Clinical and magnetic resonance observations in cerebral small-vessel disease
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General introduction

Hardening and thickening of the arterial walls probably begins after the second decade in human life and may eventually result in devastating diseases. This process is called atherosclerosis, and occurs in all parts of the arterial system, from the large muscular arteries to the small arterioles and capillaries. Atherosclerosis is usually a disease of the intima, the layer of the artery closest to the blood. The atherosclerotic plaque can be a result of the accumulation of fat, cholesterol, and fibrous tissue. The intima of the artery is usually smooth and elastic, but over time, the plaque can cause the artery to become narrowed or even completely blocked. This can lead to a variety of problems, including heart attacks, strokes, and peripheral artery disease.

Different factors can contribute to the development of atherosclerosis. Smoking, high blood pressure, high cholesterol levels, and diabetes are all risk factors. Inflammation of the small arteries may be a more direct consequence of these factors and fibrous and elastic hyperplasia with thickening of the media may lead to a more malignant result. Other factors, like infections or genetic polymorphisms may also play a role in the development of either small- or large-vessel disease.

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Hardening and thickening of the arterial walls probably begins after the second decade in human life and may eventually result in devastating diseases. This process is called arteriosclerosis, and occurs in all parts of the arterial system, from the large muscular arteries to the small arterioles and capillaries. Two main forms can be distinguished. Atherosclerosis is a disease of the intima, in which lipid-filled smooth muscle cells and macrophages (foam cells), and fibrous tissue accumulate.¹ This disease usually affects the abdominal aorta, the large renal and leg arteries, the coronary arteries and the large cerebral arteries and is therefore called large-vessel disease. The different clinical manifestations develop depending on the localization of the disease. Intermittent claudication results from large-vessel disease in the arteries of the legs, myocardial infarction from disease of the coronary arteries, and large territorial cerebral infarcts from atherosclerosis in the large cerebral arteries.

The second form of arteriosclerosis is characterized by hyaline depositions and degenerative changes in the intima and media of the small arteries of mainly the spleen, pancreas, adrenal glands, kidney and brain. This disease is also called arteriolosclerosis. In the brain affection of the small arteries may cause specific clinical symptoms: the lacunar syndromes. Why some patients develop large-vessel disease and others small-vessel disease, is unknown. Different vascular risk factors, like smoking, hypercholesterolemia and hypertension, may be associated with either small- or large-vessel disease.² Hypertension is assumed to be specifically associated with small-vessel disease. Hyalinization of the walls of the small arteries may be a more benign consequence of hypertension, and fibrous and elastic hyperplasia with necrosis of the media and intima a more malignant result. Other factors, like infections or genetic polymorphism may also play a role in the development of either small- or large-vessel disease.³,⁴

Since decades small-vessel disease in the brain has been the subject of extensive study. Three clinical manifestations are considered specific
results of small-vessel disease: lacunar infarcts, white matter disease (also called Binswangers disease) and intracerebral hemorrhages. With CT-scans and MRI, these lesions can be studied in living individuals. In a prospective cohort of 229 patients with different manifestations of both small- and large-vessel arterial disease, we studied the clinical aspects and risk factors of cerebral small-vessel disease, as shown by MRI, in comparison to large-vessel disease. In addition, in a second prospective cohort of patients presenting with an ischemic stroke, we studied the differences in the early clinical course of infarcts due to small- and large-vessel disease.

This thesis will try 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 consequences 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?

Outline of the thesis
Chapter 1 gives a review of the history of the cerebral small-vessel disease and the controversies associated with the subject. In chapter 2 we investigate differences in vascular and genetic risk factors between patients with small-vessel disease and patients with large-vessel disease. In chapter 3 we study the risk factors of pontine hyperintense MRI-lesions. These lesions are considered to be a specific form of small-vessel disease in a hitherto hardly studied localization. In chapter 4 we examine the clinical significance of these pontine hyperintense lesions. In chapter 5 we describe the small, usually asymptomatic, intracerebral hemorrhages
that we observed on MRI of patients with atherosclerosis in our cohort. In chapter 6 we examine the differences in early symptom progression in patients with small-vessel (lacunar) cerebral infarcts and those with large territorial infarcts.

References


"In chapters 3, 4, and 5 of this thesis the term “atherosclerosis” is used to denounce the whole spectrum of arterial ischemic disease, including small-vessel disease."
Intracerebral hemorrhage, a stroke subtype, is a consequence of small-vessel disease and accounts for clinical and MRI manifestations of small-vessel disease unnoticed until now?

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

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Chapter 1 gives a review of the history of the cerebral small-vessel disease and the controversies associated with the subject. In chapter 2, we investigate differences in vascular and genetic risk factors between patients with small-vessel disease and patients with large-vessel disease. In chapter 3, we study the risk factors of pontine hemorrhage MRI-lesions. These lesions are considered to be a specific form of small-vessel disease in a field hardly studied ‘locarno’. In chapter 4, we examine the clinical significance of these pontine hemorrhage lesions. In chapter 5, we describe the role of non-invasive neurological and non-contrast magnetic resonance angiography, showing brainstem and basal ganglia.