Through the looking glass: Risk factors, radiological hallmarks and cognitive function in cerebral small vessel disease
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Introduction and outline of the thesis
INTRODUCTION

Cerebral small vessel disease is described as an illness of the small blood vessels in the brain giving rise to ischemic and hemorrhagic lesions in the areas of the brain which are being supplied by small perforating arterioles, capillaries and sometimes venules. Vascular pathology in the brains of these persons consists of hyaline arteriolosclerosis, atheromatosis, endothelial damage of the small arterioles with leakage of the blood brain barrier and venous collagenosis. The most commonly affected areas are the basal ganglia and deep white matter, although radiological abnormalities can be seen in almost every part of the brain. Cerebral small vessel disease is often diagnosed using radiological markers, such as white matter hyperintensities, lacunar infarcts, microbleeds and micro-infarcts.

Both the definition and manner of diagnosis of cerebral small vessel disease has changed over time. As early as the 19th century, extensive white matter hyperintensities or leukoaraiosis, was described in post mortem brain tissue. In the same timeframe, extensive lesions in the basal ganglia, sometimes described as état criblé or lacunes were found. In 1901, Pierre Marie described pathological changes in patients with multiple lacunes, which he described as “état lacunaire”. The basal ganglia of these patients would contain many small cavities. Between 1950 and 1970 Miller Fisher conducted groundbreaking research concerning patients with so-called lacunar infarcts, small round ischemic lesions usually located in the areas of the perforating arteries supplying the basal ganglia and brainstem, which caused distinct clinical syndromes such as pure motor stroke and pure sensory stroke. Miller Fisher conducted extensive pathological research in this (small) population and found that most of these patients would exhibit arteriolosclerosis, extensive destruction of the vessel wall called lipohyalinosis, atheromata and microthrombi within the small vessels supplying the areas with lacunar infarcts. High blood pressure was identified as a risk factor associated with these abnormalities. However, the research conducted by Miller Fisher was very time consuming and therefore, pathologic data was only available from a handful of patients.

A second revival in cerebral small vessel disease research started with the appearance of radiological techniques of Computed Tomography (CT) and Magnetic Resonance Imaging (MRI). Especially the common availability of MRI in the last 20 years has enabled new progress in this research field. In vivo imaging of abnormalities normally only seen post mortem was now possible. Moreover, with the development of new imaging techniques and more powerful magnetic coils even more radiological markers are discovered and currently are being researched. The last few years there has been particular interest in microbleeds.
and micro-infarcts, which are both best detected on 7 Tesla MRI. The relevance of these abnormalities and their place within the spectrum of cerebral small vessel disease and normal ageing is still being established. The radiological abnormalities currently used as markers for cerebral small vessel disease are summarized in Figure 1.1.

With the development of these new techniques, a gradual shift in meaning and definition of cerebral small vessel disease, or at least the definition used in scientific research, has occurred. The focus shifted from examination of pathological changes to investigating radiological abnormalities. It is important to realize that these radiological abnormalities are presumably the result of cerebral small vessel disease and that it is still impossible to visualize the actual pathology of the small vessels. This causes several problems regarding the terminology and true definition of cerebral small vessel disease, its applicability to clinical practice and future research. The most commonly used markers of cerebral small vessel disease, white matter hyperintensities and lacunar infarcts, are heterogeneous regarding their radiological, clinical and pathological appearance. Studies have found varying associations between these markers of cerebral small vessel disease and possible risk factors and clinical outcome measurements. More information is thus needed on these abnormalities. Are they caused by modifiable risk factors? Are they clinically relevant? Which of these abnormalities matter most? Does this depend on measurable properties such as the specific appearance or localisation of the abnormality? This thesis focuses on the classical markers for cerebral small vessel disease, white matter hyperintensities and lacunar infarcts, as they are the most common in general clinical practice and are most easily detected on routine imaging.

Cerebral small vessel disease is common in the population. The prevalence of white matter hyperintensities and lacunar infarcts increases with age. As much as 90% of all patients >60 years have some degree of white matter hyperintensities on MRI. Around 25% of all ischemic stroke consists of lacunar infarcts. Cerebral small vessel disease has been associated with a wide spectrum of clinical diseases. The presence of white matter hyperintensities is associated with an increased risk of stroke (HR=3.3, 95% CI 2.6 to 4.4), dementia (HR=1.9, 95% CI 1.3 to 2.8) and death (HR=2.0, 95% CI 1.6 to 2.7). Patients with cerebral small vessel disease may suffer from cognitive dysfunction, gait disturbances and urinary incontinence.

There is still much debate about risk factors for the development of cerebral small vessel disease. Hypertension has been widely identified as one of the most important risk factors for white matter hyperintensities, although a direct causal relationship...
Figure 1.1: Radiological markers of cerebral small vessel disease (perivascular spaces not shown). From left to right: Transversal FLAIR image (1.5T) with (periventricular) white matter hyperintensities at baseline (A1) and progression of white matter hyperintensities at follow-up (A2). Also note the appearance of a lacunar infarct in the left centrum semiovale (arrow, A2) and slight increase of ventricle size, corresponding with subcortical atrophy; transversal FLAIR (B1), ADC (B2) and DWI (B3) with a recent lacunar infarct (<7 days) in right putamen in a patient with sensory stroke; transversal echo gradient images with increasing echotime (C1, C2, C3) with several round hypo-intensities with blooming effect, consistent with microbleeds; sagittal FLAIR image with hyperintense cortical lesion (D1), corresponding T2 weighted image with hyperintense cortical lesion and corresponding T1 weighted image with hypointense lesion with possible cortical micro-infarct. Scale bar indicates 4 mm. (Images shown in panel D1–D3, courtesy of S. van Veluw.)
remains to be elucidated, as there are also many patients with pathology proven cerebral small vessel disease without hypertension.\textsuperscript{17} Also, there are no apparent differences in prevalence of classical vascular risk factors, such as hypertension and diabetes, between patients with atherothrombotic cortical infarcts and lacunar infarcts.\textsuperscript{18} In part, this may be due to the heterogeneity of study populations. It may also be caused by the complex interplay between risk factors and genetic background, but this remains to be elucidated.\textsuperscript{1} Nevertheless, risk factors such as hypertension play a role in at least some patients and are interesting therapeutic targets. Unfortunately, treatment of hypertension or other vascular risk factors has not yet proven to be beneficial for patients with cerebral small vessel disease.\textsuperscript{19-20} Therefore, there is a need to investigate other potential modifiable risk factors. Homocysteine is one of these risk factors, as it can be easily lowered by vitamin therapy and appears to be involved in the development of cerebral small vessel disease. Homocysteine is an amino-acid formed in the methionine metabolism and high concentrations can be toxic for the endothelium.\textsuperscript{21} It has been hypothesized that homocysteine promotes cerebral small vessel disease through vascular endothelial dysfunction,\textsuperscript{22} causing leakage of the blood-brain barrier.\textsuperscript{2}

Although the effects of white matter hyperintensities and lacunar infarcts on recurrent stroke, mortality and cognition are widely recognized, their clinical effects are mainly detected on a population level and it is unclear whether the properties of these lesions, such as location or progression over time, modify the effect of the lesions on the morbidity of the individual patient. Longitudinal data concerning risk factors for the development of white matter hyperintensities and lacunar infarcts are still scarce. Identification of those patients who are at most risk of developing symptomatology appears critical. In about 1/3 of all patients with white matter hyperintensities these abnormalities progress over time. These patients could be considered to have “active” cerebral small vessel disease. Data is lacking on whether this subgroup of patients indeed have more clinical symptoms.

Terminology and definitions for imaging the features of cerebral small vessel disease vary widely. Recently, the STRIVE-collaboration proposed neuroimaging standards for research into small vessel disease,\textsuperscript{23} hereby hopefully harmonizing the definition of cerebral small vessel disease markers. Nonetheless, white matter hyperintensities and lacunar infarcts are often lumped together as markers of cerebral small vessel disease, suggesting aetiological similarity. However, they are at different ends of the spectrum of the same clinical phenotype. Probably, there are not only aetiological differences between white matter hyperintensities and lacunar infarcts, but also between different types of white matter hyperintensities and lacunar infarcts themselves. For example, anatomical location of white matter
hyperintensities seem to depend on different vascular risk factors and can modify the effect on brain atrophy. More research into radiological properties, such as anatomical location and appearance, is needed to further phenotype these radiological markers.

**Aims of the thesis**

This thesis aims to investigate several unresolved issues regarding white matter hyperintensities and lacunar infarcts, the most commonly used radiological markers of cerebral small vessel disease. First, as intensive treatment of vascular risk factors has not yet resulted in a significant decrease of dementia, cognitive dysfunction and gait dysfunction, there is need to explore other potential modifiable risk factors. Homocysteine is one of these risk factors, as it can be easily lowered by vitamin therapy and appears to be involved in the development of cerebral small vessel disease. Second, the majority of people older than 60 years have white matter hyperintensities or lacunar infarcts in some degree on imaging. Detailed information on the size of these effects and the cognitive functions most affected could provide more insight into the clinical importance. As the population most commonly affected by cerebral small vessel disease is more vulnerable due to its age, even modest effects on specific cognitive functions may considerably impact day-to-day life. Moreover, future studies designed to evaluate interventions to prevent white matter hyperintensity-associated cognitive decline benefit from increased knowledge concerning the cognitive domains most affected by these lesions. Finally, much is still unknown concerning the aetiology of both white matter hyperintensities and lacunar infarcts causing considerable heterogeneity within and between study populations using different definitions of both markers. Knowing which lesions matter most could focus future research and could help to identify patients in clinical practice who would benefit most from therapeutic interventions.

Therefore, in part I, we investigate the possible role of homocysteine as a potential new treatable risk factor for the development and progression of cerebral small vessel disease. Subsequently, in part II, we investigate the clinical implications of both white matter hyperintensities and lacunar infarcts, especially with regard to risk for stroke and death and cognitive dysfunction. Finally, in part III, we investigate possible differences in white matter hyperintensities and lacunar infarcts concerning their anatomical localisation, which would possibly suggest different aetiologies.
Study population

The majority of chapters in this thesis use data from the The Second Manifestations of ARTerial disease (SMART) study. The SMART study is an ongoing prospective cohort study in patients newly referred to the University Medical Center Utrecht with symptomatic atherosclerotic disease or risk factors for atherosclerosis, and is aimed at investigating the prevalence of concomitant arterial disease at other sites and studying the incidence of future cardiovascular events and its predictors in patients at high vascular risk. Between 2001 and 2005, patients with symptomatic atherosclerotic disease received MRI of the brain in addition to standard vascular screening as part of the SMART-MR study. Follow-up measurements took place between 2006 and 2009.

OUTLINE

In chapter 2, we investigate the cross-sectional association between homocysteine levels and white matter hyperintensities, lacunar infarcts and cognitive function. In chapter 3, the relationship between homocysteine and progression of brain atrophy and cognitive dysfunction is assessed. The longitudinal association between homocysteine levels and progression of white matter hyperintensities and lacunar infarcts is examined in chapter 4, together with the longitudinal association between homocysteine levels and kidney function at follow-up. Chapter 5 reports on the markers of cerebral small vessel disease and the risk of death ischemic stroke and cardiac complications. Chapter 6 is a meta-analysis concerning cognitive dysfunction in patients with white matter hyperintensities. In chapter 7 we investigated the relationship between presence and progression of cerebral small vessel disease and brain atrophy at follow-up. Chapter 8 reports the possible presence of either venules or arterioles within periventricular and deep white matter hyperintensities in patients with an acute lacunar infarct, providing possible evidence for different aetiologies of white matter hyperintensities regarding their anatomical location. Chapter 9 describes the differences in risk factor profile between lacunar infarcts within the deep white matter and basal ganglia. Chapter 10 discusses the cross-sectional and longitudinal association between kidney function and cerebral small vessel disease, both caused by a generalized small vessel disease. In chapter 11, the main findings of this thesis are discussed and suggestions for future research are given.
REFERENCES


