Migraine and brain changes

Meinders, I.H.

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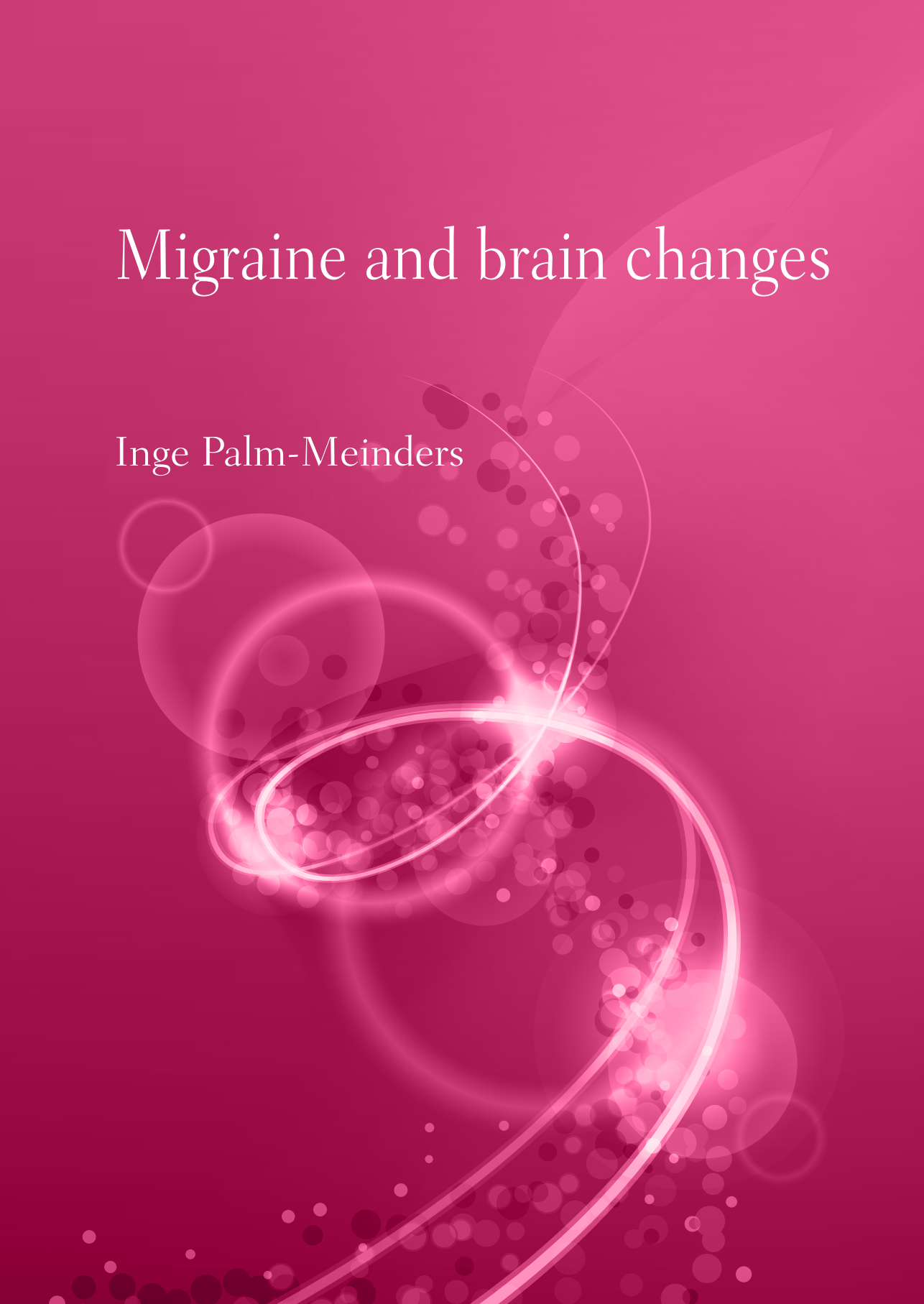
Inge Palm-Meinders



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Migraine and brain changes

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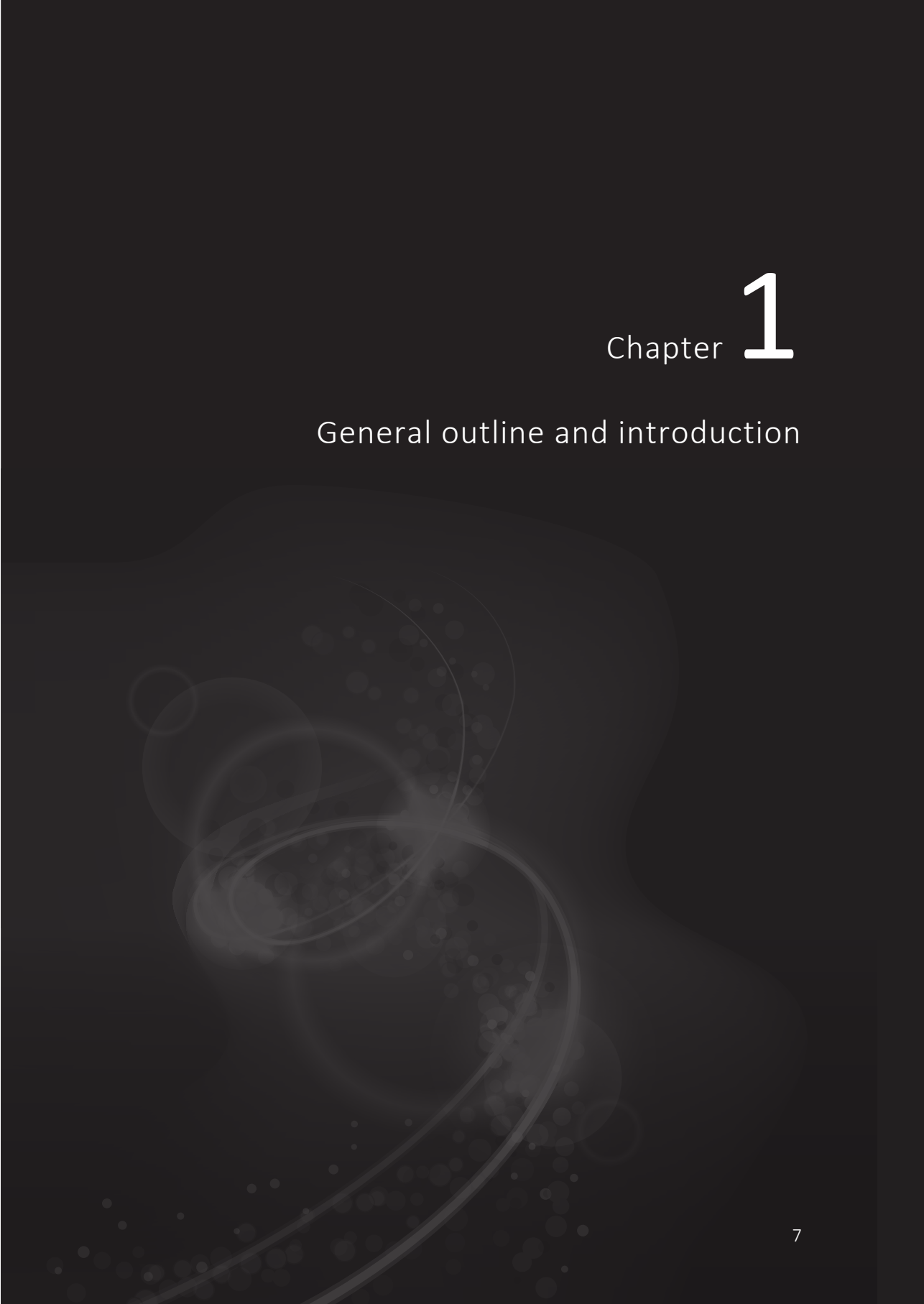
Chapter 1

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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Chapter 2

Structural brain changes in migraine

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ABSTRACT

Background. Migraine affects up to 15% of the general population.[1-3] One-third of patients with migraine have associated symptoms of neurological aura.[2,3] Previous work in the cross-sectional community-based Cerebral Abnormalities in Migraine, an Epidemiological Risk Analysis (CAMERA-1) study demonstrated a higher prevalence and greater volume of magnetic resonance imaging (MRI)–measured deep white matter hyperintensities, infratentorial hyperintensities, and posterior circulation territory infarctlike lesions in participants with migraine.[4-6] A higher volume of deep white matter hyperintensities[7] and increased prevalence of posterior circulation territory infarctlike lesions has also been demonstrated in women with migraine with aura[8] and the prevalence of deep white matter hyperintensities was increased among patients with migraine identified from neurology clinics.[9]

Context. A previous cross-sectional study showed an association of migraine with a higher prevalence of magnetic resonance imaging (MRI)–measured ischemic lesions in the brain.

Objective. To determine whether women or men with migraine (with and without aura) have a higher incidence of brain lesions 9 years after initial MRI, whether migraine frequency was associated with progression of brain lesions, and whether progression of brain lesions was associated with cognitive decline.

Design, Setting, and Participants. In a follow-up of the 2000 Cerebral Abnormalities in Migraine, an Epidemiological Risk Analysis cohort, a prospective population-based observational study of Dutch participants with migraine and an age and sex-matched control group, 203 of the 295 baseline participants in the migraine group and 83 of 140 in the control group underwent MRI scan in 2009 to identify progression of MRI-measured brain lesions. Comparisons were adjusted for age, sex, hypertension, diabetes, and educational level. The participants in the migraine group were a mean 57 years (range, 43-72 years), and 71% were women. Those in the control group were a mean 55 years (range, 44-71 years), and 69% were women.

Main outcome measures. Progression of MRI-measured cerebral deep white matter hyperintensities, infratentorial hyperintensities, and posterior circulation territory infarctlike lesions. Change in cognition was also measured.

Results. Of the 145 women in the migraine group, 112 (77%) vs 33 of 55 women (60%) in the control group had progression of deep white matter hyperintensities (adjusted odds ratio [OR], 2.1; 95%CI, 1.0-4.1; *P* = .04). There were no significant associations of migraine with progression of infratentorial hyperintensities: 21 participants (15%) in the migraine group and 1 of 57 participants (2%) in the control group showed progression (adjusted OR, 7.7; 95% CI, 1.0-59.5; *P* = .05) or new posterior circulation territory infarctlike lesions: 10 of 203 participants (5%) in the migraine group but none of 83 in the control group (*P* = .07). There was no association of number or frequency of migraine headaches with progression of lesions. There was no significant association of high vs

non-high deep white matter hyperintensity load with change in cognitive scores (−3.7 in the migraine group vs 1.4 in the control group; 95% CI, −4.4 to 0.2; adjusted *P* = .07).
Conclusions. In a community-based cohort followed up after 9 years, women with migraine had a higher incidence of deep white matter hyperintensities but did not have significantly higher progression of other MRI-measured brain changes. There was no association of migraine with progression of any MRI-measured brain lesions in men.

INTRODUCTION

White matter hyperintensities, infratentorial hyperintensities, and posterior circulation territory infarctlike lesions are believed to be of ischemic origin. In particular, white matter hyperintensities are associated with atherosclerotic disease risk factors,[9] increased risk of ischemic stroke,[10-12] and cognitive decline.[13] The associations of migraine with these MRI-measured lesions and clinical ischemic stroke [7,14] are consistent with the hypothesis that recurring migraine headaches may be associated with cerebral ischemia and that migraine-associated cerebral ischemia may be attack related. In the current study, we report associations of migraine and migraine subtype with the progression of MRI-measured cerebral ischemic lesions at the 9-year follow-up of the original CAMERA study population. In exploratory analyses, we report associations of migraine frequency, total number of migraine attacks during follow-up, and presence of current migraine headache symptoms with progression of brain lesions. In additional exploratory analyses, we determined whether progression of brain lesions was associated with cognitive decline and whether the presence of migraine headache influenced any association of brain lesion progression with cognitive decline.

METHODS

Study Population and Procedures

The original participants of the CAMERA-1 study included 295 well characterized individuals with migraine[3] and 140 age and sex-matched controls who were randomly selected from a community-based study of the general population.[1] The MRI scans were completed in 2000.[4] All participants were invited to return for follow-up scan in 2009. In 2000, the mean age of the sample was 48 years (SD, 7.8 years) and 71% were women (*e*Table 1, available at http://www.jama.com). The CAMERA-2 study, conducted in 2009, included a structured computer-guided telephone interview (programmed using Ishell software, World Health Organization), brain MRI, physical examination, and cognitive testing similar to the CAMERA-1 protocol. Participants were administered questionnaires to determine previous, current, and newly developed migraine attacks since

2000. The interview was structured so that participants could recount their history of migraine using personal benchmarks (e.g. pregnancy) for when a different pattern started and stopped. These benchmarks were used to define periods. Information was collected on migraine prophylaxis and treatment. All non-imaging data were collected blinded to diagnosis and MRI findings. To avoid introduction of false-positive differences due to upgraded MRI techniques, we used the same scanners and protocols that were used for CAMERA-1.[4] The protocol was approved by the local medical ethics committees. All participants gave written informed consent.

Outcome Measures

Primary outcome measure of this study was change in number and volume of MRI-measured deep white matter hyperintensities in individuals with migraine vs controls during follow-up. In addition, progression of posterior circulation territory infarctlike lesions as well as infratentorial hyperintensities was evaluated.

Results of automatic segmentation of white matter lesions (QBrain 1.1 software) were, if necessary, corrected manually in a conservative manner by 1 rater, in anonymized baseline and follow-up scans separately, blinded for scan order and diagnosis. Reproducibility data include (random, n = 40 of participants reanalyzed): 1.0T-scanner: p, 0.999 ($P < .001$) and 1.5T-scanner: p, 0.963 ($P < .001$). Periventricular white matter hyperintensities were attached to the lateral ventricle; other supratentorial hyperintensities were deep white matter hyperintensities, which were calculated by number, total, and mean volume for each participant. Geographical location was evaluated by normalizing the individual MRI scans with segmented lesions to standard Montreal Neurological Institute–space, and projecting the lesions (weighted for group size) of all participants per diagnostic group in a transparent 3-dimensional map (glass brain).

Infratentorial hyperintensities were hyperintense on T2- and proton-density-weighted and not hypointense on fluid attenuated inversion recovery images. Presence and progression of lesions was diagnosis, by comparing baseline and follow-up scans side by side. Reproducibility data (random, n = 40 [14%]; baseline, K = 0.908; $P = .09$ and follow-up, K = 1.000; $P < .001$). Lesion progression was defined as an increase in size, number, or both (Figure 1).

Infarctlike lesions were nonmass parenchymal defects with a vascular distribution, isointense to cerebrospinal fluid signal on all sequences, and, when supratentorial, surrounded by a hyperintense rim on FLAIR images.[4] Virchow-Robin spaces were excluded based on typical location, shape, and absence of a hyperintense rim. In the basal ganglia, only parenchymal defects larger than 3 mm in diameter were considered in order to exclude nonspecific lesions. Location and vascular territory of new and preexisting infarcts were read by 2 neuroradiologists, who were blinded to diagnosis (K= 0.87, $P <.001$). All sequences of baseline and follow-up scans were presented side by side (angulation corrected and position linked). A third senior neuroradiologist made the

final diagnosis in the 9 cases in which the 2 raters disagreed. An exploratory outcome measure of this study was the changes in cognition related to white matter hyperintensities at baseline and at follow-up. Similarly, the change in cognition between baseline and follow-up was evaluated as function of baseline and follow-up lesion volume as well as lesion volume change. For each participant, normalized test scores (*Z* scores of separate tests in domains of memory, executive function, attention, visuospatial ability, and speed) were summed to achieve a total composite cognitive score for each time point. Change in raw test scores (follow-up minus baseline) were normalized by *Z* scores. The tests, evaluating cognitive performance in the domains of memory, concentration, and attention, executive functioning, psychomotor, and processing speed, organization, fine motor skills, fluid intelligence, and visuospatial skills, consisted of the 15-word Verbal Learning Test[15]; abbreviated Stroop test,[16] consisting of 3 subtasks; verbal Fluency which is a modified version of the Symbol Digit Modalities Test; and the Purdue pegboard test.[19] In follow-up investigation, the Block Design Test from the Wechsler Adult Intelligence Scale III test battery[20] was added. Further details on cognition testing are provided in *e*Table 3 (available at http://www.jama.com).

Covariates and Definitions

Sociodemographic and medical history characteristics were assessed by interview. Educational level was dichotomized into low, primary school or less than vocational education, and high, more than higher vocational or professional education, college, or university. A diagnosis of diabetes or hypertension was based on patient report of a physician's diagnosis.

Statistical Analysis

Differences in the distributions and means of measured characteristics among the study groups were assessed with X^2, 2-tailed Fisher exact, unpaired *t*, and Mann-Whitney *U* tests and 1-way analyses of variance where appropriate. Using logistic regression, the risk for MRI outcome measures was examined by migraine diagnosis (yes/ no) and subtype of migraine (with and without aura vs controls), controlling for age, sex, educational level, hypertension, and diabetes. Statistical interactions of hypertension and diabetes for associations of migraine and MRI measured outcomes were tested for by adding the interaction terms to the models. Analyses of deep white matter hyperintensity volumes were a priori stratified by sex, based on earlier findings of increased association of migraine with MRI lesions only among women.[4] Likewise, infarct analyses were a priori stratified by anterior or posterior vascular territory. In logistic regression models, exploratory analyses were conducted on the effects of several migraine characteristics on measures of lesion progression. Associations between deep white matter hyperintensity load and normalized scores of the baseline and follow-up cognitive tests were assessed

using linear regression models, adjusting for age, sex, and educational level (model 1) and additionally for migraine (model 2) to assess the effect of migraine diagnosis. Data were analyzed using the statistical software package for social sciences (SPSS, version 17.0. for Windows).

RESULTS

Study Population

A total of 411 of 435 (95%) of baseline participants were successfully recontacted; 14 participants had moved, 4 were lost to civil registry information, and 6 had died (*e*Table 1).

Two hundred eighty-six participants (66%) underwent follow-up MRI scan (114 migraine with aura, 89 migraine without aura, 83 controls). Mean follow-up was 8.5 years (range, 7.9-9.2; SD, 0.24 years). Reasons for nonparticipation were no interest (n = 51), inability to visit the research center (n = 30), claustrophobia (n = 8), and non-neurological illness (n = 36). There was no association between responder rate and diagnosis of migraine (response rate in both migraine groups was 203 of 296 (69%) vs 83 of 139 (60%) in the control group (*P* = .07). Compared with nonparticipants, participants were younger at baseline (48 vs 50 years; *P* = .01), more often reported high educational level (52% vs 40%; *P* = .01), smoked fewer pack years (8 vs 14 years; *P* <.001; *e*Table 1), had a similar prevalence of posterior circulation territory infarctlike lesions (4%), brain infarcts (6% vs 9%; *P* = .24), and a high load of deep white matter hyperintensities (based on semi quantitative measures at baseline; 19% vs 22%; *P* = .44). At follow-up, participants in the migraine group were slightly older than those in the control group (57 vs 55 years; *P* = .03) and had a higher prevalence of diabetes (9% vs 2%; *P* = .05; TABLE 1).

Deep White Matter Hyperintensities

There were no differences in baseline and follow-up white matter hyperintensities between men in the migraine group and those in the control group (TABLE 2). However, among women, both at baseline and follow-up, deep white matter hyperintensity volume was higher in the migraine group than in the control group (baseline: 0.02 mL vs 0.00 mL; P = .009; follow-up: 0.09 mL vs 0.04 mL; P = .04). Women in the migraine group also had a higher median increase in volume of deep white matter hyperintensities (mL), as well as a higher incidence of progression (defined as > 0.01 mL) than women in the control group (yes/no, ≥ 0.01 mL) (77% vs 60%; P = .02). The incidence of deep white matter hyperintensity progression was highest among women with migraine without aura (83%; Table 2). In multivariate logistic regression analyses involving only women, migraine was independently associated with deep white matter hyperintensity

progression (adjusted odds ratio [OR], 2.1; 95% CI, 1.0-4.1; *P* = .04; TABLE 3). Similarly, women in the migraine group had a higher incidence of high progression than women in the control group (23% vs 9%; *P* = .03; Table 2). Hypertension was not associated with a higher incidence of white matter hyperintensity progression (*P* = .06). Interaction terms for hypertension (*P* = .90) and diabetes (*P* = .60) were not significant. Further exploratory analyses showed no association of the number of migraine attacks, migraine attack duration, migraine frequency, type of attack, or migraine therapy with lesion progression (*e*Table 2).

Figure 1. Brain Magnetic Resonance T2-Weighted images at baseline and follow-up from three representative participants showing progression of infratentorial hyperintensities

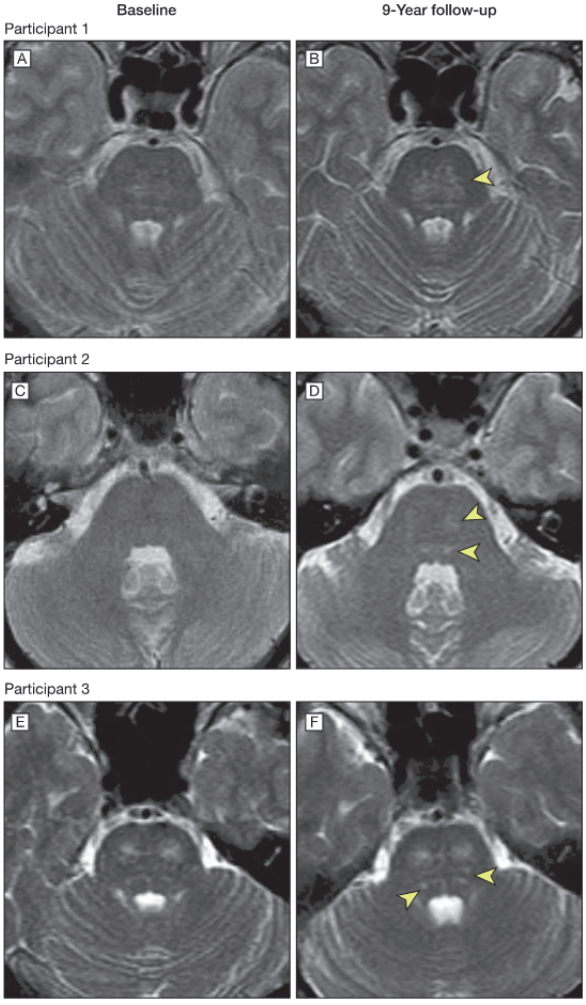


Image B shows pontine hyperintensity (arrowhead) increased in size compared with baseline image (A). Image D shows new hyperintensities (arrowheads) compared with baseline image (C). Image F shows additional hyperintensities (arrowheads) compared with baseline image (E).

Table 1. Follow-up Characteristics of Study Participants

Characteristic	Total (n=286)	Controls (n=83)	Migraine (n=203)	Migraine	
				No Aura (n=89)	Aura (n=114)
Age, mean (SD), y	57 (7.7)	55 (7.3)	57 (7.8)[f]	58 (7.5)	57 (8.0)
Women	202 (71)	57 (69)	145 (71)	64 (72)	81 (71)
Maastricht research center	128 (45)	38 (46)	90 (44)	35 (40)	55 (48)
Low education[a]	137 (48)	38 (46)	99 (49)	46 (52)	53 (47)
BMI, mean (SD)	26 (4.1)	26 (3.8)	26 (4.3)	25 (4.3)	26 (4.2)
Hypertension[b]	97 (34)	24 (29)	73 (36)	32 (36)	41 (36)
Use of antihypertensive medication[c]	79 (28)	19 (23)	60 (30)	28 (32)	32 (28)
Blood pressure, mean (SD), mm Hg[b]					
Systolic	151 (21)	152 (19)	151 (21)	148 (20)	154 (22)
Diastolic	94 (11)	94 (12)	94 (11)	92 (10)	96 (12)
Diabetes (self-reported)	20 (7)	2 (2)	18 (9)[g]	9 (10)	9 (8)
History of stroke[d]	8 (3)	0 (0)	8 (4)	2 (2)	6 (5)
History of transient ischemic attack	12 (4)	2 (2)	10 (5)	5 (6)	5 (4)
Smoking					
Ever	193 (68)	58 (70)	135 (67)	58 (65)	77 (68)
Current	67 (35)	19 (33)	48 (36)	22 (38)	26 (34)
Pack-years, mean (SD)	11 (15)	12(15)	11 (15)	13 (18)	10 (13)
Alcohol use					
None during last 12 mo	42 (15)	10 (12)	32 (16)	18 (20)	14 (12)
≥3 U/d	29 (10)	11 (13)	18 (9)	6 (7)	12 (11)
Current use of migraine medication[e]					
Triptans			25 (12.3)	8 (9)	17 (14.9)
Ergotamines			5 (2.5)	1 (1.1)	4 (3.5)
Prophylactic drugs			7 (3.4)	1 (1.1)	6 (5.3)
Oral contraceptive use, women only					
Current	16 (6)	6 (12)	10 (8)	3 (6)	7 (9)
≥ 15 y	71 (25)	24 (48)	47 (38)	21 (42)	26 (35)

Abbreviations: BMI: Body mass index calculated as weight in kilograms divided by height in meters squared.
a: Low education indicates primary school or lower vocational education. b: Hypertension self-reported physician diagnosed. c: Use of antihypertensive medication by participants with hypertension, not used as migraine prophylaxis. Mean blood pressure indicates mean of two blood pressure measurements after transcranial Doppler examination with Valsalva maneuver. d: Ischemic or hemorrhage, self-reported. e: current use of migraine medication defined as use in the year. f: compared with controls: P=.03. Unless indicated otherwise, differences were not significant (P >0.05). g: Compared with controls P=.05

The increase in total deep white matter hyperintensity volume among women with migraine was related to an increased number of new lesions rather than intensities at follow-up did not differ between groups (*P* = .97). Participants in the migraine group

had a higher incidence of 10 or more new lesions among 43 of 145 participants (30%) vs 5 of 57 in the control group (9%) (adjusted OR, 3.5; 95% CI, 1.3-9.6; *P* = 01). Among women with migraine, deep white matter hyperintensities were more diffusely distributed in the deep white matter than among controls (FIGURE 2).

Periventricular White Matter Hyperintensities

Progression of periventricular white matter hyperintensities did not differ between participants with migraine and controls. There was no association of sex, aura status, or migraine frequency with progression.

Infratentorial Hyperintensities

The prevalence of infratentorial hyperintensities at follow-up was 21% among women with migraine and 4% among controls (adjusted OR, 6.5; 95% CI, 1.5-28.3; *P* = .01; Table 3). Progression of infratentorial hyperintensities was not significantly higher among women with migraine (15%) than women in the control group (2%; adjusted OR, 7.7; 95% CI, 1.0-59.5; *P*=.05; Table 3). There was no relationship between migraine aura and number or frequency of migraine attacks with progression of infratentorial hyperintensities. Among men there were no differences in infratentorial hyperintensity prevalence or progression.

Table 2. Prevalence and Progression of Infarcts and Deep White Matter and Infratentorial Hyperintensities

	Controls (n = 83)	Migraine Headache (n = 203)	*P* Value[a]	Migraine Headache		*P* Value[a]
				Without Aura (n = 89)	With Aura (n = 114)	
Deep white matter hyperintensities						
Men, No. (%)	26 (31)	58 (29)	.7	25 (28)	33 (29)	>.99
Lesion volume, median (IQR), mL						
Baseline	0.04 (0.00-0.20)	0.02 (0.00-0.07)	.18	0.01 (0.00-0.08)	0.02 (0.00-0.09)	.76
9-y Follow-up	0.14 (0.01-0.67)	0.06 (0.08-0.34)	.36	0.05 (0.00-0.15)	0.11 (0.01-0.42)	.47
Difference	0.08 (0.01-0.43)	0.04 (0.00-0.29)	.31	0.04 (0.00-0.10)	0.08 (0.01-0.31)	.47
Lesion progression, No. (%)[b]	21 (81)	40 (69)	.30	15 (60)	25 (76)	.26
High progression, No. (%)[c]	6 (23)	12 (21)	.78	5 (20)	7 (21)	>.99
New lesions						
Median (IQR)	3 (1-11)	3 (0-8)	.64	3 (0-5)	4 (0-10)	.50
≥10, No. (%)	8 (31)	12 (21)	.41	4 (16)	8 (24)	.53
Mean volume, median (IQR)	0.03 (0.01-0.05)	0.02 (0.01-0.04)	.23	0.02 (0.01-0.07)	0.02 (0.01-0.04)	.65
Women, No. (%)	57 (69)[d]	145 (71)	.67	64 (72)	81 (71)	>.99
Lesion volume, median (IQR), mL						
Baseline	0.00 (0.00-0.04)	0.02 (0.00-0.09)	.009	0.03 (0.00-0.12)	0.01 (0.00-0.06)	.08
9-y Follow-up	0.04 (0.00-0.19)	0.09 (0.02-0.34)	.04	0.16 (0.02-0.43)	0.05 (0.01-0.28)	.03
Difference	0.02 (0.00-0.14)	0.05 (0.01-0.27)	.04	0.11 (0.01-0.36)	0.04 (0.00-0.15)	.04
Lesion progression, No. (%)[b]	33 (60)	112 (77)	.02	53 (83)	59 (73)	.17
High progression, No. (%)[c]	5 (9)	33 (23)	.03	19 (30)	14(17)	.11
New lesions						
Median (IQR)	1 (0-6)	3 (0-11)	.04	1 (0-9)	5 (0-16)	10
>10, No. (%)	5 (9)	43 (30)	.003	25 (39)	18 (22)	.03
Mean volume, median (IQR)	0.02 (0.01-0.04)	0.02 (0.01-0.03)	.97	0.02 (0.01-0.03)	0.02 (0.01-0.04)	.59

	Controls (n = 83)	Migraine Headache (n = 203)	*P* Value[a]	Migraine Headache		
				Without Aura (n = 89)	With Aura (n = 114)	*P* Value[a]
Infratentorial hyperintensities, No. (%)						
Men						
Prevalence	3 (12)	9 (16)	.75	4 (16)	5 (15)	>.99
Progression[b]	1 (4)	5 (9)	.66	2 (8)	3 (9)	>.99
Women						
Prevalence	2 (4)	30 (21)	.002	18 (28)	12 (15)	.06
Progression[b]	1 (2)	21 (15)	.01	13 (20)	8 (10)	.10
Posterior circulation territory infarctlike lesions, No. (%)[e]						
Baseline	3 (4)	11 (5)	.76	2(2)	9 (8)	.12
9-y Follow-up	3 (4)	18 (9)	.14	6 (7)	12 (11)	.46
New lesion	0	10 (5)	.07	5 (6)	5 (4)	.75
Anterior circulation or basal ganglia infarctlike lesions (non-posterior circulation territory), No. (%)						
Baseline	8 (10)	15 (7)	.63	6 (7)	9 (8)	.79
9-y Follow-up	11 (13)	20 (10)	.41	12 (11)	8 (9)	.82
New lesions	3 (4)	5 (3)	.69	2 (2)	3 (3)	>.99

Abbreviation: IQR, interquartile range, [a]P values are for differences between the control group and the migraine group and between those in the migraine group with and without aura. [b]Progression of deep white matter hyperintensities is defined as an increase in volume after 9 years (A between follow-up and baseline>0.01 mL); progression of infratentorial hyperintensities is defined as an increase in size, number, or both, [c]High progression of deep white matter hyperintensities defined as the upper 20th percentile of progression distribution, [d]For analyses of deep white matter hyperintensity progression, 2 women in the control group were excluded (leaving n = 55), because of missing baseline volumes due to software failures during lesion segmentations. Visual comparison revealed no progression between baseline and follow-up for these 2 women. [e]The number of participants with 1 or more infarctlike lesions. Three of 10 participants who already had a posterior circulation territory infarctlike lesion at baseline developed additional lesions between scans.

Table 3. Risk of Deep White Matter and Infratentorial Hyperintensities in Women by Migraine Status[a]

	Controls (n=57)	Migraine (n=145)	*P* Value	Migraine Without Aura (n=64)	Migraine With Aura (n=81)	*P* Value
Deep white matter hyperintensities						
Progression, No. (%)[b]	33 (60)[e]	112 (77)		53 (83)	59 (73)	
OR (95% CI)	1 [Reference]	2.1 (1.0-4.1)[f]	.04	2.9 (1.2-6.7)[f]	1.7 (0.8-3.5)	.23
High progression, No. (%)[c]	5 (9)[e]	33 (23)		19 (30)	14 (17)	
OR (95% CI)	1 [Reference]	2.3 (0.8-6.4)	.12	3.3 (1.1-9.9)[f]	1.6 (0.5-5.0)	.12
High increase in number, No. (%)[d]	5 (9)[e]	43 (30)		25 (39)	18 (22)	
OR (95% CI)	1 [Reference]	3.5 (1.3-9.6)[f]	.01	5.3 (1.8-15.4)[f]	2.4 (0.8-7.0)	.04
Infratentorial hyperintensities	2 (4)	30 (21)		18 (28)	12 (15)	
Prevalence, No. (%)						
OR (95% CI)	1 [Reference]	6.5 (1.5-28.3)[f]	.01	9.6 (2.1-44.1)[f]	4.4 (0.9-20.5)	.07
Progression, No. (%)[b]	1 (2)	21 (15)		13 (20)	8 (10)	
OR (95% CI)	1 [Reference]	7.7 (1.0-59.5)	.05	11.5 (1.4-92.9)[f]	5.0 (0.6-41.7)	.10

Abbreviation: OR, odds ratio. [a]OR (95% CI) are adjusted for age, education, hypertension, and diabetes. [b]Progression is defined as an increase in volume after 9 years (delta between follow-up and baseline > 0.01 mL); progression of infratentorial hyperintensities is defined as an increase in size, number, or both. [c]High progression is defined as the upper 20th percentile of progression distribution. [d]High increase in number of lesions is defined as 10 or more new lesions, which reflects the upper 20th percentile of the distribution of lesions count. [e]For analyses of deep white matter hyperintensity progression, 2 women in the control group were excluded (leaving n = 55), because of missing baseline volumes due to software failures during lesion segmentations. Visual comparison revealed no progression between baseline and follow-up for these 2 women. [f]Compared with controls: P < .05

Infarcts and Infarctlike Lesions

None of the infarctlike lesions present at baseline had disappeared. No significant association of migraine with new posterior circulation territory infarctlike lesions existed between groups (migraine group, 5% vs control group, 0%; *P* = .07; Table 2). Among participants in the migraine group, 18 (8.9%) with posterior circulation territory infarctlike lesions had a less favorable cardiovascular risk profile than the 185 participants (91.1%) without it. Those with infarctlike lesions were older (mean age, 62 vs 57 years; *P* = .006); had higher prevalences of clinically diagnosed stroke (22% vs 3%; *P* < .001) or hypertension (67% vs 33%; *P* = .005), and were more likely taking statins (39% vs 17%; *P* = .03) or platelet inhibitors (33% vs 6%; *P* < .001). There was no difference between groups for new non–posterior circulation territory infarctlike lesions (migraine group, 2.5% vs control group, 3.5%; *P* = .69; Table 2). Of those with infarcts, 21% of those in the control group vs none in the control group reported a history of clinical stroke (*P* = .10).

Cognitive Changes

There were no differences in cognitive functioning between groups at follow-up (mean composite *Z* score, migraine group, 1.2 vs control group, 0; adjusted *P* = .90; 95% CI, −2.0 to 2.0). At follow-up, deep white matter hyperintensity load was not associated with cognitive performance (mean composite *Z* score high load, −3.7 vs low load, 1.4; adjusted *P* = .07; 95% CI, −4.4 to 0.2; men and women were analyzed together, see also eTable3 for original clinical scores of the separate subtest domains). Presence of migraine did not influence this association (adjusted *P* = .30; 95% CI, −2.0 to 2.1). Individuals with a high deep white matter hyperintensity load at baseline did not experience greater change in cognitive function at the 9-year follow-up than those without a high load at baseline (mean composite Z score, −0.5 vs 0.2; adjusted *P* = .4; 95% CI, -1.7 to 0.7). Similarly, there were no significant differences between groups with respect to tests of individual cognitive domains (eTable3).

COMMENT

We prospectively evaluated associations of migraine with structure and function of the brain at the 9-year follow-up. Among men, we found no association of migraine with progression of MRI-measured brain lesions. Women in the migraine group had a higher prevalence and a greater increase of deep white matter hyperintensities than women in the control group. Although migraine was associated with a higher prevalence of infratentorial hyperintensities at follow up, there were no significant associations of migraine with progression of infratentorial hyperintensities or posterior circulation territory infarct like lesions among women. In addition, the number of migraines, frequency of migraines, migraine severity, type of migraine, and migraine therapy were not associated with lesion progression. Increase in deep white matter hyperintensity volume was not significantly associated with poorer cognitive performance at follow-up.

This study has several strengths, including the longitudinal study design, length of follow-up, the relatively well characterized cohort, use of standardized International Headache Society criteria-based diagnosis of migraine by headache experts, and sensitive and reproducible methods of MRI reading. The sensitive MRI techniques used allowed for a more detailed analysis of the brain, in particular the cerebellum.

Approximately one-third of the original baseline population could not be reinvestigated. This may have introduced selection bias. However, there were no differences in baseline MRI parameters between participants and nonparticipants and there was no imbalance between the proportions and demographic and clinical characteristics of nonparticipating individuals with migraine and controls. Because of differences between the semi quantitative baseline reading of deep white matter hyperintensities and the current quantitative volume measurements that were not available for the non-

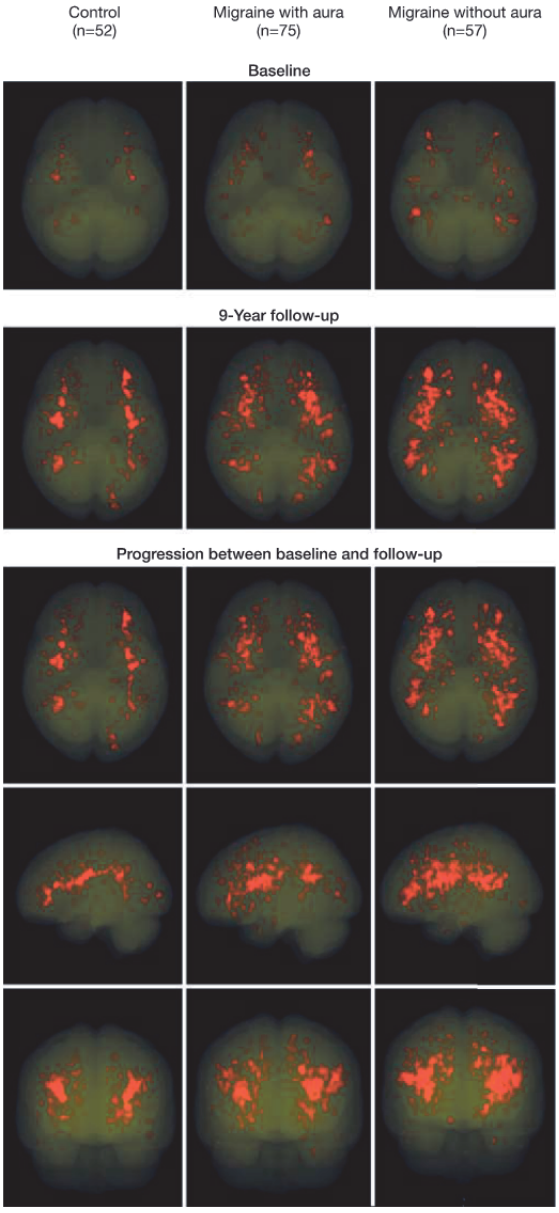
responders, additional imputation analyses to support the sensitivity of the current results could not be performed. An additional study limitation is that confidence intervals are wide (Table 3).

The number of migraine attacks, frequency of migraines, migraine severity, type of migraine headaches, and migraine therapy were not associated with lesion progression. In contrast, our baseline data showed that more frequent migraine headaches were associated with a higher prevalence of MRI findings.[4]

However, our findings at baseline regarding frequency-related difference in MRI findings was most pronounced among those in the migraine group who were 50 years or younger and less so in older patients. Thus, with increasing age of the study population, when attacks generally diminish,[1] other migraine disease-related conditions leading to white matter hyperintensities are possibly increasing, complicating the detection of migraine attack-related associations. A similar, age-dependent mechanism is also seen for the risk of stroke in participants with migraine, which is increased in young patients only.[14,21] At older age, other risk factors such as hypertension may obscure or overcome any potential role of migraine. In the present case, we hypothesize there are at least 2 different types of vascular mechanisms that may cause structural brain changes in migraine: one, which is primarily related to attacks and mainly present at younger age, and another, which is probably ongoing as part of having the disease migraine. The observation of migrainous stroke, with stroke occurring during a migraine attack, would support the hypothesis that ischemia may occur during attacks.[22] However, our finding that migraine was not significantly associated with progression of all evaluated types of brain lesions at the 9-year follow-up raises questions about the role of cerebral ischemia over time in people with migraine.[21,23]

Possible explanations for an association of migraine headache with structural brain changes include a chronic procoagulatory or proinflammatory state due to endothelial dysfunction[24,25] or elevated homocysteine levels,[26,27] or recurrent paradoxical (micro-) emboli due to right-to-left shunts.[28] Increased incidence of brain lesions among people with migraine headaches and atherosclerotic risk factors such as hypertension, diabetes, or other cardiovascular risk factors is also possible, but we did not identify any significant interactions for hypertension or diabetes. A relation with headache in general[7] cannot be excluded. Finally, sex differences seem to play an important role because progression of deep white matter hyperintensities was only found in women. This finding is in line with results from another study[8] and consistent with the higher risk of brain infarcts in women with migraine.[14] Our sample size was too small for a proper analysis of sex-related differential interaction between migraine and cardiovascular risk factors. Participants in the migraine group with posterior circulation territory infarctlike lesions, however, did have a less favorable cardiovascular risk profile than those without posterior circulation territory infarctlike lesions. Further research is needed to unravel the pathogenesis and relevance of migraine-related structural brain changes and their possible relation with ischemic events.

Figure 2. Geographical Location of All Individual Deep White Matter Hyperintensities Projected on Transparent 3-Dimensional Maps After Normalization of the Individual Magnetic Resonance Scans With Segmented Lesions to Standard Montreal Neurological Institute Space



The upper two rows display hyperintensities per study group at baseline and follow-up separately; the lower rows show the difference (i.e. progression) between baseline and follow-up in 3 directions. For visualization purposes, lesions are displayed after correction for group size, by adjusting their transparency level with a factor 0.69 for women in the migraine group with migraine with aura (n = 52/n = 75) and 0.91 for female participants with migraine without aura (n = 52/n = 57), using women in the control group as a reference.

White matter hyperintensities have been associated with cognitive deficits in the elderly[29,30] and some studies found evidence for worse cognitive performance in individuals with migraine.[31-34] We tested memory, speed, and attention[35] in all participants at baseline and follow-up and found no significant association between deep white matter hyperintensity volume and cognitive dysfunction. Most prior studies were conducted in older participants with larger deep white matter intensity volumes; this cohort is rather young with relatively little volume.[7]

In summary, in a community-based cohort followed up for 9 years, migraine was associated only with a higher incidence of deep white matter brain changes among women. There were no significant associations of migraine with progression of other brain lesions among women, and there were no associations of migraine headache with progression of any brain lesions among men. These findings raise questions about the role of migraine headaches with progression of cerebral vascular changes. The functional implications of MRI brain lesions in women with migraine and their possible relation with ischemia and ischemic stroke warrant further research.

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Role of the Sponsor: None of the funding bodies had any role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript. Disclaimer: The contents of this article are solely the responsibility of the authors and do not necessarily represent the official view of the National Institutes of Health or the Netherlands Heart Foundation. Online-Only Material: Author Video Interview and eTables 1 through 3 are available at http://www.jama.com.

Additional Contributions: We thank the research students and MR technicians for their assistance in screening and care of participants in this study.

ONLINE-ONLY MATERIAL

eTable 1. Baseline characteristics of follow-up participants and non-participants

Characteristic at baseline (CAMERA-1)	CAMERA-1 (n=435)	CAMERA-2 Total group		CAMERA-2 Migraineurs		CAMERA-2 Controls	
		Non-participants (n=149)	Participants (n=286)	Non-participants (n=93)	Participants (n=203)	Non-participants (n=56)	Participants (n=83)
Demographics							
Age at CAMERA-1, mean (SD), y	48 (7.8)	50 (7.9)$	48 (7.7)	49 (8.0)	48 (7.8)	51 (7.5)$$	46 (7.2)
Female	317 (73%)	115 (77%)	202 (71%)	73 (79%)	144 (71%)	42 (75%)	58 (69%)
Low education†	227 (52%)	90 (60%)$	137 (48%)	57 (61%)	98 (49%)	33 (59%)	39 (46%)
Physical and lab exam							
Body mass index, mean (SD)	25 (4.2)	25 (4.4)	25 (4.0)	26 (4.7)$	25 (4.1)	24 (3.8)	24 (3.6)
Blood pressure, mean (SD), mm Hg							
Systolic	134 (18)	136 (18)	134 (18)	136 (18)	133 (17)	135 (18)	135 (18)
Diastolic	91 (10)	92 (10)	91 (10)	93 (11)$	91 (9)	90 (8)	91 (10)
Hypertension*	167 (38%)	58 (39%)	109 (38%)	43 (46%)	79 (39%)	15 (27%)	30 (36%)
Diabetes	9 (2%)	2 (1%)	7 (2%)	0	4 (2%)	2 (4%)	3 (4%)
High risk cholesterol*	65 (15%)	27 (18%)	38 (13%)	17 (18%)	29 (14%)	10 (18%)	9 (11%)
Medical history							
Smoking							
Ever	287 (66%)	104 (70%)	183 (64%)	64 (67%)	125 (62%)	40 (71%)	58 (69%)
Pack-years, mean (SD)	10 (13)	14 (16)$	8 (11)	13 (16)$	8 (11)	14 (17)	10 (12)
High alcohol consumption*	44 (10%)	14 (9%)	30 (11%)	6 (7%)	16 (8%)	8 (14%)	14 (17%)
>15 yrs of oral contraceptive use (women only)	77/317 (24%)	22/115 (19%)	55/202 (27%)	15/73 (21%)	38/144 (26%)	7/42 (17%)	17/58 (29%)

Unless indicated otherwise, differences were not significant ($P>.05$)

Compared with participants $^{\$}$ $P<.05$, $^{\$\$}$ $P<.001$

†Low education indicates primary school or lower vocational education. *Hypertension CAMERA-1 defined as a systolic blood pressure of 160 mm Hg and higher or a diastolic blood pressure of 95 mmHg and higher or current use of antihypertensive drugs. High alcohol consumption defined as ≥ 3 units/day; high risk cholesterol defined as upper 15% ratio total/hdl cholesterol.

Causes of death during follow-up period

Six baseline participants had died during follow-up period: one due to malignant neoplasm of ovary, one had emphysema, one cerebral infarction, one acute peritonitis with septic shock, and two unknown causes of death. Only emphysema patient was control participant, others were migraineurs.

eTable 2. Migraine characteristics in relation to MRI outcome measures as compared to controls (Females only)

	High DWMH load at FU		Progression of DWMH load		High progression of DWMH load		Progression of IH	
Duration of migraine								
< 29 yrs	1.8 [0.6-4.9]	P=.3	2.9 [1.3-6.7]	P=.06	3.3 [1.0-9.9]	P=.08	11.2 [1.4-90.1]	P=.1
≥ 29 yrs	1.2 [0.4-3.3]		1.5 [0.7-3.2]		1.6 [0.5-5.0]		4.9 [0.6-41.8]	
low 25%	0.5 [0.1-1.6]	P=.8	0.9 [0.3-2.4]	P=.04	0.7 [0.2-2.2]	P=.5	2.1 [0.7-6.4]	P=.2
high 25%	0.7 [0.3-2.0]		0.3 [0.1-1.0]		0.6 [0.2-1.8]		0.5 [0.1-1.9]	
median (IQR) of those with lesions	23 (11-39)	P*=.2	22 (7-34)	P*=.1	23 (16-38)	P*=.1	24 (15-37)	P*=.2
median (IQR) of those without	20 (0-34)		15 (0-36)		20 (0-34)		20 (0-34)	
Migraine subtype								
without aura	1.8 [0.7-5.1]	P=.3	2.9 [1.2-6.7]	P=.2	3.3 [1.1-9.9]	P=.1	11.5 [1.4-92.9]	P=.1
with aura	1.2 [0.4-3.2]		1.7 [0.8-3.5]		1.6 [0.5-5.0]		5.0 [0.6-41.7]	
Number of headache attacks								
<median (lifetime)	1.7 [0.6-4.7]	P=.5	1.9 [0.9-4.2]	P=.9	2.8 [0.9-8.7]	P=.4	8.9 [1.1-73.3]	P=.5
≥median (lifetime)	1.3 [0.5-3.5]		2.2 [1.0-4.9]		1.9 [0.6-5.8]		6.7 [0.8-55.0]	
median (IQR) of those with lesions	271 (107-646)	P*=.9	274 (123-575)	P*=.4	263 (105-581)	P*=.6	284 (100-923)	P*=.9
median (IQR) of those without	264 (168-480)		252 (174-353)		274 (173-496)		264 (159-496)	
<median (FU only)	1.9 [0.7-5.5]	P=.3	2.1 [0.9-4.7]	P=.8	3.2 [1.0-9.9]	P=.2	12.3 [1.5-101.5]	P=.1
≥median (FU only)	1.2 [0.4-3.3]		2.2 [1.0-4.5]		1.9 [0.6-5.6]		5.3 [0.6-43.8]	
Mean attacks per month, median (IQR)								
of those with lesions	0.7 (0.4-1.9)	P*=.7	1.0 (0.5-1.6)	P*=.09	0.8 (0.4-1.8)	P*=.8	0.8 (0.5-2.2)	P*=.6
of those without lesions	0.9 (0.5-1.5)		0.6 (0.4-1.0)		0.9 (0.5-1.5)		0.9 (0.4-1.5)	

	High DWMH load at FU		Progression of DWMH load		High progression of DWMH load		Progression of IH	
Headache activity status								
inactive at baseline	3.4 [1.1-10.7]	P=.03	3.1 [1.0-9.5]	P=.4	5.3 [1.5-18.1]	P=.03	10.2 [1.1-93.1]	P=.6
active at baseline	1.1 [0.4-2.8]		1.9 [0.9-3.8]		1.7 [0.6-5.1]		7.0 [0.9-55.6]	
inactive during 9 year FU	1.8 [0.6-5.0]	P=.5	2.9 [1.0-5.4]	P=.9	2.6 [0.8-8.1]	P=.7	5.7 [0.7-47.4]	P=.2
active during 9 year FU	1.2 [0.4-3.4]		1.9 [0.9-4.1]		2.1 [0.7-6.3]		10.6 [1.3-87.0]	
Number of aura attacks								
<median (lifetime)	1.1 [0.3-4.0]	P=.8	1.7 [0.7-4.1]	P=.8	1.6 [0.4-6.2]	P=.8	5.7 [0.6-57.1]	P=.8
≥median (lifetime)	0.9 [0.3-3.3]		1.7 [0.7-4.3]		1.3 [0.3-5.0]		4.6 [0.5-45.9]	
median (IQR) of those with lesions	158 (73-411)	P*=.2	158 (68-283)	P*=.5	158 (73-411)	P*=.2	113 (26-265)	P*=.5
median (IQR) of those without	150 (49-262)		149 (43-281)		150 (49-262)		154 (65-292)	
<median at follow-up	1.1 [0.2-5.3]	P=.7	1.5 [0.5-4.2]	P=.9	1.6 [0.3-8.7]	P=.7	6.0 [0.5-77.7]	P=.6
≥median at follow-up	1.1 [0.3-4.6]		2.2 [0.7-6.7]		1.5 [0.3-6.8]		3.2 [0.2-48.1]	
Aura activity status								
inactive at baseline	2.0 [0.5-7.8]	P=.2	2.0 [0.6-6.2]	P=.8	2.7 [0.6-11.8]	P=.2	5.9 [0.5-68.5]	P=.9
active at baseline	0.8 [0.2-2.5]		1.6 [0.7-3.5]		1.1 [0.3-3.8]		5.4 [0.6-48.2]	
inactive at follow-up	0.3 [0.1-2.0]	P=.06	1.5 [0.5-4.3]	P=.4	0.5 [0.1-3.0]	P=.05	6.8 [0.6-71.4]	P=.8
active at follow-up	1.7 [0.6-4.8]		2.3 [1.0-5.0]		2.6 [0.8-8.3]		7.8 [0.9-64.3]	
Treatment								
no triptans ever used	1.4 [0.6-3.7]	P=.8	1.8 [0.9-3.7]	P=.2	2.2 [0.8-6.3]	P=.5	8.9 [1.1-69.3]	P=.2
triptans ever used	1.5 [0.4-6.0]		4.3 [1.1-16.6]		2.9 [0.7-11.8]		2.5 [0.1-42.5]	

OR with [95% CI] for comparison with controls; controls as a reference group

P-values between migraine subgroups adjusted for age, hypertension, diabetes, education; P*-values by Mann Whitney U test

DWMH=Deep white matter hyperintensities

IH=Infratentorial hyperintensities

Progression of DWMH defined as an increase in DWMH volume after 9 years (Δ CAM2-CAM1≥0.01 ml); progression of IHs defined as an increase in size and/or number of IHs; high progression of DWMH defined as the upper 20th percentile of DWMH progression distribution

eTable 3. Mean Z-scores of cognitive performance in different domains by deep white matter hyperintensity load (DWMH)

	non-high DWMH		high DWMH		*P* [95% CI] (model 1)	*P* [95% CI] (model 2)
	N	Mean (SD)	N	Mean (SD)		
Cognitive function at baseline						
Memory: immediate recall	219	0.0 (2.7)	57	-0.0 (2.5)	0.5 [-0.5 to 1.0]	0.5 [-0.5 to 1.0]
Memory: delayed recall	219	0.0 (1.0)	57	-0.1 (0.9)	0.8 [-0.2 to 0.3]	0.8 [-0.2 to 0.3]
Concentration, attention	216	0.0 (2.6)	57	-0.2 (2.5)	0.4 [-1.0 to 0.4]	0.4 [-1.0 to 0.4]
Processing speed	219	0.1 (1.0)	57	-0.3 (1.0)	0.3 [-0.4 to 0.1]	0.3 [-0.4 to 0.1]
Visuo-spatial, motor skills	187	0.2 (3.6)	50	-0.8 (2.9)	0.4 [-1.7 to 0.6]	0.4 [-1.7 to 0.6]
Executive function	216	0.1 (1.6)	57	-0.3 (1.5)	0.6 [-0.5 to 0.3]	0.6 [-0.5 to 0.3]
Cognitive function at follow-up						
Memory: immediate recall	223	0.2 (2.6)	53	-0.7 (2.7)	0.2 [-1.2 to 0.3]	0.2 [-1.2 to 0.3]
Memory: delayed recall	223	0.1 (1.0)	53	-0.3 (1.0)	0.06 [-0.6 to 0.0]	0.06 [-0.6 to 0.0]
Concentration, attention	223	0.1 (2.8)	51	-0.6 (2.4)	0.7 [-0.6 to 0.9]	0.8 [-0.6 to 0.9]
Processing speed	222	0.1 (1.0)	53	-0.4 (0.9)	0.1 [-0.5 to 0.0]	0.1 [-0.5 to 0.0]
Visuo-spatial, motor skills	219	0.4 (4.3)	53	-1.7 (4.0)	0.09 [-2.1 to 0.2]	0.09 [-2.1 to 0.2]
Executive function	223	0.3 (1.7)	51	-0.1 (1.7)	0.3 [-0.2 to 0.7]	0.3 [-0.2 to 0.7]
Fluid intelligence	166	0.1 (1.0)	30	-0.2 (1.0)	0.4 [-0.5 to 0.2]	0.4 [-0.5 to 0.2]
Overall cognitive performance						
CAMERA-1 (baseline)	184	0.3 (8.9)	50	-1.8 (8.2)	0.8 [-2.9 to 2.3]	0.8 [-2.9 to 2.3]
CAMERA-2 (follow-up)	218	1.4 (9.2)	51	-3.7 (8.9)	0.07 [-4.5 to 0.2]	0.07 [-4.5 to 0.2]

High DWMH defined as the upper quintile of DWMH distribution.

Model 1: Adjusted for age, gender, level of education; Model 2: Adjusted for age, gender, level of education, and migraine diagnosis

Z-scores indicate by how many standard deviations an observation is above or below the mean. Higher score indicates better cognitive performance

Assessment of cognitive performance

Cognitive performance was evaluated by validated, widely used, cognitive tests in a fixed order. The test battery, administered by four trained medical students, was the same for both time points (test protocol and methods were the same for baseline and follow-up) and included the 15 word Verbal Learning Test (Rey, 1985); abbreviated Stroop test (Stroop, 1935) consisting of three subtasks; verbal Fluency test (Miller, 1984); Letter Digit Substitution Test (Van der E, 2006), which is a modified version of the Symbol Digit Modalities Test; and Purdue pegboard test (Tiffin, 1948). In follow-up investigation, the Block Design Test from the WAIS-III test battery (Wechsler, 1981) was added. Higher score indicates better cognitive performance. The results of these tests were normalized by calculation of Z-scores based on total sample means and standard deviations, and added up per cognitive domain. The composite cognitive score was calculated for baseline as well as follow-up time point by adding up the separate domain Z-scores.

Cognitive domains

Memory function was composed of immediate recall and delayed recall after 20 minutes. The reading subtasks of the Stroop test measured concentration and attention ability. Executive function was scored by the interference task of the Stroop test and the word fluency task. The Letter Digit Substitution Test evaluated psychomotor speed, processing speed, and organization. Fine motor skills, motor speed, and visuo-spatial ability were evaluated by the Purdue pegboard. The Block Design Test measured fluid intelligence and visuo-spatial skills.

Statistical analysis

Using linear regression, significant difference for cognitive function test scores was examined by DWMH load (high vs. non-high) adjusted for age, gender, and educational level (model 1). Analyses on the association between high lesion load and cognitive performance were done cross sectionally for both CAMERA-1 and CAMERA-2. To assess the effect of having migraine on the relation between DWMH load and cognition, migraine diagnosis was added to the multivariate model (model 2).

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Chapter 3

Iron accumulation in migraine

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IRON HOMEOSTASIS

Iron plays an important role in many biochemical processes. In general, iron is essential for proper functioning of the body due to its involvement in oxygen transport, oxygen storage, transportation of electrons, glucose metabolism, synthesis of neurotransmitters and myelin, and DNA replication [Connor and Benkovic, 1992;Kell, 2009;Rouault and Cooperman, 2006]. The body needs to maintain iron concentrations stable, because iron shortage as well as iron excess lead to dysfunction. Excess of iron is harmful because of its role in the formation of highly reactive hydroxyl radicals, which cause damage to all components of a cell, including proteins, lipids, and DNA. The imbalance between reactive oxygen species and the ability of the body to detoxify the reactive intermediates, or to repair the resulting damage, is called oxidative stress. Oxidative stress is involved in many diseases, including neurological diseases. To prevent an excess of iron, the body regulates the amount of it by changes in uptake, storage and release in relation to its need. Recently, the protein hepcidin was found to play an important role in this process of iron homeostasis by regulating intestinal iron absorption [Ganz and Nemeth, 2011]. Ferritin is the protein that serves to store iron in a soluble and non-toxic form, to deposit it in a safe form, and to transport it to areas where it is required [Maguire et al., 1982]. Ferritin is also involved as a delivery protein in the brain [Hulet et al., 1999] and is especially present in larger concentration in the basal ganglia [Aquino et al., 2009]. Iron is important for the brain, as the brain requires relative much energy and iron is an essential component of ATP synthesis [Gordon, 2003]. In addition, iron is essential for the production of lipids and cholesterol and is therefore important in the synthesis and metabolism of myelin and neurotransmitters [Levenson and Tassabehji, 2004;Thomas and Jankovic, 2004]. Brain iron homeostasis is different from other organs because of several brain specific characteristics. First, brain tissue is protected from free influx of iron from the plasma by the blood brain barrier [Burdo et al., 2003;Burdo and Connor, 2003]. This barrier, together with the ventricular system, actively regulates iron transportation by transferring receptors on capillary endothelial cells[Connor, 1994] as well as on endothelial cells of the choroid plexus [Moos, 1996]. Second, the concentration of iron varies between different parts of the brain. Brain regions with motor function (extrapyramidal regions) contain more iron than non-motor parts [Koeppen et al., 1995].

IRON AND THE BRAIN

In 1922, Spatz already recorded the distribution of iron in the different areas of the brain by immersion of brain slices in a staining solution (Perl's stain or the Prussian Blue stain). Today, iron in the brain can be detected by using magnetic resonance imaging (MRI) and is visible on T2-weighted and T2*-weighted images as hypointensity caused

by field heterogeneity and magnetic susceptibility effects [Drayer et al., 1986a;Haacke et al., 2005]. A higher load of iron is associated with more hypointensity on the MR image [Haacke et al., 2005;Schenck, 1995]. Recent evidence shows a good correlation between conclusions on iron distribution in brain areas from post-mortem data and MR imaging [Peran et al., 2009a]. In adults, the largest concentration of iron is found in the globus pallidus, red nucleus, substantia nigra (including pars reticularis), followed by caudate nucleus and putamen. By staining of brain slices as well as by MR imaging, infants have demonstrated to have only minimal concentrations of iron in the brain [Diezel PD, 1955;Drayer et al., 1986b]. The increase in iron concentration in the brain is speculated to be associated with a change in vascularisation [Faucheux et al., 1999]. Age-specific iron accumulation in the human brain has been described as early as in 1958, by Hallgren [Hallgren and Sourander, 1958]. He already demonstrated, by staining of brain slices, an increase of especially ferritin in specific brain structures, including the globus pallidus and putamen as preferred sites during the first three decades of human life [Hallgren and Sourander, 1958]. More recent post-mortem studies have shown higher ferritin levels at older age in several basal ganglia, including caudate nucleus, putamen, substantia nigra, and globus pallidus [Connor et al., 1995;Zecca et al., 2001]. These findings have been confirmed by MR imaging results, demonstrating age-related iron increase among these basal ganglia [Bartzokis et al., 1997]. Two recent MRI studies on changes in brain iron concentration related to aging show an increase of iron in all basal ganglia with increasing age, with specific age-related iron deposition patterns for the different structures[Cherubini et al., 2009;Peran et al., 2009b]. For instance, the globus pallidus shows a clear increase of iron concentration from childhood into adulthood. Substantia nigra already contains more iron than the globus palidus at younger age and increase follows a steeper curve, whereas both putamen and caudate nucleus show a much slower rate of iron increase with aging [Aquino et al., 2009]. Furthermore, iron increase follows a precise accumulation direction from posterior to anterior and from medial to lateral parts of the basal ganglia [Aquino et al., 2009]. Below the age of 15 years, iron accumulation is largest in the medial part of the internal globus pallidus, whereas it is largest in the lateral part between the ages of 15-30 years of age [Aquino et al., 2009]. Mechanisms responsible for early accumulation in the substantia nigra and globus pallidus are not clear, but it could be the result of preferential or abnormal local neuronal uptake of iron [Bartzokis et al., 1997], abnormal transportation of iron along white matter pathways connecting these nuclei [Drayer et al., 1986a;Aoki et al., 1989] or it is based on a decreased efficiency of the usual iron transport from the basal ganglia to areas elsewhere due to age-related loss of neurons [Dietrich and Bradley, Jr., 1988;Cross et al., 1990]. After the age of 50 years, all basal ganglia show a large variability between subjects for hypointensity on MRI, because the T2 values of deep nuclei are significantly influenced by non-iron-related tissue changes, such as myelin loss or an increase in water content associated with microvascular changes [Aquino et al., 2009;Bartzokis et al., 1997;Schenker et al., 1993]. Despite the large variability of brain

iron accumulation among elderly subjects, it has been suggested that if hypointensity is found in the caudate nucleus, this could be a sign of central nervous system disease instead of being part of a normal aging process [Milton et al., 1991]. This was confirmed by a recent MRI study among elderly subjects which described presence of hypointensity of the caudate nucleus to be associated with the presence of a higher load of age-related cerebral changes, like more atrophy and a higher load of white matter hyperintensities [van Es et al., 2008]. Iron excess in the basal ganglia is damaging, because it increases the tissue's susceptibility for apoptosis and inflammation, it could lead to basal ganglia dysfunction due to decreased protein synthesis, and the tissue becomes more vulnerable for the damaging effect of reactive oxygen species. This destructive process is being summarized by Zecca as iron accumulation, invasion and increased reactivity [Zecca et al., 2004].

IRON AND NEUROLOGICAL DISORDERS

Increased iron levels in pathological relevant brain structures and iron-mediated oxidative stress are associated with several neurological disorders, including Parkinson disease, Alzheimer disease, Huntington disease, Friedreich ataxia, Amyotrophic Lateral Sclerosis, Neurodegeneration with Brain Iron Accumulation (formerly Hallervorden-Spatz syndrome), and also migraine. Every disorder has its specific mechanisms and locations of brain iron accumulation.

In Parkinson disease, iron excess has been demonstrated in the substantia nigra [Sian-Hulsmann et al., 2010;Kell, 2010;Bartzokis et al., 1997;Sian-Hulsmann et al., 2010;Kell, 2010;Gotz et al., 1990;Gorell et al., 1995;Ryvlin et al., 1995] and was found to be associated with local oxidative stress, as indicated by protein disruption [Goodwin et al., 2000] and oxidative DNA damage [Sanchez-Ramos et al., 1987;Alam et al., 1997;Poon et al., 2004a;Poon et al., 2004b].

In the brains of patients suffering from Alzheimer disease, iron accumulation occurs without the normal age-related increase in ferritin, thereby increasing the risk of oxidative stress [Zecca et al., 2004]. Iron excess is found early in the disease process in several brain structures, including the basal ganglia [Connor and Benkovic, 1992;Bartzokis et al., 1997;Bartzokis and Tishler, 2000;Bartzokis et al., 2000]. Although the origin of elevated brain iron levels is unclear, the role of iron is apparent: both senile plaques and neurofibrillary tangles, characteristic for the disease, have been shown to accumulate iron [Good et al., 1992;Levine, 1997;Sayre et al., 2000;Rottkamp et al., 2000]

In Huntington disease, iron accumulation has been demonstrated in the putamen, caudate nucleus, and globus pallidus by post-mortem studies and MRI studies [Bartzokis and Tishler, 2000;Chen et al., 1993;Dexter et al., 1992;Rutledge et al., 1987]. The iron excess contributes to oxidative stress, as indicated by protein disruption [Marnett,

2000;Stadtman, 2001] and oxidative DNA damage[Alam et al., 1997;Marnett, 2000; Poon et al., 2004a;Sanchez-Ramos et al., 1987].

Friedreich ataxia was first described by the German physician Nikolaus Friedreich in 1860 [Friedreich, 1863] and is marked by a genetic mutation causing the mitochondrial protein frataxin to be lacking, leading to impaired iron export from the mitochondria, cytoplasmic depletion, induction of plasma membrane proteins involved in iron uptake, and consequent iron overload [Berg and Youdim, 2006], including excess of iron in the dentate nucleus [Koeppen et al., 2007;Waldvogel et al., 1999].

In Amyotrophic Lateral Sclerosis (ALS), increased serum levels of ferritin have been reported [Goodall et al., 2008] and MR images of the brains of ALS patients show iron accumulation in the dentate nucleus [Langkammer et al., 2010]. Although origin of iron excess in ALS is not yet clear, increased oxidative damage to DNA, lipids, and proteins can be seen early in the disease process, which makes it plausible that iron is at least partly involved [Berg and Youdim, 2006].

Brain MRI evaluation of patients suffering from Neurodegeneration with Brain Iron Accumulation usually show iron accumulation in the globus pallidus (typical but non-specific eye-of-the-tiger sign), the substantia nigra, and the dentate nucleus [Savoiardo et al., 1993;Hayflick et al., 2003;Swaiman, 1991;Halliday, 1995] and histopathology demonstrates iron excess accompanied by neuronal loss and gliosis [Savoiardo et al., 1993;Galvin et al., 2000]. It is proposed that accumulation of cysteine, which chelates iron, causes oxidative stress and leads to the increase or iron in the basal ganglia [Berg and Youdim, 2006;Perry et al., 1985].

IRON AND MIGRAINE

Few studies have been published describing the association between migraine and iron levels in the brain. After earlier reports describing functional blood oxygenation level-dependent MR imaging demonstrating the involvement in pain of several specific brain structures, Welch and colleagues focused their attention on the periaqueductal grey matter, red nucleus and substantia nigra in relation to migraine [Welch et al., 2001]. It was speculated that, since these brain structures in particular show high iron levels and are densely populated with neurotransmitters that can generate free radicals, repeated migraine attacks and associated repeated hypoxia could result in release of free radicals and cell damage. This mechanism could be seen in those brain areas as accumulation of iron, similar to the processes already known in other neurodegenerative diseases as mentioned above.

To test this hypothesis, a clinic-based cross-sectional brain MRI study was carried out to assess iron levels by measuring transverse relaxation rates [Welch et al., 2001]. This study included seventeen migraine patients, diagnosed using International Headache Society (IHS) criteria, seventeen patients with chronic daily headache, and seven-

teen control participants; aged 20-64 years. Compared with controls, significant higher iron levels were found in the periaqueductal grey matter of the migraine and chronic daily headache patients. No differences were found between men and women, nor between migraine with and without aura. In addition, an association between iron accumulation and illness duration was found.

Because no relation was found between increased iron levels and age in this study, authors speculated that iron accumulation must be related to repeated headache attacks. Several explanations for the high iron content of the periaqueductal grey matter among migraineurs were given by the authors. First, as a result of the migraine related pain combined with oxidative stress, this structure could be abnormal highly metabolic active in migraineurs, since transferring-receptor binding is proportional to the metabolic activity of the neuron, and in turn may be influenced by nociceptive function. Overexpression of transferrin receptors might result in iron accumulation and free radical cell damage, a process that may be aggravated by eventual hypoperfusion during migraine attacks. As a consequence, metabolism and iron uptake in the remaining neurons would be increased, leading to even more iron accumulation. Second explanation for high iron concentration is the presence of gliosis, since glial cells have high iron content, but the authors found no evidence of gliosis on MR images of these participants. From this study, it was concluded that iron accumulation in the periaquaductal grey matter among migraineurs was the result of an impaired iron homeostasis, possibly associated with neuronal dysfunction or damage [Welch et al., 2001].

To evaluate these interesting findings in a larger, population-based group of migraineurs, brain MR images of 138 migraineurs (IHS criteria) and 75 matched controls were analyzed for iron concentration in deep brain nuclei as part of the CAMERA-study (Cerebral Abnormalities in Migraine, an Epidemiological Risk Analysis) [Kruit et al., 2009]. Because measurements in older subjects are increasingly influenced by non-iron related factors, analyses were separated into subjects younger than 50 years and older than 50 years. In the younger group, compared to controls, migraineurs demonstrated higher iron concentrations in several nuclei, including putamen, globus pallidus, and red nucleus. No differences were found between men and women, nor between migraine with and without aura. Among these participants under 50 years, an association was found between longer migraine duration and higher iron concentration in putamen, caudate nucleus, and red nucleus [Kruit et al., 2009]. These structures are all known to be involved in the normal central nociceptive network [Iadarola et al., 1998].

Data from both studies suggest that repeated migraine attacks, or the accompanying pain, are associated with higher iron concentration in several brain structures involved in central pain processing and migraine pathology. It is not known whether the increase in iron is caused by repetitive activation of the pain nuclei or whether the increased iron itself inflicts damage to these structures via free radicals in oxidative stress. Furthermore, theoretically, damage of these pain-processing nuclei could lead to chronification of migraine in specific patients. As to date, studies on this subject have a cross-

sectional design, the assumption that recurring attacks lead to accumulation of iron can not be verified. A longitudinal study is needed to follow-up on migraineurs and controls to carefully evaluate their general health status, headache history, course of migraine over the years, and measurements of brain iron concentration.

SUMMARY

During aging, iron accumulates in the brain, specifically in the basal ganglia, following a certain distribution pattern. Iron accumulation could be the result of neuronal loss, followed by substitution by cells with higher iron loads, or of leakage of the blood brain barrier, allowing iron to access the brain in higher concentration. Several neurological disorders, as well as migraine, are associated with iron excess in the brain. Higher brain iron concentration generates a reactive iron overload, which invades and damages neurons and other cells. It is not clear yet whether iron accumulation in basal ganglia plays a primary or secondary role in the pathogenesis.

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Chapter 4

Iron in deep brain nuclei in migraine? CAMERA follow-up MRI findings

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ABSTRACT

Introduction – In the CAMERA population-based MRI study, migraineurs below the age of 50 had decreased T2-values indicative of increased iron deposition in several deep brain nuclei. Longer migraine history was associated with lower T2-values, suggesting an association between migraine attacks and iron accumulation. In the present nine-year follow-up study of the CAMERA cohort we re-measured the T2-values in deep brain nuclei to assess the evolution over time.

Methods – Baseline and follow-up T2-values measured in several basal ganglia of 128 participants (38 control, 90 migraine) were analyzed using quantitative T2 measurements and multivariate regression analysis.

Results – T2-values of most deep brain nuclei were increased - instead of an expected further decrease when only age related iron accumulation would have played a role - compared to baseline (both among controls and migraineurs) and were not different in both groups. In migraineurs, no differences were found by gender, migraine severity or subtype.

Conclusion – This study did not provide supportive data for migraine related increased iron accumulation in deep brain nuclei, but neither is able to reject such hypotheses. Increased T2-values probably point at microstructural tissue changes, that counteracted earlier accumulated iron effects. We hypothesize that with aging migraine-induced iron-related brain changes are obscured by age-related other tissue changes.

INTRODUCTION

In normal aging, iron accumulates throughout the brain, particularly in the basal ganglia. Iron deposits are visible as diffuse hypo-intense changes in deep brain structures on T2-weighted and T2*-weighted MR images.[1;2] Specific neurodegenerative diseases (e.g. pantothenate kinase associated neurodegeneration, but also Parkinson's and Huntington's disease) are associated with increased iron accumulation in specific brain regions. In migraineurs, lower T2-values were also found in deep brain nuclei and the periaquaductal gray matter.[3;4] In the population-based CAMERA MRI-study, we reported evidence of increased iron accumulation in the putamen, globus pallidus, and nucleus ruber of migraineurs.4 An inverse relationship was found, suggestive of a causal relation between recurring attacks and accumulation of iron. Because of the cross-sectional design of the study at that time, we could verify this hypothesis. To assess whether iron accumulation is indeed associated with recurring migraine attacks, we measured T2 values in the CAMERA-2 study which is a prospective, nine-year follow-up of the original CAMERA cohort.[5]

METHODS

Study population

In the CAMERA study, we had measured brain iron in 213 participants (138 migraineurs and 75 matched controls). Clinical characteristics have been described elsewhere.[4] In short, participants (mean age 49; 69% female) from the general population were identified as migraineurs or non-migraine controls according to the International Headache Society.[6] Both groups had comparable cardiovascular risk profiles. None of the patients or controls showed clinical signs of basal ganglia dysfunction at a standard physical and neurological examination.

Magnetic Resonance Imaging

To guarantee methodological comparability with the original CAMERA study nine years earlier, we used the same scanner and scan protocol.[4] Whole brain MR images were acquired on a 1.5T scanner in Maastricht (ACS-NT; Philips Medical Systems, Best, The Netherlands). Images were acquired with 48 contiguous 3-mm axial slices (field of view 22 cm; matrix, 190-205 x 256). Pulse sequences included a combined proton density and T2-weighted fast spin-echo (repetition time/echo time, 3000/27-120) and fluid-attenuated inversion-recovery (FLAIR; repetition time/echo time/inversion time 8000/100/2000).

Quantitative T2 measurements were carried out in exactly the same way during baseline and follow-up, by applying the same post-processing steps as described before.[4] In short, the observer, who was blinded for patient characteristics, measured signal intensities (SIs) of six regions of interest, bilaterally. Regions of interest were the same as in the baseline study: putamen, putamen posterior, nucleus caudatus, globus pallidus, substantia nigra (pars reticularis and pars compacta), and nucleus ruber. T2 values were estimated using the expression T2 = (TE2-TE1)/[ln (S1/S2)], where S1 and S2 are the measured signal intensities in the early-echo (= proton density, TE1=27 ms) and late-echo (= T2, TE2=120 ms) respectively.

The protocol was approved by the local Medical Ethics Committees and all participants gave written informed consent.

Statistics

To test for any differences in the distributions and means of measured characteristics among the study groups, χ^2 tests and unpaired *t* tests were used. Linear regression analyses (controlled for age) were used to test for differences in the measured T2 values. Statistical tests were not corrected for comparison of multiple nuclei. T2 values of deep nuclei are greatly influenced by non-iron related changes after about 50 years of age. Since baseline analyses had only shown T2 differences between migraineurs and controls younger than 50 years old, we also analyzed the follow-up results in stratified subgroups younger and older than 50 years.

RESULTS

Study population

In the follow-up CAMERA MRI study, we measured T2 values in 128 of the 213participants (60%, 38 controls, 90 migraineurs; Table 1). Clinical characteristics of migraineurs and controls were similar (all p>0.05; Table 1). Participant characteristics were not significantly different between participants (n=128) and non-participants (n=85) (all clinical characteristics p>0.05). Only data from participants with follow-up MRI available were included in the analyses. Reasons for non-participation in the follow-up were: lack of interest (n=33); non-neurological co-morbidity (n=20); participation in CAMERA-2, but no re-scan (n=22), unable to establish contact before the end of inclusion (n=4); exclusion (n=5); and deceased (n=1). Mean baseline T2-values of non-participants were significantly lower than of participants, but this effect was similar for migraineurs and controls. Clinical characteristics of non-participants at the time of follow-up were not available.

Table 1. Characteristics of study participants

Characteristic	Control (n=38)	Migraine (n=90)
Age, mean (SE), yrs	55 (1.3)	58 (0.8)
Female	68%	67%
Body mass index, mean (SE)	26 (0.6)	26 (0.5)
Hypertension (self-reported, doctor-diagnosed)	29%	34%
Diabetes (self-reported)	2.6%	7.8%
Smoking, ever	68%	70%
Smoking, pack-years, mean (SE)	25 (3.5)	17 (2.0)
Duration migraine history, yrs (SE)		
Until baseline study	-	23.7 (1.2)
Until follow-up study	-	30.1 (1.4)
Estimated total number of migraine attacks (SE)		
Until baseline study	-	358 (40)
Until follow-up study	-	508 (61)

Differences between controls and migraineurs were not significant (p>0.05)

T2-values

Mean T2-values of the putamen, posterior putamen, nucleus caudatus, and substantia nigra pars compacta were increased compared to baseline in both control and migraine groups (p<0.001; Figure 1; Table 2). T2-values of the substantia nigra pars reticularis showed a non-significant decrease in controls (95% CI -8.0-0.0; p=0.05) and migraineurs (95% CI -4.6- 0.3; p=0.08). T2-values of the globus pallidus remained the same over time for both groups (p>0.1). The nucleus ruber showed a different pattern: in controls, mean T2-value decreased over time whereas it increased in migraineurs, resulting in a similar T2-value at follow-up for migraineurs and controls. Areas of the brain that were evaluated by T2-value measurement did not demonstrate focal T2 hyperintense lesions or infarcts.

Figure 1. T2 values (ms) in controls and migraineurs

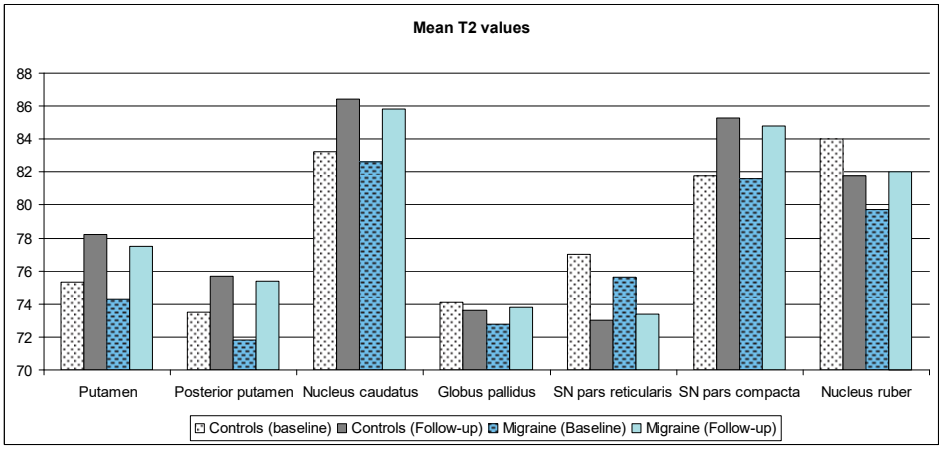

Table 2. Difference between baseline and follow-up T2-values (ms) in migraineurs and controls

	Putamen		Putamen Posterior		Nucleus Caudatus		Globus Pallidus		Substantia Nigra (pars reticularis)		Substantia Nigra (pars compacta)		Nucleus Ruber	
	CO	MIG	CO	MIG	CO	MIG	CO	MIG	CO	MIG	CO	MIG	CO	MIG
T2-value Baseline	75.3	74.3	73.5	71.8	83.2	82.5	74.1	72.9	77.0	75.5	81.8	81.6	84.0	79.7
Follow-up	78.2	77.5	75.7	75.4	86.4	85.8	73.6	73.8	73.0	73.4	85.3	84.8	81.8	82.0
[95% CI];p-value	[2.0-3.8]	[2.3-4.1]	[1.1-3.4]	[2.3-4.8]	[2.1-4.3]	[2.4-4.1]	[-2.1-2.0]	[-0.3-2.0]	[-8.0-0.0]	[-4.6-0.3]	[1.8-5.3]	[2.0-4.4]	[-6.7-2.4]	[0.0-4.6]
Baseline vs. follow-up (adjusted for age)	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	0.6	0.1	0.05	0.08	< 0.001	< 0.001	0.3	0.05

CO=controls; MIG=migraineurs

Table 3. Changes of T2 values (SD, in ms) after 9 years follow-up

Change of T2 value in:	Control (n=38)	Migraine (n=90)	95% CI	p-value (age adjusted)
Putamen	2.9 (1.6)	3.2 (1.9)	-0.6 – 0.8	0.8
Putamen posterior	2.2 (3.0)	3.6 (3.9)	-0.2 – 2.7	0.09
Nucleus caudatus	3.2 (2.1)	3.2 (2.2)	-0.9 – 0.7	0.7
Globus pallidus	-0.4 (4.9)	0.9 (4.5)	-0.6 – 3.0	0.2
Substantia nigra pars reticularis	-4.0 (12.2)	-2.0 (10.5)	-2.0 – 6.6	0.3
Substantia nigra pars compacta	3.5 (5.5)	3.2 (4.6)	-2.5 – 1.3	0.5
Nucleus ruber	-2.3 (13.7)	2.3 (10.8)	0.9 – 10.0	0.02

Negative numbers indicate a decrease in T2-value between baseline and follow-up

Thus, the changes over the years resulted in similar basal ganglia T2-values at follow-up in migraineurs and controls. Cross sectional analyses showed no differences between groups at follow-up (Table 3). No differences were found between controls and sub-groups of migraine with and without aura, nor between men and women (p>0.05). Likewise, no differences were found when analyzing only the group younger than 50 years at baseline (Table 4). Baseline T2-values of followed-up migraine participants were still lower than baseline T2-values of followed-up control participants for putamen (95% CI -2.0- -0.1);p=0.02), posterior putamen (95% CI -3.1-- -0.7); p=0.02), and nucleus ruber (95% CI -10.0 - -1.3);p=0.01)

Table 4. T2 values (SD, in ms) after 9 years follow-up

				Participants who were younger than 50 yrs at baseline		
Mean T2 value of:	Control (n=38)	Migraine (n=90)	[95% CI];p-value (age adjusted)	Control (n=29)	Migraine (n=45)	[95% CI];p-value (age adjusted)
Putamen	78.2 (2.2)	77.5 (3.5)	[-2.2-0.2];0.1	77.7 (2.0)	77.0 (2.8)	[-2.0-0.5];0.2
Putamen posterior	75.7 (2.5)	75.4 (5.2)	[-2.5-1.0];0.4	75.4 (2.4)	74.5 (3.8)	[-2.4-0.7];0.3
Nucleus caudatus	86.4 (2.4)	85.8 (3.0)	[-1.7-0.5];0.3	86.5 (2.3)	85.9 (2.7)	[-1.9-0.6];0.3
Globus pallidus	73.6 (3.0)	73.8 (3.5)	[-1.5-1.1];0.8	73.5 (2.3)	73.3 (2.4)	[-1.3-1.0];0.8
Substantia nigra pars reticularis	73.0 (3.3)	73.4 (4.2)	[-1.3-1.8];0.7	73.2 (3.6)	73.1 (4.4)	[-2.0-1.9];0.9
Substantia nigra pars compacta	85.3 (2.8)	84.8 (4.0)	[-2.2-0.5];0.2	85.4 (2.9)	84.0 (4.1)	[-3.2-0.3];0.1
Nucleus ruber	81.8 (4.0)	82.0 (4.0)	[-1.9-1.0];0.5	80.8 (3.6)	81.0 (3.2)	[-1.3-1.8];0.8

T2-values and migraine severity

Neither T2-values at follow up nor the change in T2-values over the years correlated with the estimated number of migraine attacks suffered between baseline and follow

up (p-values 0.1-0.9). Migraine activity (defined as having had at least one attack during follow-up was also not related to (change in) T2-values. Finally, migraine duration (years of migraine) was not associated with T2-values at follow up.

DISCUSSION

In contrast to the CAMERA-1 study, we failed to find differences in basal ganglia T2-values between migraineurs and controls in more or less the same study population nine years later. This was true for both the whole population and those under age 50.

We originally had hypothesized that iron accumulation was due either to disruptive iron homeostasis in dysfunctioning neurons or to repeated activation and hyperemia of nuclei associated with pain processing during migraine attacks. Although the current negative follow-up data do not support these hypotheses, the also do not necessarily reject them. In general, in the abcense of focal visible lesions, increase in T2-values can be histologically explained by cellular and axonal loss, presence of gliosis, or microinfarction.[7-9]

As once accumulated iron does not disappear from the brain, such T2-increasing changes in parenchymal microstructure have probably counteracted and overcome the T2-lowering effects of earlier accumulated iron. The disappearance of the earlier differences between migraineurs and controls might further suggest that diffuse T2-increasing changes over time are more progressive in migraineurs. Although the current data cannot prove this hypothesis, such an observation would be in line with the reported progression of diffuse T2 hyperintensities in the brainstem of migraineurs. [5] A technological explanation seems unlikely, since we used the same scanner, scanning protocol and post-processing steps.

The nucleus ruber showed a pattern, different from the other nuclei: mean T2-value in the control group decreased, whereas mean T2-value in the migraine group increased over the years. The reason for this is unknown. The migraineurs of the current cohort did not show visible hyperintense lesions in the nucleus ruber, which could have been a plausible cause for the increase in T2-value. Possibly, a migraine-specific process leading to increase in T2-signal plays a role, as the nucleus ruber is known to be involved in nociception.[10] This interesting finding calls for further research on the role of the nucleus ruber in migraine.

The mean age of the cohort was 57 years at follow up, which makes measurement of T2-values more susceptible to other age-related effects rather than iron-related factors. However, both study groups (migraineurs and controls) aged by the same amount of years.

A potential limitation of the present study is that not all participants at baseline also participated at follow-up, limiting the statistical power of the present study and potentially introducing selection bias. Although the clinical characteristics of participants and

non-participants were similar, T2-values at baseline were lower in the migraine and control non-participants, probably resulting in an overall higher T2-value among the participant group at follow up It has to be noticed that T2-weighted images are less sensitive to iron accumulation compared to T2*-weighted images. Unfortunately, T2*-weighted images were not part of the baseline and follow-up scanning protocol.

Major advantages of the present study are the population-based design with detailed clinical information allowing for sub-group analyses, and the large number of unbiased MR measurements at baseline and follow-up for which, importantly, we used exactly the same protocols and procedures to ensure technical comparability over time.

To explain the disappearance over time of the difference in T2 values between migraineurs and controls, we hypothesize that age-related signal increases have counteracted the iron-related signal decreases. The current findings, therefore, are not necessarily in conflict with previous findings.

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KEY FINDINGS

- Baseline CAMERA study reported evidence of increased iron accumulation (i.e. lower T2-values) in deep brain nuclei among migraineurs of the general population compared to non-migraineurs
- Current nine year follow-up study showed an increase of T2-values of most deep brain nuclei instead of an expected further decrease
- T2-values are known to be influenced by other (non-iron) related brain tissue changes with aging
- We hypothesize that with aging migraine-induced iron-related brain changes are obscured by age-related other tissue changes

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Chapter 5

Volumetric brain changes in migraineurs from the general population

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ABSTRACT

Objective: To assess volumetric brain changes in migraineurs from the general population in comparison with control subjects.

Methods: Structural brain changes in migraineurs from the general population-based MRI Cerebral Abnormalities in Migraine, an Epidemiological Risk Analysis (CAMERA)-2 study were assessed by state-of-the-art voxel-based morphometry. T1-weighted MR images of 84 migraineurs (52 with aura; 32 without aura) and 35 headache-free controls were evaluated. Regional volumes were compared voxel-wise, corrected for age, sex and total intracranial volume, using region-of-interest and whole-brain analyses.

Results: In region-of-interest analyses, migraineurs showed decreased grey matter volume in the visual areas V3 and V5 of the right occipital cortex, involved in visual motion processing, compared to controls ($p<0.05$, family-wise error correction). Post-hoc analyses revealed that similar changes were present irrespective of migraine aura status, disease activity and attack frequency. In exploratory whole-brain analyses ($p<0.001$, uncorrected; none surviving family-wise error correction for multiple comparisons) we identified additional structural differences in migraineurs in other cortical and subcortical areas, including white matter tracts, that are particularly involved in visual processing.

Conclusions: Migraineurs from the general population showed small volumetric brain changes, mainly in cortical areas involved in visual motion processing, compared to controls. The presence of morphological changes irrespective of the presence of migraine aura or disease activity suggests that migraine with and without aura share common pathophysiological pathways and suggests that these changes are (partially) irreversible or might have been present throughout life.

Abbreviations

CAMERA=Cerebral Abnormalities in Migraine, an Epidemiological Risk Analysis; DARTEL=diffeomorphic anatomical registration exponentiated lie algebra; FLAIR=fluid-attenuated inversion recovery; MR(I)=magnetic resonance (imaging); ROI=region-of-interest; SPM=statistical parametric mapping; VBM=voxel-based morphometry; WMHs=white matter hyperintensities

INTRODUCTION

Migraine is a common neurovascular brain disorder that is characterized by recurrent attacks of headache associated with nausea, vomiting, photophobia, and phonophobia (migraine without aura) [IHS IIIb, 2013]. In about one third of migraineurs, attacks are associated with transient focal neurologic aura symptoms (migraine with aura) [IHS IIIb, 2013]. Despite many studies investigating structural changes in migraine [For review see May, 2009; Bashir et al., 2013], it remains unclear whether, how, and to what extent migraine affects the morphology of the brain.

Voxel-based morphometry (VBM) is a frequently applied, automated, unbiased, whole brain method for comparing grey and white matter density and volume between groups on a voxel-by-voxel basis [Ashburner and Friston, 2000]. Several groups have reported VBM grey matter changes in migraine, in particular decrease in volume in pain-transmitting and pain-processing areas throughout the brain [Coppola et al., 2015; Jin et al., 2013; Kim et al., 2008; Hougaard et al., 2015; Liu et al., 2013; Rocca et al., 2008; Schmidt-Wilcke et al. 2008; Schmitz et al., 2008a; Schmitz et al., 2008b; Valfre et al., Headache 2008]. Other groups employed surface-based morphometry and found cortical thinning in areas involved in nociception [Messina et al., 2013] and cortical thickening in the somatosensory cortex [DaSilva et al., 2007] and visual motion processing areas [Granziera et al., 2006; Messina et al., 2013]. Cortical surface area was increased in regions involved in executive functions and visual motion processing while it was decreased in pain-processing areas [Messina et al., 2013].

There is, however, ongoing discussion on: (i) the relevance and specificity of these findings; (ii) the possible causes (e.g. changes in metabolism, neurotransmitter levels, or functional processing of sensory information); (iii) possible reversibility; and (iv) whether these changes are a cause or a consequence of migraine [May, 2009; Bashir et al., 2013]. Moreover, there is debate about the generalizability. The study samples were relatively small and primarily included participants with migraine from headache clinics who were likely to be affected more severely than average and also overusing acute anti-headache medications and suffering from comorbid (psychiatric) diseases which both may affect brain architecture [May, 2009; Bashir et al., 2013; Gaul et al., 2011; Schmitz et al., 2008a; Van Tol et al, 2010; Riederer et al., 2012; Franklin et al., 2013]. Finally, these VBM and surface-based morphometry studies did not always account for the increased risk of white matter and other focal ischemic brain lesions that are known to be more prevalent among participants with migraine [Kruit et al., 2004; Kruit et al., 2006; Kruit et al., 2010; Palm-Meinders et al., 2012].

In the present study we assessed cerebral grey and white matter volumes of participants with migraine from the general population by applying state-of-the-art VBM while minimizing the potential influence of the various confounders reviewed above.

MATERIALS AND METHODS

Participants

Participants originated from the CAMERA-2 study (Cerebral Abnormalities in Migraine, an Epidemiological Risk Analysis), a nine-year follow-up study on brain changes in participants with migraine and controls from the general population. Characteristics of the study population and the assessment of migraine have been described in detail elsewhere [Palm-Meinders et al., 2012]. In short, participants with migraine (diagnosed according to International Headache Society-criteria [2013]) and age- and sex-matched controls were evaluated by standardized interview, physical, and neurological examination, and brain MR imaging. The brain MR imaging protocol included a 3D T1-weighted sequence (Maastricht research center only because of technical reasons), suitable for VBM analysis, in 128 participants. Characteristics of participants scanned with (Maastricht) and without (Doetinchem) this sequence were comparable. Nine enrolled participants were excluded because of large brain infarcts (n=3) or movement artifacts (n=6), leaving n=119 participants (69% female; mean age 57 years; migraine with aura n=52, migraine without aura n=32, and controls n=35) for VBM analysis. Small, punctate white matter hyperintensities (WMHs) as frequently observed in participants with migraine [Kruit et al., 2004] were not considered an exclusion criterion. None of the included subjects had large, confluent WMHs. The study protocol was approved by the institutional review boards and all participants gave written informed consent prior to participation.

Magnetic Resonance Imaging

Structural whole brain 3D T1-weighted fast field echo images (repetition/echo time 8.6/4.6 ms; 140 sagittal 1.0 mm continuous slices; 256 mm field of view; acquisition matrix 256; acquisition voxel size 1x1x1 mm) were acquired on a 1.5T scanner (ACS-NT; Philips Medical System, Best, The Netherlands). In addition, combined proton density and T2-weighted fast spin-echo (repetition/echo time 3000/27-120 ms) and fluid-attenuated inversion recovery (FLAIR; repetition/echo/inversion time 8000/100/2000 ms) sequences were acquired to check images for structural abnormalities and to assess white matter hyperintensities and infarcts.

Voxel-based morphometry

One observer (M.C.K.) who was blinded for subject characteristics and diagnosis visually screened all MRIs for artifacts and gross structural abnormalities that might interfere with further post-processing. MRIs were processed using VBM, applying diffeomorphic anatomical registration exponentiated lie algebra (DARTEL) [Ashburner, 2007], with

default parameters in SPM8 (Statistical Parametric Mapping, Wellcome Department of Cognitive Neurology, London, United Kingdom, http://www.fil.ion.ucl.ac.uk/spm) on a MATLAB platform (The MathWorks Inc., Natick, Massachusetts; version 7.4), to localise regional differences in grey and white matter volume. The DARTEL algorithm is considered as a better inter-subject registration than normalisation algorithms in previous SPM versions [Yassa and Stark, 2009]. The VBM-DARTEL procedure included (i) checking the location of the anterior commissure in raw MRIs, (ii) segmentation into grey matter, white matter, and cerebrospinal fluid using the standard SPM8 segmentation algorithm, (iii) creation of a DARTEL template derived from non-linear deformation fields for the aforementioned segmentation procedure, and (iv) registration of all individual deformations to the DARTEL template. This registration step included modulation, which preserved the absolute amount of local grey and white matter volumes in spatially normalised images by scaling by Jacobian determinants, i.e. a correction for the distance over which a voxel had to be stretched or compressed to fit into standard space. Subsequently, (v) modulated normalised grey and white matter segments were smoothed with an 8 mm full width at half maximum isotropic Gaussian-kernel for statistical comparison. Grey and white matter segments were compared voxelwise between (subgroups of) participants with migraine and controls, by creating general linear models including all subjects with implementation of age, gender, and total intracranial volume as covariates. To exclude false positives in non-grey or non-white matter tissue, voxelwise comparisons were masked with explicit optimal threshold grey and white matter masks created using the SPM Masking Toolbox [Ridgway et al., 2009].

Statistical analyses

Statistical Package for Social Science (SPSS Inc., Chicago, IL, USA; version 17.0) was used for unpaired t-tests and χ^2 tests to compare baseline characteristics between participants with migraine and controls. Voxel-based morphometry analyses included region-of-interest (ROI) grey matter analyses and whole-brain grey and white matter analyses.

Region-of-interest analyses

Based on results from previous VBM and surface-based morphometry studies [Granziera et al., 2006; Kim et al. 2008; May 2009; May et al., 2013; Messina et al., 2013], ROI grey matter analyses were carried out in the prefrontal, insular, anterior cingulate, somatosensory and occipital cortex (visual motion processing areas V3 and V5), the thalamus and the brainstem (dorsolateral pons and periacqueductal gray). For these ROIs, Montreal Neurologic Institute (MNI) coordinates were extracted from the literature (see supplementary materials). Participants with migraine were compared to controls by applying small volume corrections ($p_{FWE\text{-}SVC} < 0.05$) by centering a 10-mm sphere around these MNI coordinates. In case of significant findings, post-hoc analyses were per-

formed to assess whether these changes, as found in comparing participants with migraine with control subjects, were similar in subgroups of participants with migraine. For these post-hoc analyses, the average volume of grey matter per voxel in significant ROI clusters were obtained for each individual and compared between controls and migraine subgroups using full factorial general linear models in SPSS correcting for age, gender and total intracranial volume. Subgroups of migraineurs were based on aura status (with or without aura), disease activity (>1 year free of attacks [inactive] vs. at least 1 attack within the last year [active]) and attack frequency (≤1 [low] or >1 attack/month [high]). In these post-hoc analyses, $p<0.05$ was considered significant.

Whole brain analyses

For whole brain analyses comparing grey and white matter between migraineurs and controls, statistical parametric maps were thresholded at a significance level of $p<0.05$, corrected for multiple comparisons using random field theory (family-wise error), which is the standard to control for multiple testing in neuroimaging data [Nichols et al., 2003]. In case of significant findings, post-hoc analyses similar to ROI-analyses were to be performed.

As this is the first VBM-study investigating a population-based sample of participants with migraine with a minimum of comorbid factors, we deemed it justified to perform additional exploratory whole brain analyses at a less stringent significance level of $p<0.001$, uncorrected for multiple comparisons and minimal cluster sizes of 20 voxels.

Localization of region-of-interest and whole brain VBM findings

The location of the most significant voxel in ROI and whole brain VBM clusters of grey and white matter volume differences were determined using two detailed atlases in consensus [Mai JK, 2007; Talairach and Tournoux, 1988]. To ascertain whether significant changes in white matter between participants with migraine and control subjects were not due to the occurrence of WMHs, the locations of VBM changes were compared to the location of WMHs. WMHs were segmented semi-automatically as hyperintense lesions on proton density, T2 and FLAIR images using QBrain as described in detail elsewhere [Palm-Meinders et al., 2012]. Lesion maps were created per subject and registered to MNI152-space. Probability maps, depicting the chance for subjects to have a lesion in a specific area, were created for the participants with migraine and controls included in the VBM analyses. Finally, these lesion maps were registered to the study-specific DARTEL space using a 12-parameter affine linear registration.

RESULTS

No significant differences were found for the demographic characteristics of participants with migraine and those of controls (Table 1).

Table 1 Characteristics of CAMERA VBM study participants

			Migraineurs		
	Total (n=119)	Control (n=35)	All (n=84)	MO (n=32)	MA (n=52)
Age, mean (SE), years	57 (0.7)	55 (1.3)	58 (0.9)	57 (1.4)	58 (1.1)
Female, No. (%)	82 (69)	25 (71)	57 (68)	21 (66)	36 (69)
Low education[†], No. (%)	60 (50)	17 (49)	43 (51)	17 (53)	26 (50)
Body mass index, mean (SE)	26 (0.3)	26 (0.6)	25 (0.4)	25 (0.5)	26 (0.5)
Hypertension[‡], No. (%)	35 (29)	9 (26)	26 (31)	8 (25)	18 (35)
History of stroke[‡], No. (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Current medication, No. (%)					
Prophylactics	N/A	N/A	2 (2%)	0	2 (4%)
Abortive treatment	N/A	N/A	48 (57%)	16 (50%)	32 (62%)
Triptans	N/A	N/A	12 (14%)	4 (13%)	8 (15%)
Ergotamines	N/A	N/A	2 (2%)	1 (3%)	1 (2%)
Total intracranial volume, mean (SE), liter	1.12 (0.11)	1.14 (0.12)	1.12 (0.11)	1.12 (0.10)	1.11 (0.12)
DWMH volume, median (IQR), milliliter	0.06 (0-0.35)	0.06 (0-0.35)	0.08 (0-0.36)	0.06 (0-0.35)	0.11 (0-0.39)
Right-handed, No. (%)	102 (86)	31 (89)	71 (85)	29 (91)	42 (81)
Migraine attacks per year[#], mean (SE)	N/A	N/A	16.5 (2.2)	16.3 (2.7)	16.7 (3.2)
Migraineurs with high attack frequency[#], No. (%)	N/A	N/A	42 (50)	17 (53)	25 (48)

MA=migraine with aura, MO=migraine without aura, DWMH=deep white matter hyperintensity, SE=standard error, IQR=interquartile range, No.=number, N/A=not applicable No differences between groups (all p>0.05)

[†] Low education indicates primary school or lower vocational education

[‡] Hypertension and history of stroke were self-reported, based on a previous physician's diagnosis

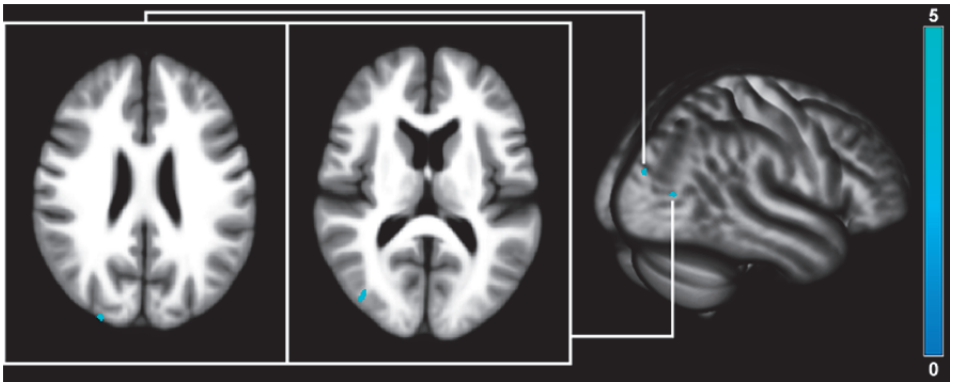
[#] Mean number of lifetime migraine attacks; high migraine attack frequency defined as on average ≥1 attack per month

Region-of-interest analyses

In ROI analyses (Figure 1), grey matter volumes ($p_{FWE\text{-}SVC}$ <0.05, family wise error, small volume correction) were smaller in the V3 ($p_{FWE\text{-}SVC}$=0.025; x 26/y -87/z 22) and MT+/V5 ($p_{FWE\text{-}SVC}$=0.031; x 38/y -76/z 11) areas of the right occipital gyrus of participants with migraine compared to those of controls. In post-hoc analyses, migraine subgroups displayed roughly the same pattern of grey matter volume decrease in these areas, compared to controls (Table 3). However, in migraineurs with inactive disease (attack-free

for more than one year), the decrease in average grey matter volume per voxel in the MT+/V5 area was not statistically significant, compared to controls. Decrease of grey matter volume in the MT+/V5 was significantly more pronounced in migraineurs with active disease and high attack frequency; this was not the case for the V3A area. No differences were found between migraineurs and controls for the other ROIs (prefrontal, insular, anterior cingulate, somatosensory and, the thalamus and the brainstem).

Figure 1 Region-of-interest analyses



Region-of-interest analyses: axial slices (left) and volume rendering (right) of significant grey matter volume decreases in the right area V3 (left panel) and V5 (right panel) between migraineurs and controls; color bar represent Z-values. Pictures depicted in radiological convention.

Table 2 Region-of-interest (ROI) analyses, post-hoc analyses: average grey matter volume per voxel in significant ROI clusters comparing migraineurs and migraine subgroups to controls and to each other (small volume correction (p_{FWE}<0.05)

	V3	p*	p†	V5	p*	p†
Controls (n=35)	0.416 (0.074)			0.385 (0.089)		
Migraine (n=84)	0.366 (0.063)	<0.001		0.327 (0.074)	0.001	
MA (n=32)	0.370 (0.067)	<0.001	0.60	0.325 (0.073)	<0.001	0.84
MO (n=52)	0.360 (0.057)	<0.001		0.330 (0.076)	0.003	
Active (n=47)	0.359 (0.066)	<0.001	0.38	0.315 (0.068)	<0.001	0.04
Inactive (n=37)	0.376 (0.059)	0.01		0.345 (0.078)	0.06	
HF (n=32)	0.352 (0.061)	<0.001	0.28	0.299 (0.058)	<0.001	0.002
LF (n=52)	0.373 (0.064)	0.003		0.344 (0.077)	0.03	

MA=Migraine with aura; MO=Migraine without aura
Active migraine= at least 1 attack within the last year
HF=High migraine attack frequency and LF=Low attack frequency; cutoff at 'high' is >1 attack per month in the year before examination. Values represent the mean volume of grey matter per voxel in significant cluster, denotation mean (standard deviation). p*=p-value for comparing migraine and migraine subgroups to controls; p†=p-value for comparing migraine subgroups to each other

Whole brain analyses

In whole brain analyses, no significant differences were found in grey or white matter when comparing migraineurs to controls ($p<0.05$, family-wise error correction for multiple comparisons).

Exploratory whole brain analyses ($p<0.001$, cluster extend threshold 20 voxels, uncorrected for multiple comparisons) confirmed smaller grey matter volumes in the right occipital gyrus of patients with migraine compared to controls as already found with ROI grey matter analyses. In addition, these analyses demonstrated: (i) larger grey matter volumes in the left angular, right middle temporal, left precentral and right superior frontal gyrus, and the left lateral geniculate nucleus; (ii) smaller grey matter volumes in the uvula of the left cerebellum; and (iii) smaller white matter volumes bilaterally in the occipital lobe and the stria medullaris of the thalamus, and unilaterally in the left frontal lobe (Table 4). These regional decreases in white matter volume did not correlate with deep white matter hyperintensities (Figure 2). Increased white matter volumes were not observed.

Table 3 Increases and decreases in grey and white matter between migraineurs vs. control subjects ($p<0.001$, uncorrected for multiple comparisons, cluster extend threshold 20 voxels)

	BA	L/R	DARTEL coordinates			k_E	Z-score
			x	y	z		
Grey matter increases							
Angular gyrus[1]	39	L	-50	-61	17	432	3.92
Precentral gyrus[2]	6	L	-51	-1	31	58	3.87
Middle temporal gyrus[3]	21	R	54	-32	-6	65	3.52
Superior frontal gyrus[4]	9	R	8	53	28	39	3.45
Lateral geniculate nucleus[5]	N/A	L	-21	-27	-5	27	3.33
Grey matter decreases							
Occipital gyrus[6]	19	R	26	-87	22	34	3.47
Cerebellum, uvula[7]	N/A	L	-14	-43	-42	68	3.44
Middle occipital gyrus[8]	19	R	38	-76	11	44	3.39
White matter increases	-	-	-	-	-	-	-
White matter decreases							
Occipital white matter[1]	N/A	R	29	-78	15	173	4.48
Occipital white matter[2]	N/A	R	15	-80	10	386	4.24
Stria medullaris of thalamus[3]	N/A	R	5	-8	9	90	4.06
Stria medullaris of thalamus[4]	N/A	L	-3	-13	5	44	3.91
Occipital white matter[5]	N/A	R	42	-69	20	23	3.77
Occipital white matter	N/A	R	27	-86	14	105	3.64
Occipital white matter[6]	N/A	L	-22	-70	15	457	3.64
Occipital white matter[7]	N/A	L	-9	-85	5	30	3.34
Frontal white matter[8]	N/A	L	-34	16	19	30	3.23

BA=Brodmann area, L=left, R=right, k_E=cluster size, N/A=not applicable; number 1-8 represent axial slices in Figure 2, grey matter (top row) and white matter (bottom row)

Figure 2 Volume rendering images and axial slices of increases (yellow) and decreases (light blue) in grey matter and of decreases (green) in white matter between migraineurs vs. control subjects ($p<0.001$, uncorrected for multiple comparisons, cluster extend threshold 20 voxels). Axial slices from left to right correspond with numbers 1-8 in table 4 for grey matter (top row) and white matter (bottom row). Decreases in white matter are shown in relation to deep white matter hyperintensities in migraineurs (red) and controls (dark blue). Color bars represent Z-values (0-5) or probability of voxels being deep white matter hyperintensities (1-10%). Pictures depicted in radiological convention.

DISCUSSION

In this first population-based assessment of volumetric changes in the migraine brain, we found decreased grey matter volume in the V3 and V5 areas of the right occipital gyrus in migraineurs compared to controls. Migraine subgroups (i.e. migraine with or without aura, active or inactive disease, low or high attack frequency) displayed roughly the same pattern of differences in these areas as compared to controls. In exploratory whole brain analyses, we identified structural differences in other cortical and subcortical areas that are particularly involved in sensory processing.

Cortical areas involved in visual processing

In the present study, we found decreased grey matter volumes in participants with migraine in the visual areas V3 and V5 of the extrastriate cortical areas of the occipital gyrus (Brodmann area 19). These cortical areas are involved in motion processing. These findings are in line with previous VBM findings [Jin et al., 2013], but seem to contradict the reported cortical thickening in visual processing areas in participants with migraine as assessed with SBM [Granziera et al., 2006; Messina et al., 2013]. This apparent discrepancy might, however, be explained by the fact that local grey matter volume is not only defined by thickness of the cortex but also by other parameters such as cortical folding patterns and total surface area of the cortex.

Structural changes in cortical visual (motion) processing areas might be related to hyperexcitability (i.e. increased cortical responses of the visual cortex to intense, repetitive or long-lasting stimulation) [Aurora and Wilkinson 2007], to distorted cerebral metabolic homeostasis or to changes in local neurotransmitter compositions [Reyngoudt et al., 2011; Siniatchkin et al. 2012]. Whether such changes are inherited, congenital, or acquired remains to be determined. Changes in cortical responsiveness might explain well-known clinical symptoms of participants with migraine such as increased sensitivity to visual (light), auditory (sound) and tactile stimuli (allodynia). These might also relate to lack of habituation to repeated visual stimulation [Ambrosini and Schoenen 2006] and interictal deficits in visual motion processing [McKendrick et al., 2004; Shepherd et al., 2012] in migraine with and without aura. Cortical spreading depression, the electrophysiological correlate of migraine aura, might also be due to cortical hyperexcitability [Datta et al., 2013; Ferrari et al., 2015] and may begin in visual motion processing areas [Hadjikhani, 2001].

Participants with migraine who had not experienced migraine attacks in the year before MR scanning (with most being attack-free for over 5 years) still showed changes in the right occipital gyrus (V3 area) compared to healthy controls. Therefore, these changes appear to be irreversible, at least partially, or may have existed throughout life. Grey matter volume decrease in the visual area V5 was more pronounced in active migraineurs and those participants with a high attack-frequency which suggests that

these volume decrease may (in part) be attack-related. As no significant differences were found for these areas between migraineurs with and without aura, these changes appear to be independent from presence of aura symptoms.

Subcortical areas involved in visual processing

In exploratory whole brain analyses, next to cortical areas involved in visual processing, we found increased grey matter volume in the lateral geniculate nucleus in migraineurs compared to controls. This thalamic structure processes visual input from the optic chiasm to the primary visual cortex [Maleki et al., 2012] and is, like the cortical areas found in ROI analyses, associated with visual motion processing [Ungerleider et al., 1984]. The lateral geniculate nucleus is also thought to attenuate light perception in the absence of visual contrast [Hubel and Livingstone, 1990] and has been suggested to play a role in photophobia in migraine [Boulloche et al., 2010]. Previous studies already described an altered structure [Granziera et al., 2006] of this nucleus and increased oxygen metabolism after visual stimulation [Datta et al., 2013].

White matter tracts involved in visual processing

We found bilateral volume decrease in the occipital white matter adjacent to visual processing cortical areas. Previously, with diffusion tensor imaging [Granziera et al., 2006; Rocca et al., 2008], reduced fractional anisotropy was found in white matter tracts in the middle temporal area [Granziera et al., 2006] and optic radiation tracts of participants with migraine [Rocca et al., 2008], possibly due to increased axonal diameter [Granziera et al., 2006; Rocca et al., 2008]. However, our results of decreased white matter volume make less myelination due to abnormal maturation or axonal loss a more likely explanation.

Theoretically, white matter changes as identified with VBM might be caused by WMHs which are known to be more prevalent in migraine [Kruit et al., JAMA 2004; Palm-Meinders et al., JAMA 2012]. WMHs show a drop in MR T1-signal due to gliosis and appear as relatively grey areas and therefore may be falsely classified by VBM segmentation tools as grey matter, despite their location in the deep white matter. However, the white matter decreases we found in the visual pathways did not co-localize with WMHs (Figure 2).

Differences with previous studies

Although previous studies notably described difference in areas known to be primarily involved in pain processing [Coppola et al., 2015; DaSilva et al., 2007; Hougaard et al., 2015; Jin et al. 2013, Kim et al., 2008; Liu et al,. 2013; Rocca et al., 2014; Schmidt-Wilcke et al., 2008; Schmitz et al., 2008; Valfre et al., 2008], these areas were less prominent in

our study. Apart from differences in image acquisition and post-processing, and statistical thresholding, an explanation might be that the migraineurs from the CAMERA-cohort have had less frequent exposure to pain compared to the participants from headache clinics in the other studies, who tend to suffer from more severe migraines. A recent study from Hougaard et al. explicitely found no alterations in cortical structures of areas involved in visual processing in migraine patients with visual aura [Hougaard et al., 2016]. Again, differences in participant characteristics, numbers of participants, and post-processing methods could explain the indiscrepancy of findings across publications.

Previous studies showed that adaptive remodeling due to chronic pain might be reversible and disappear shortly after adequate therapy [May, 2009; May, 2011]. We showed that part of (cortical) grey matter changes were still present long after the last migraine attack.

Our study also has limitations. Despite a reasonably large sample size, we were not able to find significant differences, corrected for multiple comparisons, in whole brain grey or white matter when comparing migraineurs to controls. Therefore, precaution should be taken in interpreting the results of the exploratory whole brain analyses. Further, in general, it is difficult to translate VBM changes to specific alterations at microscopic level as the technique is strongly depending on local T1 MRI signal intensity which is influenced by local tissue composition, including number and size of neurons, configuration of the extracellular space, presence of specific compounds (like iron, myelin, and neurotransmitters), homeostatic balance, and actual macro- and microvascular perfusion. Because whole brain T1 weighted images could be acquired only in the CAMERA-2 MRI study and not also in the 9-year earlier CAMERA-1 baseline study, we could not study changes over time. Moreover, the cross-sectional design of our study precludes analysis of whether the observed structural brain changes are a cause or a consequence of migraine.

In summary, we found alterations mainly in cortical grey matter structures involved in visual motion processing in 'average' migraineurs from the general population. These findings confirm and extend knowledge from previous surface-based morphometry and VBM studies in participants with migraine from specialized headache centers.

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Chapter 6

Systemic right-to-left shunts, ischemic brain lesions, and persistent migraine activity

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ABSTRACT

Objective: To assess whether migraine in the general population is associated with increased risk of systemic right-to-left shunts (RLS) and whether RLS are associated with increased prevalence of brain infarcts and persistent recurrence of migraine attacks at older age.

Methods: Brain MRI and transcranial Doppler with air contrast in 166 unselected migraineurs (mean age 6 SD 56 6 7.7 years; 70% women; n = 96 migraine with aura) and 69 controls (mean age 6 SD 55 6 7.6 years; 65% women) from the general population.

Results: Participants with migraine with aura more frequently had Valsalva-induced RLS (60%), in particular large-sized, compared to controls (42%; odds ratio [OR] 2.1; 95% confidence interval [CI] 1.1–3.9; *p*=0.02) and participants with migraine without aura (40%; OR 2.3; 95% CI 1.2– 4.3; *p*=0.01). They also more frequently had spontaneous RLS (35%) than participants with migraine without aura (17%; OR 2.6; 95% CI 1.3–5.6; *p*=0.01) but not compared to controls (26%; OR 1.6; 95% CI 0.8–3.1; *p*=0.2). Participants with migraine with aura and spontaneous RLS more frequently had persistent migraine activity (85%) than participants with migraine without spontaneous RLS (63%; OR 3.4; 95% CI 1.2–10.1; *p*=0.03). Nine percent of participants with RLS had silent posterior circulation infarcts compared to 3% of participants without RLS (OR 2.8; 95% CI 0.9–9.3; *p*=0.08), independent of migraine status. RLS were not associated with white matter lesions.

Conclusions: RLS are more prevalent in migraineurs with aura but do not explain the increased prevalence of silent posterior circulation infarcts or white matter lesions in migraineurs. Spontaneous RLS are associated with persistent migraine.

GLOSSARY

CAMERA=Cerebral Abnormalities in Migraine: An Epidemiological Risk Analysis Study; **CI**=confidence interval; **CSD**=cortical spreading depression; **MB**=microbubble; **OR**=odds ratio; **PFO**=patent foramen ovale; **RLS**=right-to-left shunts; **TCD-c**=transcranial Doppler with air contrast

INTRODUCTION

Epidemiologic and animal studies have suggested a complex relation between migraine, ischemic brain lesions, and systemic right-to-left shunts (RLS).[1–6] Participants with migraine had higher prevalence of subclinical deep white matter hyperintensities and brain infarcts,[2,3,5] migraine with aura was associated with increased prevalence of ischemic stroke [1,7] and RLS,[4,6] and RLS were more prevalent in patients with cryptogenic stroke.[8,9] In uncontrolled and open-label studies,[10–12] but not in a sham-controlled study,[13] closing patent foramen ovale reduced migraine attack frequency and risk of stroke recurrence.[14,15]

In mice, carotid injection of small experimental emboli induced cortical spreading depression (CSD),[16,17] the electrophysiologic correlate of migraine aura and a putative trigger for migraine attacks.[18] Altogether, microemboli through RLS might cause cerebral ischemia and might trigger attacks of migraine with aura. Thus while in most migraineurs attacks cease, recurring spontaneously at older age,[19] in migraineurs with RLS, attacks might continue recurring. Most of these data, however, were obtained in patients from headache clinics who likely were more severely affected than the average migraineur. It thus is uncertain whether and to what extent these conclusions can be extrapolated to the migraineur at large.

In the present study, we assessed whether RLS are (1) more prevalent in migraineurs from the general population, (2) associated with a higher prevalence of ischemic brain lesions on MRI, and (3) associated with ongoing migraine activity. To this end, we assessed and correlated (1) presence, type, and size of RLS; (2) presence and type of ischemic brain lesions; and (3) migraine activity, defined as number of attacks in the preceding year in a cohort of unselected but well-defined migraineurs (n = 203) and controls (n = 83) from the general population-based Cerebral Abnormalities in Migraine: An Epidemiological Risk Analysis Study Part 2 (CAMERA-2).[3] As CAMERA-2 is a 9-year follow-up of the CAMERA-1 study,[2] in which all migraineurs were initially diagnosed and characterized, we could reliably analyze both still active migraineurs in whom attacks were still recurring and inactive migraineurs in whom attacks had meanwhile ceased recurring.

METHODS

Study population and procedures

Study participants were invited from the CAMERA-2 study,[3] which was primarily designed to assess the prevalence, incidence, and progression of MRI-detectable ischemic brain lesions in migraineurs over a 9-year follow-period from the CAMERA-1 study.[2]

In CAMERA-1, 295 well-characterized individuals with migraine[20] and 140 controls who were randomly selected from a community-based study of the general population

were included and assessed with brain MRI in 2000.[2,21] For CAMERA-2, all original CAMERA-1 participants were invited in 2009 for a follow-up study, which included a structured computer-guided telephone interview, brain MRI, physical examination, and cognitive testing, all similar to the CAMERA-1 protocols.[3] Although MRI scanners had significantly improved over the follow-up period, we decided to use the same MRI scanners in CAMERA-2 as in CAMERA-1 to preclude finding changes solely due to improved technology and sensitivity. Transcranial Doppler with air contrast (TCD-c) was performed on the same day as the MRI. MRI and TCD-c were performed and read without knowledge of migraine status.

Standard protocol approvals, registrations, and patient consents

The study was approved by the ethics committees and participants gave written informed consent.

Outcome measures

The primary outcome measure was the prevalence of RLS in migraineurs with and without aura compared to controls. Secondary outcome measures were the prevalence of ongoing recurrence of migraine attacks (defined as having had at least one migraine attack in the previous 12 months)[22] in migraineurs with RLS compared to migraineurs with migraine but no RLS, and ischemic brain lesions in participants with RLS compared to those without.

RLS

Presence of RLS was determined by TCD-c in accordance with international guidelines and recent recommendations.[23] Briefly, the right cubital vein was cannulated with a 20-G indwelling catheter. A microbubble (MB) medium was prepared by mixing 9 mL saline, 1 mL air, and 0.5 mL of participants' own blood at least 10 times vigorously between 2 syringes connected by a 3-way tap and injected with the participant in supine position while insonating the middle cerebral artery through the temporal bone window. We used a hand-held 2-MHz probe connected to a Doppler system (Multi Dop T2 [DWL, Sipplingen, Germany], Pioneer TC 8080 [Nicolet, Kleinostheim, Germany], or PMD 100 or ST3 [Spencer Technologies, Seattle, WA]). Signal recording was commenced 10 seconds before application of the contrast medium and halted after 60 seconds recording time. The procedure was carried out 3 times in a standardized and fixed order: in the first measurement, to detect spontaneous RLS, contrast medium was injected during normal breathing. In the second and third measurement, to detect RLS after provocation, contrast medium was injected and followed after 5 seconds by a 5-second Valsalva maneuver. Participants were instructed and coached in a standardized way to press

firmly with their mouth closed to produce a Valsalva maneuver. The procedure was performed by 2 experienced investigators (H.K. and I.H.P.-M.) blinded for MRI findings and migraine diagnosis; participants were instructed not to talk about their medical history. TCD-c investigation was performed immediately after MRI on the same day.

Offline reading started after completion of the study. Two experienced observers (R.W.K. and W.H.M.) rated presence and size category of RLS, blinded to participant characteristics. Passing MBs were unequivocally characterized acoustically by the typical chirping sound and visually by the spike-like appearance in the frequency spectrum. RLS were rated according to number of MBs detected during 60 seconds of each TCD-c investigation: no RLS (0 MB), small (1–9 MB), or large (> 9 MB). The interrater agreement for presence of RLS was excellent ($K = 0.95$; $p < 0.001$).

MRI

As suggested recently,[24] we replaced the previously used term infarct-like lesions[2,3] with silent infarcts. Silent infarcts were defined as non-mass parenchymal defects with a vascular distribution, isointense to CSF signal on all sequences, and when supratentorial, surrounded by a hyperintense rim on fluidattenuated inversion recovery images.[2] Virchow-Robin spaces were excluded based on typical location, shape, and absence of a hyperintense rim.[2] In the basal ganglia, in order to exclude nonspecific lesions, only parenchymal defects larger than 3 mm in diameter were considered.[2] Location and vascular territory of new and preexisting infarcts were read by 2 experienced neuroradiologists (M.C.K. and Junya Konishi), who were blinded to diagnosis. The interrater agreement was excellent ($k = 0.87$; $p<0.001$).[2]

White matter lesions were segmented automatically. Deep white matter hyperintensities were located supratentorial and not attached to the lateral ventricle.[2] High volume of deep white matter lesions (upper 20th percentile) was used as variable. For infratentorial hyperintensities, presence vs absence was used.

Migraine and ongoing recurrence of migraine attacks

Participants were asked during a telephone interview whether they ever had had migraine attacks and, if so, what the average attack frequency had been prior to CAMERA-1 and since then. One participant who was classified as control at CAMERA-1 had become migraineur without aura during the follow-up period. Participants who fulfilled the criteria of migraine at CAMERA-1 but had stopped experiencing migraine attacks during last year of follow-up were considered currently inactive lifetime migraineurs[22] The interview was structured by using personal benchmarks (e.g., pregnancy) for when a different migraine pattern had started or stopped.[3] These benchmarks were used to define periods and to compute the average migraine attack frequency (expressed as mean number of attacks per month).Information was collected on migraine prophylaxis

and treatment. Active recurrence of migraine attacks was defined as having had at least one migraine attack in the 12 months[22] prior to the CAMERA-2 MRI investigation.

Table 1 characteristics of study participants

			Migraine		
Characteristic	Total (n=235)	Controls (n=69)	Migraine (n=166)	Aura (n=96)	No aura (n=70)
Age, mean (SD),y	56 (7.7)	55 (7.6)	56 (7.7)	56 (8.0)	57 (7.6)
Women	161 (69)	45 (65)	116 (70)	69 (72)	47 (67)
BMI, mean (SD)	25.5 (3.9)	25.9 (4.1)	25.3 (3.9)	25.3 (3.3)	25.3 (4.6)
Hypertension[a]	73 (31)	22 (32)	51 (31)	31 (32)	20 (29)
Diabetes[a]	15 (6)	0 (0)	15 (9)[c]	7 (7)	8 (11)
Myocardial infarction[a]	5 (2)	3 (4)	2 (1)	1 (1)	1 (1)
Cardiac arrhythmia[a]	25 (11)	5 (7)	20 (12)	15 (16)	5 (7)
Pulmonary embolism[a]	3 (1)	0 (0)	3 (2)	1 (1)	2 (3)
Deep venous thrombosis[a]	7 (3)	2 (3)	5 (3)	3 (3)	2 (3)
History of transient ischemic attack[a]	10 (4)	1 (1)	9 (5)	4 (4)	5 (7)
History of stroke[b]	7 (3)	0 (0)	7 (4)	3 (3)	1 (1)
Smoking					
Ever	159 (67)	46 (67)	113 (68)	66 (69)	47 (67)
Pack years, mean (SD)	17 (16)	17 (16)	17 (15)	15 (14)	20 (18)
Postmenopausal state or ovariectomy	86 (66)	23 (58)	63 (70)	35 (66)	28 (76)
Current medication use					
Platelet inhibitors	20 (9)	7 (10)	13 (8)	9 (9)	4 (6)
Oral contraceptives	2 (1)	0	2 (2)	2 (3)	0
Hormonal substitution	3 (2)	1 (2)	2 (2)	2 (3)	0
Beta blockers	37 (16)	11 (16)	26 (16)	17 (18)	9 (13)
ACE inhibitor	9 (4)	4 (6)	5 (3)	4 (4)	1 (1)
Antiepileptic	1 (0)	0	1 (1)	1 (1)	0
Migraine years, mean (SD)	NA	NA	30 (12)	32 (12)	27 (12)[d]
Age at migraine onset, mean (SD)	NA	NA	22 (12)	21 (11)	22 (11)
Mean attack frequency per year	NA	NA	12 (22)	15 (24)	19 (21)
Ongoing recurrence of attacks	NA	NA	101 (106)	68 (71)	33 (47)

Abbreviations: ACE=angiotensin-converting enzyme; BMI=body mass index (calculated as weight in kilograms divided by height in meters squared); NA =not applicable.

Active migraine= migraine attacks during the last 12 months. Postmenopausal state= at least 3 months no menstruation or history of ovariectomy (unknown postmenopausal state due to hysterectomy in 31). Data are presented as n (%) unless otherwise specified. Oral contraceptives and hormonal substitution data presented as n (%) among women. Unless indicated otherwise, differences were not significant ($p > 0.05$).

[a] Cardiovascular history self-reported, doctor diagnosed.

[b] Ischemic or hemorrhage, self-reported, doctor diagnosed.

[c] Compared with controls; $p = 0.007$.

[d] Compared with migraine with aura; $p = 0.01$.

Study population

Of the 435 original participants of CAMERA-1, 286 (66%) underwent a follow-up MRI scan (migraine with aura: n = 114; migraine without aura: n = 89; nonmigraine controls: n = 83).[3] Mean follow-up was 8.5 years (range 7.9–9.2; SD 0.24 years).[3] Of these, 272/286 (95%) agreed to undergo TCD-c. Usable TCD-c data could be obtained from 235/272 (86%) participants: in 23/272 (8%), no adequate bone window was found, 9/272 (3%) had no adequate cubital venous access, and in 5/272 (2%) offline analysis was not possible due to technical failures. The 37 participants for whom no usable TCDc was available were otherwise comparable to the participants with usable TCD-c data with respect to age, sex, cardiovascular history, and migraine status.

As explained before,[3] there were no obvious reasons to assume that there was a serious selection bias from CAMERA-1 to CAMERA-2, which could have materially affected the results.[3]

Reasons for nonparticipation were no interest (n = 51), inability to visit research center (n = 30), claustrophobia (n = 8), and non-neurologic illness (n = 6).[3] There was no association between participation rate and diagnosis of migraine. Compared to nonparticipants, participants were slightly younger, more frequently reported high educational level, and smoked fewer packyears.[3]

Covariates and definitions

Sociodemographic and medical history characteristics were assessed by telephone interview.[3] Cardiovascular risk diagnoses were based on patient report of a physician's diagnosis.[3] In women, postmenopausal state was defined as last menstruation at least 3 months previously or a history of ovariectomy.

Statistical analysis

Differences in the distributions and means of characteristics among the study groups were tested with x^2, 2-tailed Fisher exact, unpaired t, and MannWhitney U test when appropriate. The presence of ongoing migraine attack recurrence was examined by RLS diagnosis (yes/no) using a model adjusting for age, sex, and postmenopausal state. Likewise, using logistic regression, the risk of MRI outcomes was examined by RLS diagnosis (yes/ no) and migraine and age as covariates.

Based on findings in previous studies, we decided beforehand to conduct 3 specific analyses. First, because an increased prevalence of RLS had only been found for migraine with aura,[4,6] we analyzed the prevalence of RLS separately for migraine with and without aura. To detect a difference of 20% in RLS frequency with a power of 0.8 and a set at 0.05, we would need 162 participants (total number in 2 arms). Second, because silent infarcts were found increased only in the posterior cerebral circulation,[2] we ana-

lyzed their presence separately for this part of the circulation. Finally, because higher prevalence of deep white matter lesions was only found in women with migraine,[3] we conducted this analysis stratified for sex. All performed statistical tests are shown in text or tables; reported p values are not corrected for multiple testing as this study was an exploratory hypothesis-generating study rather than confirmatory research. Data were analyzed using Statistical Software Package for Social Sciences (SPSS version 20.0; IBM, Armonk, NY).

RESULTS

Clinical and demographic data of the participants are summarized in table 1. Except for diabetes, there were no differences between migraineurs and controls in age, sex, or cardiovascular history.

Table 2 summarizes the prevalence of RLS among the various study groups. Of the migraineurs with aura, 60% had RLS vs 42% of controls (unadjusted odds ratio [OR] 2.1; 95% confidence interval [CI] 1.1–3.9; p=0.02) and 40% of migraineurs without aura (OR 2.3; 95% CI 1.2–4.3; p=0.01). Large RLS were found in 45% of migraineurs with aura vs 28% of controls (OR 2.1; 95% CI 1.1–4.2; p=0.03) and 20% of migraineurs without aura (OR 3.3; 95% CI 1.6–6.6; p=0.01). The prevalence of spontaneous large RLS was low in migraineurs without aura (1%) compared to controls (16%) and migraineurs with aura (19%). Otherwise, there were no differences in the prevalence of spontaneous RLS among the various groups.

We correlated the presence of total and spontaneous RLS with ongoing recurrence of migraine attacks in the last year as shown in table 3. Migraineurs with spontaneous RLS more frequently had ongoing recurrence of migraine attacks (76%), vs migraineurs without spontaneous RLS (55%) (unadjusted OR 2.6; 95% CI 1.2–5.6; p=0.01). When analyzed separately for migraine with and without aura, overrepresentation of participants with migraine with ongoing recurrence of migraine attacks was only found in migraineurs with aura and spontaneous RLS (85%) vs without spontaneous RLS (63%) (unadjusted OR 3.4; 95% CI 1.2– 10.1; p=0.02). These results did not change after adjusting for age, sex, and postmenopausal state. Furthermore, migraine inactivity was not due to higher use of migraine prophylactic agents (data not shown). Mean attack frequency was not correlated with the presence or absence of spontaneous RLS (data not shown).

Table 2. Prevalence of right-to-left shunt types

Right-to-left shunt	Controls (n=69)	Migraine with aura (n=96)	*P* Value [a]	Migraine without aura (n=70)	*P* Value [b]	*P* Value [c]
Spontaneous	18 (26)	34 (35)	0.2	12 (17)	0.2	0.01
Small no.(%)	7 (10)	16 (17)	0.2	11 (16)	0.3	0.9
Large no.(%)	11 (16)	18 (19)	0.6	1 (1)	0.02	0.001
Total after provocation	29 (42)	58 (60)	0.02	28 (40)	0.8	0.01
Small no.(%)	10 (15)	15 (16)	0.8	14 (20)	0.4	0.5
Large no.(%)	19 (28)	43 (45)	0.03	14 (20)	0.3	0.01

Data are expressed as number (%)

Small shunt defined as passage of 1-9 microbubbles. Large shunt defined as passage of at least 10 microbubbles.

[a] *P* value Controls vs Migraine with aura

[b] *P* value Migraine without aura vs controls

[c] *P* value Migraine with aura vs migraine without aura

Table 3. Prevalence of ongoing recurrence of migraine attacks by presence and subtype of right-to-left shunt

	Migraine (all)		Migraine with aura		Migraine without aura	
	With RLS	Without RLS	With RLS	Without RLS	With RLS	Without RLS
Spontaneous RLS	n = 46	n = 120	n = 34	n = 62	n = 12	n = 58
Ongoing recurrence	35 (76)	66 (55)[a]	29 (85)	39 (63)[a]	6 (50)	27 (47)
Total RLS	N = 86	N = 80	N = 58	N = 38	N = 28	N = 42
Ongoing recurrence	57 (66)	44 (55)	44 (76)	24 (63)	13 (46)	20 (48)

Abbreviation: RLS = right-to-left shunts.

Data are expressed as n (%). [a] $p < 0.05$ Unless indicated otherwise, differences were not significant ($p > 0$ .05).

Table 4 and table e-1 on the Neurology® Web site at Neurology.org summarize the prevalence of MRI detectable brain lesions by RLS type in the 229/235 (97%) participants who underwent TCD-c and for whom MRI data were available. Prevalence of silent infarcts in the posterior cerebral circulation in participants with RLS (9%) was not different from those without RLS (3%; OR 2.8; 95% CI 0.9–9.3; p=0.08). This was irrespective of migraine status (data not shown).

The risk of posterior circulation silent infarcts was further assessed using a multivariate regression model (with migraine presence, RLS presence, and age as covariates). Higher age (p=0.004) and possibly RLS (p=0.08), but not migraine (p=0.7), were associated with an increased infarct risk. No significant associations were found between RLS (subtypes) and deep white matter lesions, also not when stratified for sex.

Table 4. Prevalence of MRI findings by RLS type

	Spontaneous RLS			Total RLS		
	No RLS N=167	RLS N=62	*P* Value[a]	No RLS N=118	RLS N=111	*P* Value[b]
Any brain infarct-like lesion	23 (14)	7 (11)	0.6	13 (11)	17 (15)	0.3
Multiple infarct-like lesions	9 (5)	2 (3)	0.5	3 (3)	8 (7)	0.1
Silent brain infarct posterior circulation	10 (6)	4 (7)	0.9	4 (3)	10 (9)	0.08
Infratentorial hyperintensities	23 (14)	13 (21)	0.2	20 (17)	16 (14)	0.6
High volume deep white matter hyperintensities	31 (19)	13 (21)	0.7	20 (17)	24 (22)	0.4

Data are expressed as number (%).

Abbreviations: RLS, Right-to-left shunt; Any brain infarct indicates a brain infarct in any vascular territory. Multiple brain infarct-like lesions indicates more than one infarct-like lesion in any vascular territory. High volume deep white matter hyperintensities defined as upper 20th percentile.

Progression DWML : progression yes or no within follow up.

[a] *P* Value: No spontaneous RLS vs Spontaneous RLS [b] *P* value : No RLS vs RLS.

DISCUSSION

We assessed and correlated (1) presence, type, and size of RLS, (2) presence and type of ischemic brain lesions on MRI, and (3) persistent migraine activity in a large and unbiased general population-based cohort of phenotypically well characterized migraineurs and controls. We found, first, that in particular large-sized RLS are more prevalent among migraineurs with aura but not in migraineurs without aura. Second, migraineurs with aura and spontaneous RLS more often had ongoing migraine activity compared to migraineurs with aura without RLS or migraineurs without aura with or without RLS. Third, participants with RLS did not have more silent infarcts in the posterior cerebral circulation, irrespective of whether or not they also had migraine. There was no association of RLS with white matter lesions.

Our finding that RLS are more prevalent in migraineurs with aura from the general population is well in line with observations from clinic-based studies[4,6] and extends the RLS-migraine association from selected severe cases who are attending headache clinics to the average patient with migraine with aura. Two previous population-based studies, however, failed to find an association between RLS and migraine,[25,26] most likely due to limited statistical power, use of detection methods with only limited sensitivity to identify RLS, and, possibly, selection bias. In the first study,[25] 79% of participants had migraine with aura, whereas in the general population only one third of migraineurs have migraine with aura.[21] Moreover, in that study, transthoracic echo was used, which is known to have a lower sensitivity to detect RLS compared to TCD-c.[27] The second study[26] most likely was underpowered, with only 42 participants with migraine with

aura and 44 with migraine without aura. Moreover, RLS might have been missed in many participants as the TCD signal was assessed within 10 seconds after injection of contrast, which generally is considered too soon.[28] Use of TCD-c, which is more sensitive to detect RLS than the other methods generally used,[27] and the longer time window (60 seconds), which increases the chances of detecting very small cardiac shunts, may explain why we found somewhat higher RLS prevalences than were found in other studies.[4,6,25,26] Two clinic-based studies[29,30] assessed RLS with TCD-c in chronic (high frequent) migraine but with inconsistent findings: 66%[30] vs 37%.[29] Control groups such as participants with episodic migraine or participants without migraine were lacking in both studies.

The relationship between RLS and migraine with aura is intriguing and might be explained at least in part by shared genetic factors.[31] Alternatively, there might be a direct causal relationship.[32] In mice, it was shown that carotid injection of small particles or air emboli injected could evoke CSD,[16] the electrophysiologic correlate of migraine aura and a putative trigger for migraine attacks.[18] Migraineurs who were injected with agitated saline developed EEG alterations and headache attacks, particularly those with large RLS.[17] Finally, in a small open-label study, 87% of migraine patients with RLS had a 50% or greater reduction in migraine frequency when using the emboli-preventing drug clopidogrel.[33] It has also been hypothesized that substances like amines and other chemicals might bypass the pulmonary filter in participants with RLS, precipitating migraine attacks in susceptible individuals.[11] A direct relationship between RLS and migraine in at least some people is further suggested by our finding that participants with migraine with aura (but not those without aura) more often had ongoing migraine activity if they also had spontaneous RLS. As TCD cannot distinguish between cardiac and pulmonary RLS, we cannot determine which type is most relevant in migraine. Trials testing the migraine attack-reducing effect of closing patent foramen ovale (PFO), the most frequent cause of RLS,[11] traditionally included participants with both migraine with and without aura, and participants with Valsalva-induced rather than spontaneous PFO.[10–13] Whereas retrospective studies[10–12] showed promising results, a prospective, randomized, sham-controlled trial[13] failed to show any effect. Interestingly, preliminary results of the open-label but randomized Percutaneous Closure of PFO in Migraine with Aura (PRIMA) trial comparing PFO closure with antimigraine medication suggested selective elimination of attacks of migraine with aura in participants in whom large spontaneous PFOs had been closed (presented at the Transcatheter Cardiovascular Therapeutics Meeting, Washington, DC, September 2014).

Presence of RLS was not associated with higher prevalence of silent infarcts in the posterior circulation; this is in line with studies reporting that RLS is not associated with specific ischemic patterns.[34]

Furthermore, there was no association of RLS with deep white matter hyperintensities or infratentorial hyperintensities, which is in line with other studies.[35,36]

The design and study population of the present study allow for a broad extrapolation of the results to the average migraine patient. Although still too small for additional subgroup analyses, the study sample should be considered large in view of the fact that all participants had brain MRI. Moreover, the study participants were drawn from a phenotypically well-defined, general population-based, long-term follow-up study,[20,37] and their clinical characteristics covered a wide range of disease severities and attack frequencies. The fact that even patients were included in whom attacks had ceased recurring enabled reliable analysis of the relationship between RLS and persistent migraine activity at older age. Compared to methods used in most other studies, TCD-c, although less specific for subtype, is more sensitive for detecting RLS. Finally, both TCD-c and MRI were performed and interpreted by investigators who were strictly blinded to the clinical diagnoses and characteristics of the participants.

Migraine with aura, but not without aura, is associated with increased prevalence of in particular large RLS. Spontaneous, but not Valsalva-induced, RLS are associated with persistent recurrence of migraine attacks beyond the age most patients normally cease having attacks. Finally, RLS were not associated with increased risk of ischemic brain lesions, irrespective of comorbid migraine status.

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Table e-1. MRI findings by RLS type, odds ratio unadjusted [OR] and adjusted [OR]

Spontaneous RLS	OR unadjusted	Model 1 OR adjusted[a]
Any silent brain infarct	OR 0.8 (0.3-1.9)	OR 0.9 (0.4-2.3)
Multiple silent brain infarcts	OR 0.6 (0.1-2.8)	OR 0.8 (0.2-4.3)
Silent infarct posterior circulation	OR 1.1 (0.3-3.6)	OR 1.5 (0.4-5.2)
Infratentorial hyperintense lesions	OR 1.6 (0.8-3.5)	OR 1.9 (0.9-4.3)
High volume deep white matter lesions	OR 1.2 (0.6-2.4)	OR 1.4 (0.7-3.0)
Total RLS		
Any silent brain infarct	OR 1.5 (0.7-3.2)	OR 1.5 (0.7-3.3)
Multiple silent brain infarcts	OR 3.0 (0.8-11.5)	OR 3.2 (0.8-12.9)
Silent infarct posterior circulation	OR 2.8 (0.9-9.3)	OR 3.0 (0.9-10.0)
Infratentorial hyperintense lesions	OR 0.8 (0.4-1.7)	OR 0.8 (0.4-1.6)
High volume deep white matter lesions	OR 1.4 (0.7-2.6)	OR 1.4 (0.7-2.7)

Abbreviations: RLS, Right-to-left shunts; Any silent brain infarct indicates infarct in any vascular territory. Multiple silent brain infarcts indicate more than one infarct in any vascular territory.
High volume deep white matter lesions defined as upper 20th percentile
[a] Model 1: adjustments for diagnosis of migraine and age.

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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.

Chapter 8

Nederlandse samenvatting en conclusies

Het doel van dit proefschrift was het onderzoeken van de prevalentie en progressie van veranderingen in de hersenen van migrainepatiënten uit de algemene bevolking in de longitudinale CAMERA-2 studie (Cerebral Abnormalities in Migraine an Epidemiological Risk Analysis-study). Daarnaast is gekeken naar mogelijke oorzaken en consequenties van deze veranderingen. In het kader van mogelijke consequenties is het cognitief en cerebellair functioneren van de migrainepatiënten en controles in kaart gebracht.

Hoofdstuk 2 beschrijft de prevalentie en progressie van hersenlesies, vastgesteld door middel van MRI, en de relatie met cognitief functioneren. We hebben aangetoond dat, na 9 jaar follow-up, er bij mannen geen verband is tussen migraine en aanwezigheid noch progressie van diverse typen hersenlesies. Bij vrouwen met migraine is er echter een grotere incidentie van diepe witte stof afwijkingen. Migraine ernstmaten – aantal aanvallen, de duur, de frequentie ervan – houden geen verband met de mate van progressie. Progressie van witte stof afwijkingen werd vooral gezien als nieuwe lesies, minder vaak waren het groter wordende reeds bestaande lesies. Voor wat betreft de periventriculair gelegen witte stof afwijkingen: hierin was geen verschil tussen migraine en controle deelnemers. Ook infratentoriële hyperintensiteiten zagen we vaker bij vrouwen met migraine dan controles. Er werd echter ook hier geen relatie aangetoond met migraine aura of migraine-ernst. Tijdens de follow-up periode bleken tien mensen met migraine en geen enkele controle proefpersoon nieuwe infarcten ontwikkeld te hebben in het posterieure stroomgebied. We concluderen dat het hebben van migraine een risicofactor is voor de aanwezigheid en progressie van deze typen hersenlesies bij vrouwen in de algemene bevolking.

Het verband tussen ijzer en het brein in het algemeen en ijzer in migraine-hersenen in het bijzonder wordt beschreven in hoofdstuk 3. Het lijkt alsof (de pijn van) herhaaldelijk optredende migraineaanvallen geassocieerd is met een hogere ijzerconcentratie in verschillende structuren van de hersenen die betrokken zijn bij centrale pijnverwerking en migrainepathologie. Het precieze mechanisme is niet duidelijk. In hoofdstuk 4 is gekeken naar de aanwezigheid van ijzer en ijzerstapeling in de basale ganglia van de CAMERA-deelnemers door middel van metingen van de T2-waarden op MRI tijdens baseline en follow-up. Migrainepatiënten onder de 50 jaar hadden namelijk op baseline afgenomen T2-waarden, suggestief voor op een verhoogde ijzerdepositie, in diverse diepe hersenkernen. Na 9 jaar bleken T2-waarden van de meeste van die kernen echter toegenomen te zijn – in plaats van de verwachte verdere afname. Daarbij werd er bij follow-up geen verschil meer gevonden tussen migrainepatiënten en controles, in min of meer dezelfde groep deelnemers. Verschillende mogelijke verklaringen voor deze bevindingen worden besproken in dit hoofdstuk. Eén mogelijkheid is dat de verouderingsgebonden toename van signaal de ijzergerelateerde afname van het signaal tegenwerkt of verbloemt.

Hoofstuk 5 beschrijft de structurele hersenveranderingen in het CAMERA-cohort gemeten door middel van voxel-based-morphometry. Region-of-interest analyses – gebaseerd op eerder werk in dit veld – lieten in de visuele gebieden V3 en V5 van de

rechter occipitale cortext kleinere grijze stof volumes zien in migrainepatiënten vergeleken met controles. Dit hoofdstuk beschrijft mogelijke verklaringen voor deze bevindingen, zoals dat deze hersenveranderingen veroorzaakt kunnen zijn door aanpassingen als reactie op chronische pijn, hyperexcitabiliteit, verstoorde metabole homeostase in de hersenen en veranderingen in lokale neurotransmittersamenstelling.

In hoofdstukken 2-5 zijn diverse migraine-gerelateerde hersenveranderingen beschreven. Een logische verklaring voor het optreden van deze schade lijkt ischemie tijdens de hoofdpijnaanvallen. Ischemie kan echter niet alle bevindingen verklaren en het lijkt erop dat er ook een meer chronische oorzaak is voor de veranderingen, zoals (i) een versterkte bloedplaatjesaggregatie of staat van ontsteking als gevolg van endotheeldysfunctie, of (ii) herhaaldelijk optreden van paradoxale (micro-)embolieën als gevolg van rechts-links-shunting.

Hoofdstuk 6 beschrijft de prevalentie van een rechts-links-shunt (RLS) en de relatie met ischemische hersenlesies en migraine persistence (=migraineaanvallen blijven houden bij het ouder worden). Bij de migrainepatiënten met aura werd er een hogere prevalentie van RLS gevonden en bovendien bleken spontane shunts geassocieerd te zijn met migraine persistence. Valsalva-geïnduceerde RLS, met name de grotere shunts, kwamen vaker voor bij migraineurs met aura dan bij controles of dan bij migraineurs zonder aura. Degenen die zowel migraine met aura als een spontane shunt hadden, bleken een groter risico te hebben op het houden van migraineaanvallen op oudere leeftijd. Los van het hebben van migraine bleken degenen met een RLS vaker een infratentorieel infarct te hebben dan degenen zonder RLS. Migraine met aura en RLS zijn comorbiditeiten, maar het onderliggende mechanisme is niet duidelijk. Cerebrale emboli kunnen wellicht migrainesymptomen veroorzaken, hoewel dit zeldzaam is. Er is tot op heden geen overtuigend bewijs dat het sluiten van een RLS invloed heeft op de migraine aanvalsfrequentie.

Hebben de in migrainepatiënten aangetoonde hersenlesies functionele consequenties? Vanwege de hogere prevalentie van infarcten bij migraine specifiek in het cerebellum, hebben we in het CAMERA-cohort gekeken naar het cerebellair functioneren van de deelnemers door middel van een gedegen cerebellaire testbatterij (Koppen, Palm-Meinders et al. Cephalalgia 2017). De domeinen van fijne motoriek (Purdue Pegboard), ruimtelijk inzicht (block-design test), motorisch leren (prisma adaptatie test), geconditioneerde respons leren en executieve functie (eyeblink conditioning test) en balans (body-sway test) zijn geanalyseerd. Migraineurs en controles bleken vergelijkbaar te scoren op de cerebellaire testen. Degenen met een infarct in het cerebellum scoren ook hetzelfde, behalve dat ze de assembly taak van het pegboard minder goed doen (deze test fijne motoriek). Migrainepatinënten uit de gewone populatie scoren dus niet slechter dan deelnemers zonder migraine, ondanks dat ze een hoger risico hebben op cerebellaire lesies.

Witte stof afwijkingen zijn in het algemeen geassocieerd met een verminderd cognitief functioneren. Daarnaast hebben veel migrainepatiënten subjectieve cognitieve

klachten tijdens en vlak na een migraineaanval. Om die reden is het cognitief functioneren in het CAMERA-cohort onderzocht tijdens baseline en na 9 jaar follow-up, zoals beschreven in hoofdstuk 2. Cognitief functioneren bleek vergelijkbaar te zijn voor migrainepatiënten en controles. Bij follow-up was de aanwezigheid van diepe witte stof afwijkingen niet geassocieerd met cognitief functioneren en de aanwezigheid van migraine had geen invloed hierop. Deelnemers met een hoge lesie load tijdens baseline hadden ook geen sterkere achteruitgang van het cognitief functioneren in de 9 jaar follow-up periode dan degene die geen hoge load hadden op baseline.

Concluderend kunnen we zeggen dat migraine bij vrouwen geassocieerd is met een groter risico op hersenveranderingen en een grotere progressie van hersenlesies. De precieze onderliggende mechanismen zijn niet duidelijk, maar het lijkt erop dat er zowel aanvalsgerelateerde alsook meer chronische oorzaken een rol spelen. Hoewel migraine een hoger risico op hersenlesies met zich meebrengt, lijkt de aanwezigheid van deze lesies geen consequenties te hebben voor de migrainepatiënt voor wat betreft het cognitief of cerebellair functioneren. Daarmee is de boodschap van de bevindingen, zoals beschreven in dit proefschrift, geruststellend voor migrainepatiënten en hun artsen.

Chapter 9

Curriculum Vitae

Inge Palm-Meinders was born in Eindhoven on March 5th 1980. She graduated from the Eckart Pleincollege in Eindhoven, enrolled in Educational Science at the Leiden University in 1999 and started to study medicine at Leiden University in 2000. Between 2000 and 2005 she became involved in several research projects at the Faculty of Social Sciences as well as the Anatomical-Embryological Laboratory and also at the departments of Pathology and Radiology of the Leiden University Medical Center (LUMC). These research projects had various topics, e.g. evaluating the compliance of the two-year old child, examining pathology of 19th century skeletons, studying hypoxic-ischemic encephalopathy in neonates, and assessing wall shear stress in carotid arteries of elderly men and women. These projects resulted in several graduate theses and scientific publications. In 2004, Inge obtained her master's degree in medicine and in 2006 her medical degree.

After obtaining her medical degree, she enrolled in the PhD programme described in this thesis, under the supervision of Prof. M.A. van Buchem, Prof. M.D. Ferrari, Dr. M.C. Kruit, and Dr. G.W. Terwindt at the departments of Radiology and Neurology of the LUMC. The work described in this thesis was presented during several national and international scientific conferences. It received a number of awards, including 'Prof. Dr. Saxena Prize of best scientific publication in the headache field' and some 'Best Presentation' awards, for example awarded by the European Headache and Migraine Trust. Grants were received from the Netherlands Heart Foundation and the National Institutes of Health.

After moving to Maastricht in 2012, she continued to work on the CAMERA-study at the LUMC, while working at WVMConsult in Limburg in the field of occupational health medicine. Simultaneously she started to work at the Centra voor Integrale Revalidatie en Arbeidsactivering Nederland (CIRAN). In 2017, she was appointed as a physician in the Dutch Obesity Clinic (NOK). In the meantime, she married Miguel and her three sons were born: Laurens (2007), Valentijn (2011), and Koen (2015).

Chapter 10

List of publications

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