function. However, there was a significant interaction between homocysteine and age for all outcome measurements. After stratifying in two groups of <65 years and ≥65 years, there was a significant association between hyperhomocysteinemia and progression of subcortical atrophy (ventricular fraction B=0.16%, 95% CI 0.01 to 0.31), independent of vascular risk factors and large infarcts in the group of patients ≥65 years. Moreover, hyperhomocysteinemia was significantly associated with decline in executive function (z-score B=-1.03, 95% CI -1.67 to -0.40). This association attenuated somewhat after additional adjustments for progression of WMH volume and subcortical atrophy, suggesting that the association between hyperhomocysteinemia and decline in executive functioning was at least partly explained by progression of cerebral small vessel disease and ventricular enlargement.

In chapter 4, we examined the longitudinal association between homocysteine levels and progression of WMHs and lacunar infarcts in 663 patients (mean age 57±9 yrs). Moreover, because it is likely that small vessel disease is not limited to the brain but is rather a generalized disease, we also examined the relation between homocysteine levels and presence and progression of kidney dysfunction. After adjusting for age, sex, follow-up time and vascular risk factors, hyperhomocysteinemia was significantly associated with increased risk of WMH progression (OR=2.4, 95% CI 1.5 to 4.1), lower estimated glomerular filtration rate at follow-up (B=−3.4 ml/min, 95% CI -5.9 to -0.9) and borderline significantly associated with new lacunar infarcts (OR=1.8, 95% CI 0.9 to 3.4). This longitudinal data not only underlines the role for homocysteine in the development of cerebral small vessel disease, but also show that homocysteine is involved in the development of a generalized small vessel disease in which both brain and kidney are affected.

The second part of the thesis investigates the clinical implications of WMHs and lacunar infarcts. Chapter 5 reports on the effect of cerebral small vessel disease on the risk of death, ischemic stroke and cardiac complications in 1309 patients (mean age 59±10 yrs) of the SMART cohort. WMH volume was associated with an increased risk of vascular death (HR=1.03, 95% CI 1.01 to 1.05, per ml increase) and future ischemic stroke (HR=2.6, 95% CI 1.3 to 4.9, highest quintile WMH volume). Likewise, patients with lacunar infarcts (n=229) showed and increased risk of vascular death (HR=2.6, 95% CI 1.4 to 4.9), but also non-vascular death (HR=2.7, 95% CI 1.3 to 5.3). These results show that regardless of underlying atherosclerotic disease, patients with WMHs and lacunar infarcts have greater morbidity and mortality but that these differ according to radiological marker.
WMHs are the most common radiological markers for cerebral small vessel disease and are seen in the majority of the population. They are associated with cognitive dysfunction, but little is known about the actual size of domain-specific effects of presence, progression and localization of WMHs on cognition. Chapter 6 provides a meta-analysis concerning the effects of WMHs on cognition, with particular attention to their location and progression. 23 cross-sectional studies and 14 longitudinal studies were included with a total of 8685 and 7731 participants, respectively. Meta-analysis was possible in 33 of the 37 studies. In contrast with previous hypotheses that emphasize frontal lobe dysfunction, presence of WMHs was significantly associated with modest cognitive decrements in all examined domains (overall effect size \( r = -0.10, 95\% \text{ CI} -0.13 \) to \(-0.08\)), with similar effects sizes observed for cognitive decline over time (overall effect size \( r = -0.10, 95\% \text{ CI} -0.13 \) to \(-0.05\)). Progression of WMHs was associated with greater cognitive decline (overall effect size \( r = -0.16, 95\% \text{ CI} -0.27 \) to \(-0.09\)), particularly for general intelligence and attention & executive functions. These results show that, although the effects are small, WMHs are not benign, affect all cognitive functions, and are especially harmful when progressing over time.

Brain atrophy has been associated with cognitive dysfunction and dementia and has been implicated as a possible mediator in the association between cerebral small vessel disease markers and cognitive decline. In chapter 7, we investigated whether severity and progression of periventricular, deep WMHs and lacunar infarcts were associated with progression of brain atrophy. With automated brain segmentation, total brain, cortical gray matter, ventricular volumes as measures of global brain atrophy, cortical brain atrophy and subcortical brain atrophy were estimated and expressed relative to intracranial volume (%). In 565 patients (mean age 57±9 yrs) without large infarcts we found that patients with higher periventricular WMH volumes had a greater decrease of cortical gray matter volume and greater increase of ventricular volume over time (\( B = -1.73\% , 95\% \text{ CI} -3.15\% \) to \(-0.30\% \), per 1% WML volume increase; \( B = 0.12\% , 95\% \text{ CI} 0.04\% \) to 0.20%). Moreover, patients with progression of WMH volume corresponded had an even greater decrease in cortical gray matter volume (\( B = -0.45\% , 95\% \text{ CI} -0.9\% \) to 0%) and greater increase in ventricular volume (\( B = 0.15\% , 95\% \text{ CI} 0.1\% \) to 0.2%). Similarly, presence of lacunar infarcts was associated with brain atrophy, although with greater decline in total brain volume global atrophy (\( B = -0.25\% , 95\% \text{ CI} -0.49\% \) to \(-0.01\% \)). Progression of lacunar infarcts was associated with a greater decrease of total brain (\( B = -0.30\% , 95\% \text{ CI} -0.59\% \) to 0.01%) and cortical gray matter volume (\( B = -0.81\% , 95\% \text{ CI} -1.43\% \) to \(-0.20\% \)). These results show that cerebral small vessel disease indeed induces brain atrophy, although the effect of WMHs and lacunar infarcts differ.
Chapter 12

Summary

The final part of the thesis focuses on the possible differences in aetiology between WMHs and between lacunar infarcts related to their anatomical location and therefore vascular territory. In chapter 8, we used ultra-high field MRI (7T MRI) to explore the perivascular distribution of deep and periventricular WMHs. We counted 232 WMHs in total (interpatient range 0-50). 69.8% of all counted WMHs contained a central blood vessel (interpatient range 33%–100%). Periventricular WMHs were more likely to contain a central blood vessel than deep WMHs (88.4% vs. 56.9%, p≤0.0001). Of all WMHs, 55.6% contained a venule. Periventricular WMHs were also more likely to contain a venule than deep WMH (79.3% vs. 39.5%, p≤0.001). The results underline the vascular aetiology of WMHs, and suggest that both arterioles and venules are involved, possibly dependent on anatomical location.

There is evidence that lacunar infarcts can have different aetiologies as well, possibly related to their anatomical localisation and vascular territory. In this case, one would expect that lacunar infarcts in different anatomical locations would result from different risk factor profiles. Chapter 9 reports on the risk factor profiles of patients with new lacunar infarcts in the basal ganglia and deep white matter. In 669 patients (mean age 57±9 yrs) of the SMART-MR study we investigated several vascular risk factors and the risk of new lacunar infarcts in deep white matter and basal ganglia. During follow-up, there were 66 new lacunar infarcts in the basal ganglia and 68 new lacunar infarcts in the deep white matter. Age, history of cerebrovascular disease and baseline WMH volume increased the risk of incident lacunar infarcts in both basal ganglia and deep white matter and basal ganglia. Hyperhomocysteinemia only increased the risk of lacunar infarcts in the basal ganglia (RR=2.0, 95% CI 1.0 to 4.2), whereas carotid stenosis >70% (RR=2.5, 95% CI 1.2 to 5.0), smoking (per packyear: RR=1.01, 95% CI 1.01 to 1.03), hypertension (RR=3.4, 95% CI 1.2 to 9.7) and progression of WMH volume (RR=2.4, 95% CI 1.1 to 5.2) increased the risk of lacunar infarcts in the deep white matter. These results show that risk factor profiles differ for new lacunar infarcts in deep white matter and basal ganglia, suggesting a different aetiology.

Decreased kidney function has been repeatedly associated with cerebral small vessel disease, possibly co-occurring simultaneously as another marker for a generalized small vessel disease. However, it has also been suggested that kidney function could be a contributor to cerebral small vessel disease through decreased clearance of toxic metabolites. In chapter 10, the longitudinal association between kidney function and presence and progression of cerebral small vessel disease was investigated. Although a higher estimated glomerular filtration rate (better kidney function) was associated with less white matter hyperintensity volume at baseline (per 10 ml/min, B=-0.04%, 95% CI -0.06% to -0.01%), there was no association between kidney function and progression of WMHs or new lacunar infarcts.
This suggests that kidney function represents end-organ damage in a generalized small vessel disease rather than being a contributor, which is in line with the results of chapter 4.

To conclude, the studies presented in this thesis show that homocysteine is probably involved in the development of a generalized small vessel disease throughout the body, in which cerebral small vessel disease and kidney dysfunction can be considered end-organ damage. Moreover, increased homocysteine levels can affect cognition through other pathways than cerebral small vessel disease. Homocysteine is thus an interesting and potential therapeutic target for future randomized trials. Possible treatments are important, because both WMHs and lacunar infarcts have deleterious effects on brain volume and mortality and morbidity. WMHs are ubiquitous and have an impact on more cognitive domains than previously thought. Patients with progression of WMHs are especially vulnerable for cognitive dysfunction and cognitive decline over time, making it critical to identify these patients for future interventions. Moreover, this thesis shows that although WMHs and lacunar infarcts are used to describe the same “cerebral small vessel disease”, there are substantial differences with respect to their effects. In future trials, it is critical to define WMHs and lacunar infarcts with respect to their anatomical location as there are probable underlying aetiological differences.