Migraine and brain changes

Meinders, I.H.

Chapter 7

Summary

The general objective of this thesis was to assess presence and progression of brain changes in migraine patients of the population-based longitudinal Cerebral Abnormalities in Migraine an Epidemiological Risk Analysis-study (CAMERA-2 study). Furthermore, some possible causes and functional consequences of these brain changes were evaluated.

Chapter 2 describes the prevalence and progression of brain changes as measured by MR imaging and the relation between migraine and brain lesions with cognitive performance. After a nine-year follow-up, there were no differences between male migraine patients and controls in brain lesion presence or progression. Women with migraine, on the other hand, showed higher incidence of deep white matter hyperintensities. Migraine severity characteristics - number of attacks, duration, frequency - were not associated with progression of lesions. Progression was marked by increased number of new lesions, rather than increase in the size of preexisting lesions. There were no differences in prevalence or progression of periventricular white matter hyperintensities between migraine patients and controls. Infratentorial hyperintensities were also found more often among migraine women compared to controls. Again, no relation was found with migraine aura or migraine severity. Finally, 10 migraineurs versus none of the controls showed new infarcts in the posterior circulation territory. Therefore, among females from the general population, migraine is a risk factor for presence and progression of white matter hyperintensities.

The association between migraine and iron in the brain is described in Chapter 3. Previously it has been suggested that (the pain of) repeated migraine attacks might cause iron accumulation in brain structures involved in central pain processing. In Chapter 4, iron deposition and accumulation in the basal ganglia of the CAMERA-participants is evaluated by measuring T2-values at baseline and follow-up time points. At baseline, migraineurs below age 50 had decreased T2-values indicative of increased iron deposition in deep brain nuclei. After nine years, T2-values of most deep brain nuclei were increased rather than further decreased as we had expected. Furthermore, there were no differences anymore between migraineurs and controls. Possibly, age-related signal increases might have counteracted the iron-related signal decreases.

Chapter 5 describes structural brain changes in the CAMERA-cohort, as measured with voxel-based morphometry of anatomic MR images. In region-of-interest analyses, migraineurs showed decreased grey matter volume in the visual areas V3 and V5 of the right occipital cortex compared to controls. We discuss possible explanations for these findings, such as brain changes caused by adaptive remodeling due to chronic pain, hyperexcitability, distorted cerebral metabolic homeostasis, and changes in local neurotransmitter compositions.

Several kinds of migraine-associated brain changes are discussed in chapters 2-5. The occurrence of ischemia during attacks seems a logical explanation for the development of lesions. But ischemia cannot explain all findings. Possible alternative explanations for an association of migraine headache with structural brain changes include: (i) a

chronic procoagulatory or proinflammatory state due to endothelial dysfunction or elevated homocysteine levels; or (ii) recurrent paradoxical (micro-)emboli as a result of right-to-left shunting.

In Chapter 6, the prevalence of right-to-left shunt (RLS), and its association with ischemic brain lesions and migraine persistence is described. Among migraineurs with aura, the prevalence of RLS is increased and spontaneous RLS are associated with persistent recurrence of migraine attacks at older age. Valsalva-induced RLS, in particular the larger ones, are also more prevalent among migraineurs with aura than among controls or migraineurs without aura. Having both migraine with aura and a spontaneous RLS increases the likelihood of persisting migraines. Irrespective of having migraine or not, individuals with RLS tend to have more often infratentorial infarct-like lesions than those without RLS. Migraine with aura (but not without) and RLS are comorbid conditions, but the biological mechanism remains speculative. Cerebral emboli are probably able to induce migraine symptoms, although this is rare. There is no evidence that closure of a RLS modifies migraine frequency.

Do the brain lesions observed in migraine patients have functional consequences? Because of the higher risk in migraine of infarcts in specifically the posterior territory, cerebellar functioning of the CAMERA-2 study participants was evaluated by means of a robust cerebellar test battery (Koppen, Palm-Meinders et al. Cephalalgia 2017). The domains of fine motor skills (Purdue Pegboard), visuospatial ability (Block-design test), limb learning (prism-adaptation task), learning-dependent timing (eyeblink-conditioning task), and balance capabilities (body-sway test) were analyzed. Migraine patients and controls showed similar performance on all cerebellar functioning tests. Those with a cerebellar infarct performed similarly, except for a worse assembly task of the Purdue Pegboard, which tests fine motor skills. It can be concluded that – despite a higher risk of cerebellar ischemic lesions – migraine patients from the general population do not show impaired cerebellar functioning.

In general, white matter hyperintensities are linked to impaired cognitive performance. Furthermore, many migraine patients have cognitive complaints during or shortly after an attack. Cognitive performance was therefore evaluated in the same population at baseline in the CAMERA-1 study and, nine years later, in the CAMERA-2 study (Chapter 2). Cognitive functioning was similar for migraine patients and controls, deep white matter hyperintensities were not related to impaired cognitive performance, and migraine had no influence on this association. Participants with high lesion load at baseline did not experience greater change in cognitive function at 9-year follow-up than those without high lesion load at baseline. Similarly, there were no significant differences between groups with respect to tests of individual cognitive domains.

In summary, migraine was associated in women with increased risk of brain changes and greater progression of existing brain lesions. The underlying pathophysiological mechanisms are not yet clear, but both attack- and permanent disease-related mechanisms seem to be involved. The increased prevalence of brain lesions did not result in

impaired cognitive or cerebellar performance. Migraine severity was not correlated with number of lesions or degree of lesion progression. Our findings are reassuring for migraine patients and their doctors.