Migraine and brain changes

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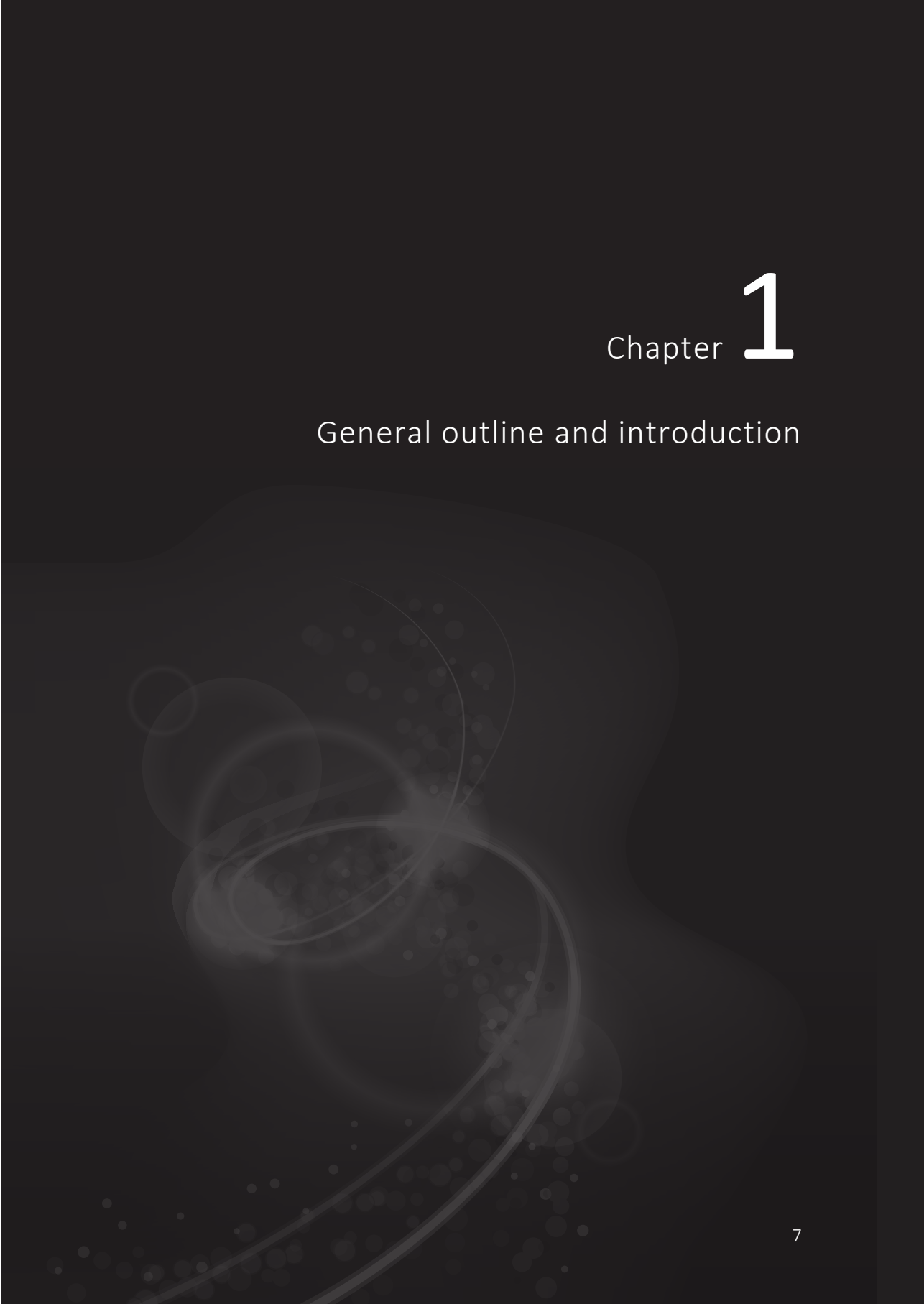
Chapter 1

General outline and introduction



This thesis reports on brain changes in migraine and its possible causes and consequences.

MIGRAINE

Migraine is a common, chronic, multifactorial neurovascular brain disorder, affecting 15% of adults. Migraine is the 3rd most common and 7th most disabling disease in the world[1], and is responsible for the highest socio-economic burden of any brain disorders in Europe[1, 2]. It is characterized by recurrent attacks of disabling headache and associated features of autonomic nervous system dysfunction (migraine without aura, MO). Up to one third of patients also have neurological aura symptoms (migraine with aura, MA).[3, 4] For a long time, migraine was believed to be just an episodic disorder without permanent effects on health, other than being disabling during the attack. However, in the last three decades, associations have been reported between migraine and cerebrovascular diseases as well as cardiovascular diseases.

MIGRAINE AND BRAIN CHANGES

Contrary to being just a harmless condition, in the past decades it has become clear that suffering from migraine may have permanent negative consequences to the brain. Accumulating evidence shows that migraine is linked to the risk of having migrainous infarction, ischemic and hemorrhagic stroke, and white matter changes in the brain.

Migrainous infarction, defined as an ischemic stroke developing during migraine with aura, is a rare complication of migraine. In this situation a migraine attack and the occurrence of brain damage are directly linked, which suggests a shared pathophysiological pathway. But, although this phenomenon has already first been described long ago, the exact pathophysiology is still not yet fully understood.[5, 6]

An increased risk of clinical ischemic stroke in migraine patients, irrespective of migraine attacks, has been shown by several epidemiological studies. This increased risk notably affects younger women with migraine, in particular those with higher attack frequency and MA.[7-9]

In addition to clinical infarction, silent cerebral infarcts are also more prevalent among migraineurs as was shown by the CAMERA-1 study (the baseline part of the CAMERA-study).[10] Silent infarcts are defined by the presence of a brain parenchymal defect of vascular origin, confirmed by CT or MRI, in the absence of neurological symptoms and signs and a history of clinical stroke or TIA.

From the moment MR imaging became available, studies have reported on white matter hyperintense signal abnormalities (WMHs) in migraine patients.[11, 12] Most initial studies suffered from methodological issues (e.g. selection bias, no IHS-criteria for mi-

graine diagnosis, etc.) and presented conflicting results, leading to difficulties in interpretation.[13] The CAMERA-1 study was designed to overcome these problems, and was the first study that provided clear answers. The study showed that migraineurs from the general population were indeed at increased risk of posterior circulation territory infarcts, and that the higher risk was most pronounced among migraine with aura patients with a higher attack frequency. Further, women with migraine were found to be at significantly increased risk of deep (not periventricular) WMHs. This increased risk was not explained by other cardiovascular risk factors. Similarly, infratentorial hyperintense lesions (IHLs) were found to be more prevalent among migraineurs.[10, 14-16] These findings were subsequently confirmed by other groups[17-19]

The CAMERA-1 study also demonstrated that migraine patients have increased iron deposition in multiple deep brain nuclei in line with clinic-based studies[20-25]. The underlying mechanisms, however, remained elusive.

Because the CAMERA-1 study had a cross-sectional design, it was not possible to draw any conclusion on a possible causal relationship between migraine attacks and brain changes. Therefore, a follow-up study was needed to assess the development of new brain changes or progression of existing brain changes over time.

In the present thesis I describe studies evaluating the incidence and evolution of brain changes and associated migraine features in the CAMERA-cohort over a period of 9 years. In addition, possible causes and functional consequences were assessed.

In Chapter 2, I describe a study assessing whether migraineurs have a higher incidence and greater volume-increase of WMHs, IHLs and infarcts over time compared to a non-migraine control group. We also assessed possible cognitive consequences of (progressive) WMLs. In chapters 3 and 4 we describe follow-up study on iron accumulation in the basal ganglia of migraineurs. In chapter 5 we compared other types of structural brain changes between migraineurs and non-migraine controls by evaluating overall and regional gray and white matter structure using state-of-the-art voxel based morphometry analyses.

POSSIBLE CAUSES

Now that we know that migraine is associated with several types of brain changes, it is important to explore possible causes and consequences.

One suggested potential cause of brain lesions in migraine patients is the higher prevalence of a right-to-left shunt (RLS) in migraine patients. RLS is an abnormal communication between the right (venous) circulation and the left (arterial) circulation. Several structural abnormalities can cause right-to-left shunting, although the most prevalent cause is a patent foramen ovale (PFO)[26], a remnant from the fetal period, which is located in the atrial septum of the heart.

In the last two decades, several clinic based case-control studies demonstrated a two to threefold increased prevalence of RLS in migraine with aura patients, as measured using Transcranial Doppler with air contrast.[27, 28] A recent review reported that PFO was more prevalent in migraine with aura patients (pooled OR 2.54; 95%CI 2.01-3.08)[29], but a population based study evaluating the presence of RLS in migraineurs and non-migraine controls of the general population was lacking up to that moment.

Therefore, I describe in Chapter 6 the prevalence of RLS in migraineurs and controls of the population-based CAMERA-cohort. RLS has been linked to increased risk of stroke in several studies, especially among younger persons.[30] In addition, among young ischemic stroke patients, those with a RLS are believed to be at higher risk of having migraine with aura.[31] It has been suggested that emboli, passing from the venous systemic circulation through a RLS to the systemic arterial circulation may both trigger migraine aura attacks and may cause (sub)clinical ischemic infarcts, thus providing a possible explanation for a link between migraine (aura), RLS and stroke. Supporting evidence for this theory was found in a recent study, showing that injecting emboli into the carotid artery of mice caused cortical spreading depression, linking emboli to migraine aura.[32] In chapter 6 I also describe the association in the CAMERA-cohort between RLS, ischemic brain lesions and persisting migraine activity.

POSSIBLE CONSEQUENCES

It is of great importance to migraine patients to know if brain changes might have functional consequences. In the study described in chapter 2, we assessed cognitive function in migraineurs with and without brain lesions.

CEREBELLAR FUNCTION

Because in the CAMERA-1 study, a higher prevalence of specifically cerebellar located infarcts was found among migraine patients, a logical question was whether these lesions might have any functional consequence? In other studies, migraine was linked to cerebellar dysfunction[33-36], possibly due to cerebellar ischemic lesions. These earlier studies, however, were clinic-based and thus included patients who were likely more severely affected than the 'average' migraineurs from the general population. Furthermore, those studies lacked neuro-imaging correlation. In the CAMERA-population, migraine patients show normal cerebellar functions despite having increased prevalence of ischaemic lesions in the cerebellar posterior lobe.[37]

Cognitive function

Clearly, the diagnosis of migraine is not as harmless as was thought before. As described above, migraine is linked to the presence and progression of white matter hyperintensities. In general, in the elderly, WMH have been linked to worse cognitive performance[38-41]. Moreover, several papers have described cognitive dysfunction among migraineurs[42-49]. Migraine patients often complain about cognitive difficulties during or directly after their migraine attacks[46, 50] In one of our own studies, migraineurs had no impaired attentional or working-memory functioning in the two days after an attack. They did, however, show impairments in the processing of global visual features compared with controls, both between and immediately after an attack.[51]
Little is known about the effect of WMH on cognitive function in migraineurs. Recently, the Epidemiology of Vascular Aging study has evaluated this complex relation and demonstrated no evidence that migraine in itself, or in combination with structural brain lesions, results in cognitive impairment.[17] Chapter 2 of this thesis describes cognitive functioning of the CAMERA-participants with and without migraine and whether high WMH load might be associated with reduced cognitive performance.

AIM OF THIS THESIS

The general aims of this thesis were: (i) to evaluate the presence and progression of brain changes and (ii) to analyze possible causes and consequences for these brain changes in the population-based longitudinal CAMERA-study.

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