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

The results of this thesis will be discussed in three parts. The first part will consider the possible role of homocysteine as a treatable risk factor for the development of cerebral small vessel disease. In the second part the clinical implication of white matter hyperintensities (WMHs) and lacunar infarcts are discussed. Finally, the third part will concentrate on the heterogeneity in pathology, presentation and implications of WMHs and lacunar infarcts.

I. Homocysteine

Several potentially modifiable vascular risk factors, such as hypertension, smoking and diabetes, have been associated with cerebral small vessel disease (CSVD). The strongest and most consistent association is with hypertension. Nevertheless, strict regulation of blood pressure has not been proven to prevent incident stroke in patients with lacunar stroke at presentation (treated group HR=0.81, 95% CI 0.64 to 1.03, p=0.08).¹ Moreover, many patients with CSVD do not present with lacunar stroke and whether treatment of traditional vascular risk factors can reduce small vessel disease load and reduce progression of cognitive dysfunction and gait disturbances remains unclear. One randomized controlled trial in which patients without stroke had intense vascular risk factor control versus regular treatment, showed a small reduction in progression of WMHs but failed to show any effect of intense treatment on clinical endpoints.²³ Therefore, identification of other potential treatable risk factors for cerebral small vessel disease is important. Homocysteine, an amino-acid formed during methionine metabolism, could be an important contributor in cerebral small vessel disease. It is involved in both macrovascular disease, such as large vessel atherosclerosis,⁴ and microvascular disease.⁵ It is of particular interest because homocysteine levels can be regulated by folic acid, vitamin B6 and B12 and could therefore be a potential target for therapy.⁶

Several chapters of this thesis focus on the role of homocysteine in the development of CSVD and cognitive dysfunction. Homocysteine has repeatedly been associated with markers of cerebral small vessel disease in cross-sectional studies in healthy persons and patients with macrovascular disease,⁷,⁸ but longitudinal studies are scarce and do not show clear associations.⁹,¹⁰ In chapter 2 we confirm the cross-sectional association between elevated homocysteine level and WMHs, lacunar infarcts and cognitive dysfunction.¹¹ Interestingly, this association was strongest in older patients. Moreover, in chapter 4 we report a significant longitudinal association between homocysteine level and progression of WMH volume and lacunar infarcts, which suggests that homocysteine is a contributor in the development
and more importantly, the progression of cerebral small vessel disease. Because the present study is the first to show a significant association between homocysteine levels and progression of WMHs, replication in another cohort is necessary. Nevertheless, these results implicate a role for homocysteine in the development of cerebral small vessel disease. Supporting evidence for this view comes from chapter 4, in which we show that increased homocysteine levels were associated with both progression of cerebral small vessel disease and decreased kidney function at follow-up. It has long been hypothesized that cerebral small vessel disease is actually a component of a more generalized small vessel disease, which affects organs throughout the body. For example, retinopathy and nephropathy have been cross-sectionally associated with markers of cerebral small vessel disease and changes in the microvasculature of the retina and glomeruli are comparable to those in the brain. The observation that elevated homocysteine levels are associated with two separate markers of small vessel disease, ie cerebral small vessel disease and kidney function, provides a stronger argument for the possible role of homocysteine in the development of a generalized small vessel disease.

The association of higher homocysteine levels with worse cognitive functioning in one of our studies confirms earlier reported results in healthy populations. Similar to those studies, the associations found in our study did not change significantly when adjusting for co-existent WMHs, suggesting that cognitive functioning is influenced by other factors than subcortical damage seen on MRI. It is possible that small vessel disease markers are only a marker or cause cognitive dysfunction through other pathways. For example, cognitive dysfunction could be mediated through brain atrophy. This will be further discussed in part II. Conversely, there could be a direct toxic effect of homocysteine on the brain, independent of cerebral small vessel disease. However, in chapter 3 we show that homocysteine levels associated with progression of brain atrophy and cognitive dysfunction are partially attenuated after adjusting for presence of cerebral small vessel disease, suggesting at least a mediating presence of small vessel disease (Figure 11.1A+B).

The characteristics of the SMART study population have to be considered when discussing the results. The SMART study is a hospital based cohort of patients with atherosclerotic disease. This has an impact on the external validity of the results presented in this thesis. The patients in this study had relatively high homocysteine levels compared to healthy populations. This probably lowered the threshold to detect any effects of homocysteine on markers of cerebral small vessel disease and cognition. It has already been suggested to focus therapeutic efforts on those patients with relatively high homocysteine levels. Moreover, solely based on this data, we cannot rule out the possibility that atherosclerotic...
disease is a prerequisite for the observed associations. However, in additional analyses adjusting for severity, extent and type of atherosclerotic disease, we found similar results for all associations, suggesting that homocysteine acts on cerebral small vessel disease and cognition independent of atherosclerotic disease. Finally, when available, results from population based studies also showed similar effects of homocysteine.

II. Clinical implications of white matter hyperintensities and lacunar infarcts

Over 90% of healthy people older than 60 years have some degree of WMHs on MRI. With increasing age and morbidity most people will receive at least one radiological examination of the brain during life, and physicians need to know what the consequences are. The question is whether and to what extent the presence of these radiological abnormalities is clinically relevant. A recent meta-analysis concerning the association between presence of WMHs and the risk of stroke and incident dementia showed a hazard ratio of 3.3 (2.6 to 4.4) and 1.9 (95% CI 1.3 to 2.8) respectively. In chapter 5 we showed that in patients with known atherosclerotic disease, those with signs of cerebral small vessel disease on MRI have a similar increased risk of vascular death (HR=2.6, 95% CI 1.6 to 4.9). This suggests that the effects of CSVD are independent of underlying atherosclerotic disease. Therefore, it is important to look for signs of cerebral small vessel disease as this influences the prognosis of patients regardless of their physical condition. A particularly interesting finding was also that patients with cerebral small vessel disease have an increased risk of non-vascular death as well. Although this result has to be interpreted carefully due to the low number of events in the analysis, it does fit with the idea that cerebral small vessel disease is one marker of a more generalized small vessel disease in which more organs are effected. In this regard, patients with a generalized small vessel disease could be considered frailer and therefore more likely to die from any cause.

Although it is quite well known that WMHs increase the risk of developing dementia, more quantitative effects of WMHs on particular cognitive functions are less well known. However, even modest effects on specific cognitive functions may considerably impact day-to-day life. In chapter 6, we performed a meta-analysis to provide an overview of the quantitative effect of WMHs on specific cognitive domains with particular attention to the differential effects regarding their localisation and progression. In contrast with the common conception that WMHs are mostly associated with impairments in processing speed and attention & executive function, there was a robust and consistent – albeit small – negative
Figure 11.1A+B  Possible pathways for effects of cerebral small vessel disease markers on cognition. Effects can be mediated by other processes influenced by markers, such as brain atrophy (A) or there is a direct effect on cognition (B). Note that risk factors, such as homocysteine can also have a direct effect on markers and cognition (dotted lines), in which radiological markers could even be an epiphenomenon.
effect on global cognition, with similar effect sizes for every cognitive domain. In this meta-analysis, progression of WMHs – a sign of active cerebral small vessel disease – was associated with larger cognitive deficits. The studies that examined longitudinal change of cognition showed that attention & executive function was the most sensitive cognitive domain to progressive WMHs. The pathophysiological process driving this cognitive dysfunction remains to be elucidated however. There are several hypotheses. First, WMHs and lacunar infarcts damage mainly the white matter, and it has been hypothesized that the cognitive dysfunction complaints mainly come from subcortical damage. This would explain the presumed strong association with frontal lobe dysfunction (processing speed and executive functioning). However, this is in contrast with our finding that WMHs (located in the subcortical matter) have a detrimental effect on almost every cognitive domain, including memory and intellectual functioning. Moreover, there is much heterogeneity in the association between cerebral small vessel disease and cognitive dysfunction. It could be that anatomical localisation and the aetiology of the lesion could differ and therefore there effects on cognition as well. This will be discussed in more detail in the next paragraph. A third hypothesis is that WMHs and lacunar infarcts are not directly associated with cognitive dysfunction, but serve as an intermediate factor in the relation between brain atrophy and cognition (Figure 11.1A+B). Brain atrophy is a common finding on Magnetic Resonance Imaging (MRI) in the older population.\textsuperscript{21} Extent and progression of brain atrophy is associated with cognitive decline and conversion to dementia.\textsuperscript{22,23} Cerebral small vessel disease is associated with cognitive decline and dementia as well.\textsuperscript{19} As disturbances of white matter integrity contribute to brain atrophy, the effects of CSVD could be mediated through developing brain atrophy.\textsuperscript{24} In chapter 6, we show that WMHs and lacunar infarcts are associated with decreased brain volumes; especially gray matter volumes, which mostly represent the cortex. Moreover, progressive lesions, considered to be active lesions, are more strongly related to increased brain atrophy. Our results are in line with the results of another study that examined the effects of subcortical lacunar infarcts on the projecting cortical (gray matter) area. When white matter was damaged by a lacunar infarct, the corresponding cortical area showed significant thinning.\textsuperscript{25} In this respect it is interesting to know that cortical thinning in certain areas is also associated with motor dysfunction, one of the other clinical consequences of cerebral small vessel disease.\textsuperscript{26} Finally, it could also be possible that WMHs, lacunar infarcts and brain atrophy are all merely radiological markers for another underlying process. It will be interesting to see how the concept of cortical micro-infarcts could fit in this model with cortical atrophy, but data on the prevalence of micro-infarcts in selected cerebral small vessel disease groups is lacking.
III. Heterogeneity of white matter hyperintensities and lacunar infarcts

Traditionally, WMHs and lacunar infarcts have been lumped together as markers of cerebral small vessel disease. However, there is much heterogeneity regarding their clinical implications and risk factor profiles. It is therefore important to realize that they are at different ends of the spectrum of the same clinical phenotype. Probably, there are not only aetiological differences between WMHs and lacunar infarcts, but also between different types of WMHs and lacunar infarcts themselves. There is considerable pathological heterogeneity of WMHs that look similar on conventional MRI. Patients with differing patterns of lacunar infarcts have a different prognosis. These differences could be explained by several factors. The anatomical localisation of WMHs could be of importance. Many epidemiological studies have used a distinction between periventricular WMHs (occurring within 1 cm of the lateral ventricles) and deep WMHs. Although arbitrary, this distinction has shown that periventricular and deep WMHs differ regarding their risk factor profile and clinical effects. In chapter 6, we also show that periventricular WMHs are more strongly associated with progression brain atrophy than deep WMHs. Although the distinction has been based on an arbitrary decision, it could be that the anatomical difference between periventricular and deep WMHs concerns their vascularisation. Periventricular WMHs usually surround the ependymal veins while deep WMHs often lie within the watershed area of the deep white matter. In chapter 8, we report on the possible vascularisation of periventricular and deep WMHs. We show a markedly difference between periventricular and deep WMHs regarding presence of blood vessels within these lesions, suggesting differing aetiologies. Moreover, we consistently showed more venular structures within periventricular WMHs, suggesting a central role for the veins in the development of periventricular WMHs. Early pathological studies have shown a remarkable amount of perivenular collagenosis in patients with cerebral small vessel disease, suggesting a larger role for the veins than previously thought.

For lacunar infarcts, this influence of anatomical localisation is also seen. In chapter 9, we show that lacunar infarcts in the deep white matter have a different risk factor profile than those in the basal ganglia. These findings are in line with an earlier study. It seems that lacunar infarcts in the deep white matter are more associated with extensive and progressive WMHs (Figure 9.2). This is in line with clinical practice, when patients with extensive white matter disease tend to have new lacunes within these white matter lesions at follow-up.
Anatomically, the deep white matter is a watershed area, supplied by the terminal vessels coming, on the one hand, from the subarachnoid circulation and, on the other hand, the deep perforating (lenticulostriatal) arteries. Arteriolosclerosis, decreased cerebral blood flow, impaired autoregulation and blood-brain barrier damage can cause hypoperfusion and subsequent ischemia in the deep white matter. Hypertension, and carotid stenosis are involved in the development of arteriolosclerosis and hypoperfusion respectively. On the other hand, it is more likely that lacunar infarcts in the basal ganglia are caused by more acute infarction, such atheromatic closure of the (proximal) perforating arteries as opposed to the more chronic development of lacunar infarcts in the deep white matter (and most often, within deep WMHs). This possible aetiological difference is of importance concerning future research. In most studies, location of lacunar infarcts is not distinguished and this could cause considerable heterogeneity. Although it is not recommended to define and describe different lacunar lesions, because the precise underlying pathophysiological processes are unknown, we would recommend distinguishing lacunar infarcts according to their anatomical localisation to enhance phenotyping and reliability of future studies.

**FUTURE PROSPECTS AND IMPLICATIONS**

**I Homocysteine**

The studies described in chapter 2, 3 and 4 implicate that homocysteine as an interesting target for a randomized controlled trial. Indeed, the VITATOPS trial, an internationally conducted double blind randomized trial in which patients with a first ever stroke were treated with vitamin B or placebo, showed a risk ratio (RR) of 0.91 (95% CI 0.82 to 1.00, p=0.05) for the primary outcome (stroke, myocardial infarction, death) in patients on therapy. Because the confidence interval reached one the trial was considered to be negative. However, keeping in mind the risk reduction of traditional secondary prophylaxis, the additional risk reduction achieved in this trial was impressive. This becomes even more apparent when considering the fact that vitamin B therapy is inexpensive, widely available, and without significant side-effects. Interestingly, subgroup analyses showed a stronger risk reduction for the primary endpoint (stroke, myocardial infarction, or vascular death) in patients with small vessel stroke (RR=0.81, 95% CI 0.69 to 0.96).

In future therapeutic trials it is recommended to focus more on secondary endpoints such as cognitive dysfunction, as the power to achieve a significant effect on primary endpoints such as stroke and death in patients already using secondary prophylaxis needs to be very
high. A recent prespecified post hoc analysis and meta-analysis concerning the effect of homocysteine lowering therapy did not find any effect on MMSE score after therapy with a median follow-up time of 2.8 years. However, the MMSE test is a relatively crude measure of cognitive function since it is susceptible to ceiling effects in high-functioning populations and has a low sensitivity for cognitive impairment short of (Alzheimer’s) dementia. Patients were not selected on having cerebral small vessel disease, in which homocysteine is more likely to play an active role. Also, a median follow-up time of 2.8 years may simply be too short a period to find any significant cognitive changes. Therefore, it would still be opportune to perform a randomized trial in selected patients with cerebral small vessel disease with particular interest in cognitive deterioration in specific cognitive domains (preferably those mostly affected by cerebral small vessel disease) and radiological markers of CSVD, such as WMHs as secondary endpoints. Before embarking on an intricate study with multiple cognitive evaluations it would be preferable to perform a pilot study with progression of WMHs as a surrogate marker as only few patients (58–70 patients) per treatment arm would be needed.

II Clinical importance of white matter hyperintensities and lacunar infarcts

Although it is clear that WMHs and lacunar infarcts have relevant clinical implications, selection of those patients at highest risk seems to be critical, as the majority of people will have some degree of WMHs over time. The results in this thesis point out that patients with progression of WMHs are those at the highest risk. However, the development of cerebral small vessel disease is probably a slow process that progresses over decades and it is adamant to identify these patients preferably before they show progression of white matter lesions. Future studies should evaluate whether there are markers that can predict progression. As cerebral small vessel disease is a multifactorial disease, vascular risk factors, life style risk factors and genetic factors should be explored in a longitudinal study to develop a risk score for these patients. This will also help in future therapeutic trial, to identify those patients that would benefit most of therapy.

Furthermore, the relationship between WMHs, lacunar infarcts and concurrent or subsequent brain atrophy should be investigated, in particular how this association relates to clinically important outcome measurements such as motor and cognitive function and whether clinical complaints are mainly driven by subcortical lesions, brain atrophy or both. Future studies should also further investigate whether there is a direct causal relationship...
between subcortical lesions and atrophy or whether subcortical lesions are just an epiphenomenon in small vessel disease and another pathology explains brain atrophy. Because of their location in the cortex, in particular micro-infarcts are an interesting finding that could function as the missing link between the prevalence of cerebral small vessel disease, brain atrophy and clinical outcome measurements. However, data on the prevalence of micro-infarcts in selected cerebral small vessel disease groups compared to the normal population is lacking and until now no studies have been published with clinically relevant outcome measurements.

III Heterogeneity of cerebral small vessel disease markers

The most important source of heterogeneity of cerebral small vessel disease markers comes from their definition and how this definition differs between studies. To eliminate as much “idiopathic” heterogeneity as possible, standardized definitions are necessary. Recently, the STRIVE-consortium has recently proposed neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. With respect to the relationship between different radiological abnormalities new imaging techniques such as diffuse tensor imaging (DTI) can give us more insight into which pathways are more relevant for cognitive function than measuring WMH load alone. For example, DTI has shown us that the effect of a lacunar infarcts expands beyond the lesion itself in the affected white matter pathway. Moreover, DTI can identify possible early damage in normal appearing white matter. Another possibility is to explore other radiological abnormalities associated with cerebral small vessel disease. The spectrum of cerebral small vessel disease has been expanded with microbleeds, perivascular spaces and micro-infarcts. Ultra high field imaging (7T MRI) is especially capable of showing these new radiological abnormalities in detail. It could very well be that these abnormalities – together with WMHs and lacunar infarcts - are each correlated with different clinical outcomes. For example, it is believed that microbleeds are involved in the development of haemorrhages in cerebral small vessel disease, whereas WMHs are more correlated with clinical lacunar (ischaemic) syndromes. Future studies should evaluate whether presence of one or more of these individual abnormalities is correlated with different clinical phenotypes.
REFERENCES


