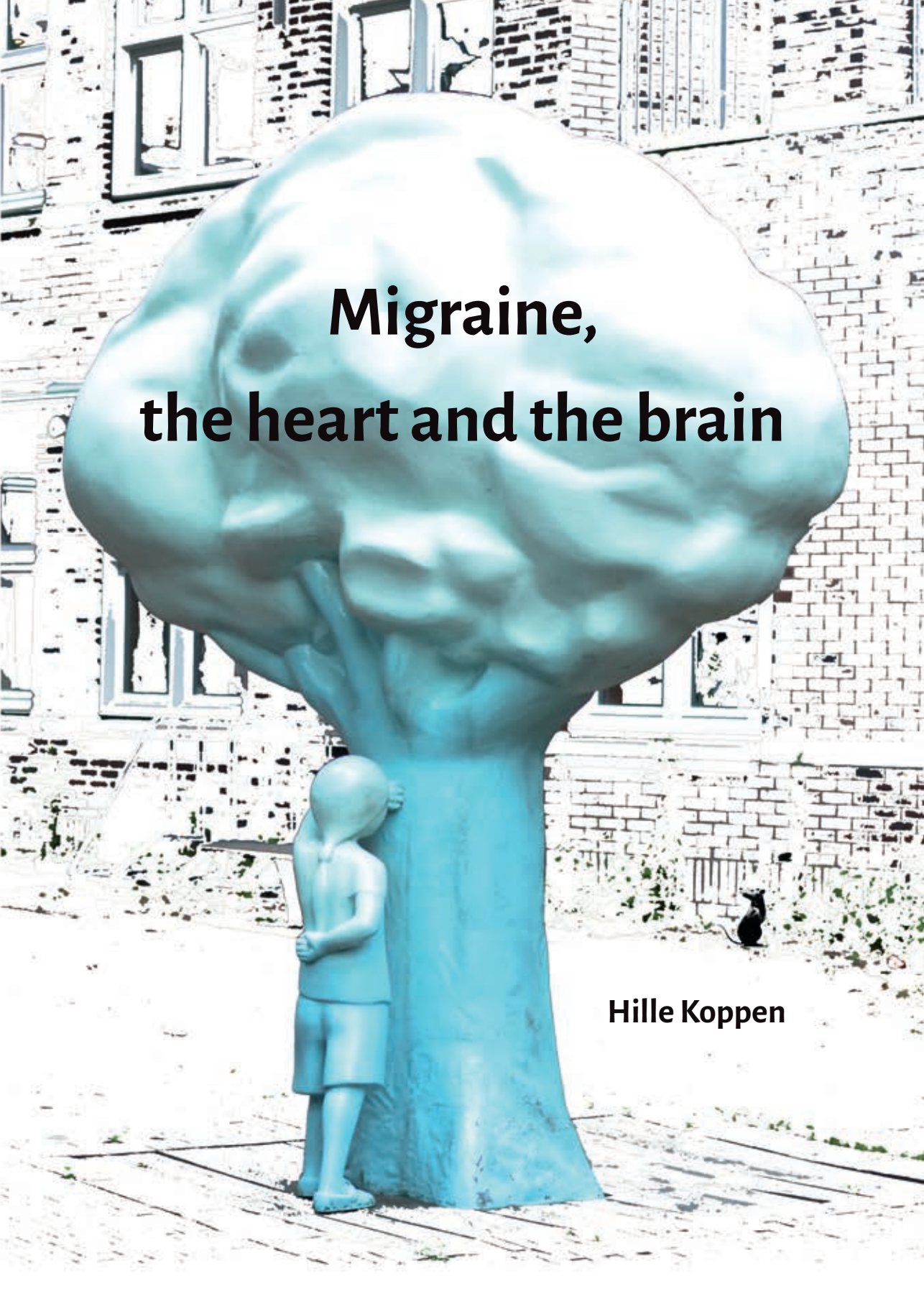

Migraine, the heart and the brain

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Content

Chapter 1

Introduction

What is migraine?

Migraine is a common, multifactorial, neurovascular brain disorder with great impact on patients. [1-3] The disease affects 12% of adults[4] and is characterized by attacks of severe headache accompanied by nausea, vomiting, and hypersensitivity to light and sound, for up to three days (migraine without aura).[5] In one-third of patients, attacks may be accompanied by transient neurological visual or sensory symptoms (migraine with aura).[5] The frequency of attacks differs among patients, from one each year to several per week. About 50% of the patients suffer attacks at least twice a month, 25% at least weekly,[6] and three percent suffer from migraine and headaches at least half the time.[3] On average, every day at least 24 million people in the Europe and the US together suffer from migraine. Consequently migraine worldwide ranks among the most disabling diseases.[7;8]

What is the relation between migraine and brain ischemia?

Already more than 25 years ago the relation between migraine and stroke was first hypothesized.[9] Migraine has been suggested to be an independent risk factor for both cerebral[10] and myocardial infarction.[11] A meta-analysis of 14 case-control studies showed an increased risk of ischemic stroke in both patients with migraine with and without aura. [12] The increased risk in migraine with aura (but not in migraine without aura) was also found in the large prospective Womens Health study. Nearly 28000 healthy women aged 45 years or older were followed for 10 years, and women who had active migraine with aura had an increased risk for ischemic stroke (OR 1.74, CI 1.23-2.46).[13] A later meta-analysis showed that the pooled relative risk of ischemic stroke among migraineurs (both with and without aura) was 1.7 (95% CI 1.3-2.3), however this risk was only in found women. The risk was highest in women below the age of 45.[14] The association between migraine and ischemic stroke is further supported by the occurrence of migrainous infarction (ischemic stroke in the same area of the brain coinciding or following a migraine aura), which is a rare complication of migraine. Migrainous infarction makes up 0.2 % of ischemic strokes, and the posterior circulation territory (PCT) is specifically affected.[15] The presence of a patent foramen ovale (to be discussed in the second part of this thesis) in patients with these migrainous infarctions was higher than in the general population.[15]

Not only clinical brain infarcts (that cause noticeable symptoms), but also silent brain infarcts (without any noticeable symptoms) have been associated with migraine.[16] Clinical imaging studies in migraine patients also suggested that the risk of silent white matter brain lesions (not stratified for deep or peri-ventricular location) was increased four times among migraineurs compared to controls. In this study gender or migraine subtype were not specified.[17] It is not known if clinical infarcts, silent infarcts and white matter lesions share the same pathophysiological mechanism. Because earlier studies had methodological limitations and were mostly clinic-based, likely investigating a more severe migraine phenotype, results could have been biased. An unbiased, population-based study, assessing the prevalence of silent infarcts and white matter brain lesions in a wide spectrum of migraine patients from the general population was required.

Background and outline of this thesis

To investigate the association between both silent infarcts, white matter lesions and migraine the Cerebral Abnormalities in Migraine, an Epidemiological Risk Analysis (CAMERA-I) study was performed from 1999-2000. For this study subjects with migraine and controls aged 30 to 60 years were randomly selected from the Genetic Epidemiology of Migraine (GEM) study. The GEM study was a large population study in the 90ths in two county population registries in the Netherlands to assess the prevalence of migraine.[6] Migraine patients were identified with a three-step procedure including a semi-structured interview by telephone. The lifetime prevalence of migraine in women was 33% and in men 13% and migraineurs suffered a median of 12 migraine attacks per year; 25% had at least two attacks per month. For the CAMERA-I study brain magnetic resonance imaging (MRI) was performed in 435 participants (134 patients with migraine without aura, 161 patients with migraine with aura, and 140 controls). The CAMERA-I study demonstrated a higher prevalence and greater volume of deep white matter hyperintensities, infratentorial hyperintensities, and posterior circulation territory infarcts in participants with migraine.[18;19] In migraineurs with a higher attack-rate, the risk of lesions was higher, which was found suggestive of a potential causal relationship. But, because this was a cross-sectional study no causal relationship could be established. The findings from the CAMERA-I study thus raised several questions;

1) Are the lesions a consequence of repeated migraine attacks? If so, does age at onset, duration of attacks or migraine subtype (with or without aura) influence the amount of these lesions?
2) Is there a causal relationship between migraine attacks and brain lesions or is the increased risk eg. due to increased co-morbidity of other risk factors for brain ischemia? For example are cardiac right-to-left shunts, which were more prevalent among migraineurs in clinical based studies, related to these brain lesions?
3) What are the consequences of ischemic brain lesions for migraine patients? Are these lesions associated with any functional impairment?

These questions asked for a longitudinal (population) based study and additional investigation of cause and consequences. Before coming to the aims of this thesis the current knowledge on these topics will be addressed in the following three paragraphs of this introduction.

I. Relation between migraine and ischemic brain lesions

Silent brain infarcts

The CAMERA-I study demonstrated that migraine subjects from the general population had significantly more often silent infarcts in the posterior circulation. This risk was increased more than seven times, notably in migraine with aura (Odds ratio (OR 12.9 (95% CI 1.6-101)), adjusted for age and sex.[18] In the original publication[18] the term "infarct-like lesions" was used, because we had no direct proof that the lesions were true infarcts. However based on a recent radiological-histological correlation-study we can now use the term "infarcts".[20] The large population based Reykjavik study confirmed the higher prevalence of posterior circulation infarcts among migraineurs by following 1996 men and 2693 women for 26 years and showing that migraine with aura in midlife was associated with late-life silent infarcts (OR 1.4, 95% CI 1.1-1.8), mainly in women. These silent infarcts were located more frequently in the cerebellum (OR 1.9, 95% CI 1.4-2.6) compared to women without headache.[21] In addition, in the population based Vascular Aging study, which included 780 subjects between 60-70 years of age, a history of migraine with aura was associated with silent brain infarcts (OR 3.4, 95%CI 1.2- 9.3).[22] In that study however, silent infarcts were predominantly located outside the cerebellum. Although these studies like the CAMERA-I study were population based, the MRI data was also only cross-sectional, so no causal relationship could be established.

Supratentorial deep white matter hyperintensities

White matter hyperintensities have been associated with migraine in several studies. A meta-analysis on data from case-control studies, in which patients with concomitant cardiovascular diseases had been excluded, indicated a fourfold increased risk of white matter abnormalities (periventricular and deep localization taken together) for migraine patients compared with controls.[17] The CAMERA-I study investigated white matter hyperintensities in migraine patients and controls and showed that women with migraine were two times more likely to have a high load of deep white matter hyperintensities (OR 2.1, 95% CI 1.0-4.1) independent of migraine subtype.[18] The risk was higher in those with higher attack frequency: in those with ≥1 attack/ per month (OR 2.6; 95% CI 1.2-5.7). Several years later, the Vascular Aging study confirmed this higher prevalence by indicating that migraineurs with aura more frequently had a high volume load of deep white matter hyperintensities (OR 12.4, 95% CI 1.6-99.4). The confidence interval however was wide, limiting the accuracy of the point estimate of this finding.[23]

Infratentorial hyperintense lesions

Infratentorial hyperintense lesions are high-signal areas found on T2-weighted brain MR scans in infratentorial brain structures (cerebellum and brainstem), but are not real parenchymal defects (so not infarcts). Only few studies have been reporting on infratentorial hyperintense lesions, therefore etiology and consequences of these lesions are uncertain. Both microvascular ischemic damage [24-25] and edema[26] have been suggested as an explanation of these lesions. The increased prevalence of infratentorial hyperintense lesions among patients with atherosclerosis,[26] hypertension,[27] diabetes mellitus,[28] chronic kidney disease,[28] cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)[29] and vascular dementia[24] all suggests that small vessel disease lies at the origin of infratentorial hyperintense lesions.

In the CAMERA-I study, infratentorial hyperintense lesions were identified in 13/295 (4.4%) subjects with migraine and in 1/140 (0.7%) controls (p=0.04). The majority of the cases (n=12) showed hyperintensities (mostly bilateral) in the pontine region of the brainstem.[30] Subjects with infratentorial hyperintense lesions more often also had supratentorial white matter lesions (p<0.05). Migraine type, attack frequency, age at onset, or treatment status did not differ between migraineurs with and without infratentorial hyperintense lesions.

The association between migraine and both silent infarcts and white matter lesions can be spurious (associations in which the association is actually caused by bias), causal (migraine as an independent risk for ischemia, or ischemia as a cause of migraine), or migraine and ischemia are connected by a confounder. This confounder may be a genetic factor, for example specific genes could predispose one to both suffering from migraine and cardiovascular disease. The occurrence of both migraine aura and ischemic strokes and deep white matter lesions due to a genetic cause is for example seen in patients with CADASIL. In CADASIL migraine with aura can be the first symptom, at a mean age of 30 years, whereas ischemic stroke and transient ischemic attacks occur at a mean age of 47 years.[31] Other confounders might be vascular anatomical variants which have been described more frequently in migraine with aura, like posterior circle of Willis anomalies[32] or right-to-left shunts.[33] These anatomical variant will be explained in more detail in part II of this introduction. The results of the CAMERA-II study, focusing on the relation between migraine and progression of ischemic brain lesions will be described in **Chapter II.**

In summary, the baseline part of the population-based CAMERA-study showed migraine to be associated with subclinical infarcts in the cerebellum as well as infra- and supratentorial T2 hyperintense lesions, the latter however only among females. Although an association between attack frequency and lesion load had been suggested, only a longitudinal design could further evaluate a cause-consequence relationship of this association. It is unknown whether migraine characteristics (aura, attack frequency, medication use) correlate with an increased lesion load over the years. This will be addressed in **Chapter II.** Furthermore, it was suggested that other comorbid conditions might play a role, such as the presence of a right-to-left shunt of the heart. This will be explained in detail in the following paragraph.

II. Migraine and the heart and its relation to ischemic brain lesions

Right-to-left shunts

Since 1998, several clinic based case-control studies have reported a two to three times increased prevalence of right-to-left shunts (RLS) in migraine with aura subjects compared to controls and subjects with migraine without aura.[33;36] A RLS is an abnormal communication between the systemic right (venous) circulation and

the left (arterial) circulation. Several structural abnormalities can cause right-to-left shunting. The most frequent cause is a patent foramen ovale (PFO),[37] a remnant from the fetal period located in the atrial septum of the heart. Other causes of RLS are actual defects of the cardiac septum (atrial septum defect, ASD) and pulmonary arteriovenous malformations (PAVM) or fistulas.[38] Most imaging studies that evaluated the presence of RLS in migraine patients, however, only aimed for detecting PFO or ASD but did not include the pulmonary causes. A systematic review reported that PFO was more prevalent in migraine with aura patients than in the general population. The reported pooled risk was increased more than two times (OR 2.54, 95%CI 2.01-3.08).[39] Following that study, two case-control studies evaluating PFO prevalence were published and found no increased PFO prevalence in migraine with aura.[40;41] Due to technical limitations (low sensitivity of trans-thoracic echo and short evaluation time) small PFOs could have been missed in these studies, which may be an explanation for a lower prevalence. Non-cardiac causes of RLS like PAVM generally are not detected with cardiac echography. No studies in migraineurs and controls have been done evaluating the prevalence of PAVM.

In healthy subjects 71% were found to have a RLS (38% had a PFO, 28% had a PAVM, 5% had evidence of both using trans-thoracic echo (TTE)[42] In this study, any appearance of left-sided heart micro-cavitations was considered positive for a RLS, which is the lowest threshold possible and explains the rather high prevalence of RLS. It was shown that patients with hereditary haemorragic teleangiectasia who had PAVM more frequent had migraine with aura compared to patients without PAVM.[43] The prevalence of migraine without aura was not increased in subjects with a PAVM.

To summarize, RLS detected by transcranial doppler was associated with migraine with aura in case-control studies.[33;36] More specific, PFO detected by cardiac echography was associated with migraine with aura[39] and PAVM patients more frequent had migraine with aura than subjects with no PAVM.[43] However, a population based study evaluating the presence of all types of RLS in migraineurs and non-migraine controls was lacking up to this moment. In **Chapter III,** I describe the prevalence of RLS in migraineurs and controls in a population based study. I hypothesized that RLS is more frequent in migraine with aura.

What are the pathophysiological explanations for the association between RLS and migraine?

One proposed mechanism was the transport through the RLS of venous blood constituents which are normally not (or at decreased levels) present in the arterial circulation. Such postulated constituents were venous (paradoxical) emboli and serotonin.[44] In a mice study it was shown that small particulate or air emboli injected into the carotid artery were able to evoke a cortical spreading depression (CSD) without causing ischemia, hereby linking emboli to migraine aura.[45] In a small open label study it was shown that 87% of migraine patients with RLS had a 50% or greater reduction in migraine frequency when using the emboli-preventing drug clopidogrel.[46] In **Chapter IV** a review is given of different causes of embolic material and its ability to cause migraine aura attacks.

Non-shunting cardiac abnormalities

Patients who underwent pulmonary vein ablation, during or after this procedure had a new onset of migraine, or an increase of migraine attack frequency.[47;48] During this procedure a catheter is placed in the left atrium and small scars are made locally. Emboli in the left (atrial) circulation, without the presence of a RLS, are thus associated with migraine in humans. Another example of a non-shunting disease is Marfan syndrome, a connective tissue disorder with aortic root dilatation as one of the major symptoms. In one study an association between Marfan syndrome and migraine with aura was reported.[49] However, conflicting case reports have been published with both new onset but also cessation of migraine with aura after interventional procedures of the aortic root.[50;51] We hypothesized that the presence of aortic root pathology in Marfan syndrome increases the prevalence of migraine. In **Chapter V** migraine prevalence in Marfan syndrome patients with and without aortic root pathology is described.

RLS and ischemic brain lesions

PFO, the most prevalent cause of RLS, has been associated with an increased risk of stroke in several studies in patients with stroke, specifically in young patients.[52;53] This however were studies not specific in migraine patients. Furthermore in ischemic stroke patients aged <45 years of age, those with RLS had a higher risk also to have migraine with aura.[54] Large population studies have shown that migraine with aura is associated with an increased risk for ischemic stroke (RLS status in subjects was not known).[10]

The remaining question to be answered is, if RLS explains (silent) infarcts in migraine. If that is true, one could think of a continuous spectrum with emboli triggered migraine aura attacks on one side and (sub-) clinical ischemic stroke on the other side. RLS enables emboli passing from the venous circulation to the brain, and consequences of emboli might be transient or permanent. Studies describing silent ischemic lesions and PFO or RLS are scarce, and did not show a relation between RLS and white matter lesions.[55;56] In **Chapter III** we describe RLS and its relation with silent infarcts in the CAMERA-II study.

Cardiac monitoring in high dose verapamil.

The heart can also be influenced by preventive medication as used for cluster headache or familial hemiplegic migraine. Treatment guidelines recommend verapamil in doses which usually exceed those generally used in cardiovascular disease. Although cardiac adverse events and EKG abnormalities are relatively common, evidence-based guidelines for screening and monitoring patients on high dose verapamil are lacking. Using the Delphi method we questioned clinical experts in cardiac rhythm disorders to formulate EKG guidelines for the pretreatment screening and monitoring of headache patients using high dose verapamil.(Chapter VI)

III. Migraine and brain function and impact of ischemic lesions on brain function of migraineurs

All previous studies on motor- and cognitive function in migraine patients were done without correlation with findings on MRI of the brain. Several studies indicated that migraineurs in between their attacks (interictally) have impaired cognitive functions like memory[57] executive function[58] and visual processing.[59] However other studies did not find cognitive impairment interictally.[60;61] Also interictal impaired cerebellar or balance function have been reported.[62-64] These studies were mostly clinic based and unblinded (i.e., investigators were aware of patient or control status), which are both regarded as important methodological limitations. Whether MRI findings in the brain, such as white matter lesions or silent infarcts influence cognition and other brain functions in migraineurs in unknown. Present knowledge on cognitive performance as well as motor function in migraineurs will be summarized. In addition, literature on white matter lesions and cognitive functions will be evaluated.

Migraine and inter-ictal cognitive function.

Studies comparing cognitive functioning of migraine patients in the interictal phase with controls are abundant but have shown inconsistent findings. One of the aims of this thesis was to investigate if migraine subjects had an impaired cognitive function compared to controls, and whether brain changes found with MRI in migraine subjects were associated with impaired cognitive function **(Chapter II)**

Migraine and impaired post-ictal cognitive function.

The CAMERA-study investigated cognitive function in migraine not related to an attack (inter-ictally). I investigated also specific post-ictal effects of the migraine attack, in a separate study. Many migraine patients report mild cognitive complaints, like slowing of reaction and memory problems, during both the ictal- and the post-ictal phase.[65;66] One study investigating after-effects of a migraine attack failed to find differences in cognitive function, even though patients did report subjective impairments.[66] The available findings suggest a number of candidate processes but a systematic model on the impact of migraine on human information processing is lacking. In **Chapter VIII** a number of theoretically motivated, well understood cognitive tasks are described, that allowed us to track most of the processing stream from perception over attention to working memory.

White matter hyperintensities and cognitive function and migraine

Several studies report a relation between the presence of white matter hyperintensities (WMH) and decreased cognitive function.[67;68] However, the presence of WMH among younger people is rare and therefore the number of studies on this subject among healthy, younger adults from the general population is limited. In our cohort of migraineurs and controls, we had the opportunity to evaluate the cognitive performance in younger, healthy participants from the general population and to assess whether there is an association with the presence of WMH (deep as well as periventricular). Furthermore, we were able to evaluate the role of having migraine on this association. **(Chapter II)**

Migraine and cerebellar function

Several studies showed that subclinical cerebellar ischemic lesions were more prevalent in migraineurs than controls.[18;69] Furthermore impaired cerebellar functions were reported in migraineurs in other studies.[62;70;71] So far, direct comparison between these ischemic lesions and functional cerebellar outcomes in migraineurs was lacking.

In **Chapter VII** cerebellar function is evaluated with five separate validated tests and outcomes are correlated with MRI imaging of the cerebellum.

Aims of this thesis

Aim of this thesis was to investigate the progression of ischemic brain lesions in the CAMERA cohort over a time-period of 9 years follow up and to relate this to migraine characteristics. The main question was if in migraine patients more progression of these lesions occurred, and secondly if repeated migraine attacks were associated with more progression? (Part I, chapter II)

The second aim was to study the association of right-to-left shunts with migraine. (Part II, chapter III and IV). Chapter III describes the prevalence of RLS among migraineurs and controls, and whether the presence of these shunts is associated with ischemic brain lesions in migraineurs. Chapter IV gives an overview of different embolic materials passing a RLS which has been associated with migraine attacks. In Chapter V the presence of migraine in Marfan patients is investigated and specific the contribution from aortic root abnormalities.

The third aim was to assess a broad range of brain functions in migraineurs and controls and evaluate whether there is an association with the demonstrated structural brain changes.(Part I Chapter II **and** Part III, Chapter VII). In this part also the effect on cognitive functions investigated shortly after a migraine attack (Chapter VIII).

In Chapter IX the results of all the studies are summarized and future perspectives are discussed.

Reference List

1 Goadsby PJ, Lipton RB, Ferrari MD. Migraine--current understanding and treatment. *N Engl J Med* 2002;346:257-270.

2 Terwindt GM, Ferrari MD, Tijhuis M, Groenen SM, Picavet HS, Launer LJ. The impact of migraine on quality of life in the general population: the GEM study. *Neurology* 2000;55:624-629.

3 Diener HC, Dodick DW, Goadsby PJ, Lipton RB, Olesen J, Silberstein SD. Chronic migraine--classification, characteristics and treatment. *Nat Rev Neurol* 2011;8:162-171.

4 Rasmussen BK. Epidemiology of headache. *Cephalalgia* 2001;21:774-777.

5 The International Classification of Headache Disorders, 3rd edition (beta version). *Cephalalgia* 2013;33:629-808.

6 Launer LJ, Terwindt GM, Ferrari MD. The prevalence and characteristics of migraine in a population-based cohort: the GEM study. *Neurology* 1999;53:537-542.

7 Jensen R, Stovner LJ. Epidemiology and comorbidity of headache. *Lancet Neurol* 2008;7:354-361.

8 Vos T, Flaxman AD, Naghavi M et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012;380:2163-2196.

9 Benson MD, Rebar RW. Relationship of migraine headache and stroke to oral contraceptive use. *J Reprod Med* 1986;31:1082-1088.

10 Kurth T, Chabriat H, Bousser MG. Migraine and stroke: a complex association with clinical implications. *Lancet Neurol* 2012;11:92-100.

11 Bigal ME, Kurth T, Santanello N et al. Migraine and cardiovascular disease: a population-based study. *Neurology* 2010;74:628-635.

12 Etminan M, Takkouche B, Isorna FC, Samii A. Risk of ischaemic stroke in people with migraine: systematic review and meta-analysis of observational studies. *Bmj* 2005;330:63.

13 Kurth T, Gaziano JM, Cook NR, Logroscino G, Diener HC, Buring JE. Migraine and risk of cardiovascular disease in women. *Jama* 2006;296:283-291.

14 Schurks M, Rist PM, Bigal ME, Buring JE, Lipton RB, Kurth T. Migraine and cardiovascular disease: systematic review and meta-analysis. *Bmj* 2009;339:b3914.

15 Wolf ME, Szabo K, Griebe M et al. Clinical and MRI characteristics of acute migrainous infarction. *Neurology* 2011;76:1911-1917.

16 Pavese N, Canapicchi R, Nuti A et al. White matter MRI hyperintensities in a hundred and twenty-nine consecutive migraine patients. *Cephalalgia* 1994;14:342-345.

17 Swartz RH, Kern RZ. Migraine is associated with magnetic resonance imaging white matter abnormalities: a meta-analysis. *Arch Neurol* 2004;61:1366-1368.

18 Kruit MC, van Buchem MA, Hofman PA et al. Migraine as a risk factor for subclinical brain lesions. *Jama* 2004;291:427-434.

19 Kruit MC, Launer LJ, Ferrari MD, van Buchem MA. Infarcts in the posterior circulation territory in migraine. The population-based MRI CAMERA study. *Brain* 2005;128:2068-2077.

20 De Cocker LJ, van Veluw SJ, Biessels GJ et al. Ischaemic cavities in the cerebellum: an ex vivo 7-tesla MRI study with pathological correlation. *Cerebrovasc Dis* 2014;38:17-23.

21 Scher AI, Gudmundsson LS, Sigurdsson S et al. Migraine headache in middle age and late-life brain infarcts. *Jama* 2009;301:2563-2570.

22 Kurth T, Mohamed S, Maillard P et al. Headache, migraine, and structural brain lesions and function: population based Epidemiology of Vascular Ageing-MRI study. *Bmj* 2011;342:c7357.

23 Kurth T, Mohamed S, Maillard P et al. Headache, migraine, and structural brain lesions and function: population based Epidemiology of Vascular Ageing-MRI study. *Bmj* 2011;342:c7357.

24 Bastos Leite AJ, van der Flier WM, van Straaten EC, Scheltens P, Barkhof F. Infratentorial abnormalities in vascular dementia. *Stroke* 2006;37:105-110.

25 Tortorella P, Rocca MA, Colombo B, Annovazzi P, Comi G, Filippi M. Assessment of MRI abnormalities of the brainstem from patients with migraine and multiple sclerosis. *J Neurol Sci* 2006;244:137-141.

26 Kwa VI, Stam J, Blok LM, Verbeeten B, Jr. T2-weighted hyperintense MRI lesions in the pons in patients with atherosclerosis. Amsterdam Vascular Medicine Group. *Stroke* 1997;28:1357-1360.

27 de Seze J, Mastain B, Stojkovic T et al. Unusual MR findings of the brain stem in arterial hypertension. *AJNR Am J Neuroradiol* 2000;21:391-394.

28 Ichikawa H, Takahashi N, Mukai M, Akizawa T, Kawamura M. Asymptomatic large T2 high-signal pontine lesions that are different from ischemic rarefaction. *J Stroke Cerebrovasc Dis* 2008;17:394-400.

29 Chabriat H, Mrissa R, Levy C et al. Brain stem MRI signal abnormalities in CADASIL. *Stroke* 1999;30:457-459.

30 Kruit MC, Launer LJ, Ferrari MD, van Buchem MA. Brain stem and cerebellar hyperintense lesions in migraine. *Stroke* 2006;37:1109-1112.

31 Dichgans M, Mayer M, Uttner I et al. The phenotypic spectrum of CADASIL: clinical findings in 102 cases. *Ann Neurol* 1998;44:731-739.

32 Cavestro C, Richetta L, L'episcopo MR, Pedemonte E, Duca S, Di PC. Anatomical variants of the circle of willis and brain lesions in migraineurs. *Can J Neurol Sci* 2011;38:494-499.

33 Anzola GP, Magoni M, Guindani M, Rozzini L, Dalla VG. Potential source of cerebral embolism in migraine with aura: a transcranial Doppler study. *Neurology* 1999;52:1622-1625.

34 Welch KM, Nagesh V, Aurora SK, Gelman N. Periaqueductal gray matter dysfunction in migraine: cause or the burden of illness? *Headache* 2001;41:629-637.

35 d'Onofrio F, Barbanti P, Petretta V et al. Migraine and movement disorders. *Neurol Sci* 2012;33 Suppl 1:S55-S59.

36 Tembl J, Lago A, Sevilla T, Solis P, Vilchez J. Migraine, patent foramen ovale and migraine triggers. *J Headache Pain* 2007;8:7-12.

37 Sarisoy S, Aydin OF, Sungur M et al. The relationship between migraine and right-to-left shunt in children. *Eur J Pediatr* 2011;170:365-370.

38 Pejhan S, Rahmanijoo N, Farzanegan R, Rahimi M. Surgically Treatable Pulmonary Arteriovenous Fistula. *Ann Thorac Cardiovasc Surg* 2011.

39 Schwedt TJ, Demaerschalk BM, Dodick DW. Patent foramen ovale and migraine: a quantitative systematic review. *Cephalalgia* 2008;28:531-540.

40 Rundek T, Elkind MS, Di Tullio MR et al. Patent foramen ovale and migraine: a cross-sectional study from the Northern Manhattan Study (NOMAS). *Circulation* 2008;118:1419-1424.

41 Garg P, Servoss SJ, Wu JC et al. Lack of association between migraine headache and patent foramen ovale: results of a case-control study. *Circulation* 2010;121:1406-1412.

42 Woods TD, Harmann L, Purath T et al. Small- and moderate-size right-to-left shunts identified by saline contrast echocardiography are normal and unrelated to migraine headache. *Chest* 2010;138:264-269.

43 Post MC, van Gent MW, Plokker HW et al. Pulmonary arteriovenous malformations associated with migraine with aura. *Eur Respir J* 2009;34:882-887.

44 Wilmshurst P, Nightingale S. Relationship between migraine and cardiac and pulmonary right-to-left shunts. *Clin Sci (Colch)* 2001;100:215-220.

45 Nozari A, Dilekoz E, Sukhotinsky I et al. Microemboli may link spreading depression, migraine aura, and patent foramen ovale. *Ann Neurol* 2010;67:221-229.

46 Spencer BT, Qureshi Y, Sommer RJ. A retrospective review of clopidogrel as primary therapy for migraineurs with right to left shunt lesions. *Cephalalgia* 2014;34:933-937.

47 Jordaens L, Janse P, Szili-Torok T, Van BY. Migraine accompagnee after transseptal puncture. *Neth Heart J* 2010;18:374-375.

48 Noheria A, Roshan J, Kapa S, Srivathsan K, Packer DL, Asirvatham SJ. Migraine headaches following catheter ablation for atrial fibrillation. *J Interv Card Electrophysiol* 2011;30:227-232.

49 Knudsen S, Russell MB. Increased risk of migraine in Marfan's syndrome? *Acta Neurol Scand* 2006;114:281-286.

50 Staals JE, Braun KP, van Loo-Maurus KE, Vles JS. Stenting for coarctation of the aorta precipitating migraine with aura. *J Child Neurol* 2007;22:321-323.

51 Shahar E, Borenstein A, Filk D. Severe migraine associated with coarctation of aorta: complete recovery following balloon dilation. *J Child Neurol* 2000;15:826-827.

52 Serena J, Jimenez-Nieto M, Silva Y, Castellanos M. Patent foramen ovale in cerebral infarction. *Curr Cardiol Rev* 2010;6:162-174.

53 Overell JR, Bone I, Lees KR. Interatrial septal abnormalities and stroke: a meta-analysis of case-control studies. *Neurology* 2000;55:1172-1179.

54 Pezzini A, Grassi M, Lodigiani C et al. Predictors of migraine subtypes in young adults with ischemic stroke: the italian project on stroke in young adults. *Stroke* 2011;42:17-21.

55 Adami A, Rossato G, Cerini R et al. Right-to-left shunt does not increase white matter lesion load in migraine with aura patients. *Neurology* 2008;71:101-107.

56 Dinia L, Bonzano L, Albano B et al. White matter lesions progression in migraine with aura: a clinical and MRI longitudinal study. *J Neuroimaging* 2013;23:47-52.

57 Le Pira F, Zappala G, Giuffrida S et al. Memory disturbances in migraine with and without aura: a strategy problem? *Cephalalgia* 2000;20:475-478.

58 Camarda C, Monastero R, Pipia C, Recca D, Camarda R. Interictal executive dysfunction in migraineurs without aura: relationship with duration and intensity of attacks. *Cephalalgia* 2007;27:1094-1100.

59 Coleston DM, Chronicle E, Ruddock KH, Kennard C. Precortical dysfunction of spatial and temporal visual processing in migraine. *J Neurol Neurosurg Psychiatry* 1994;57:1208-1211.

60 Gaist D, Pedersen L, Madsen C et al. Long-term effects of migraine on cognitive function: a population-based study of Danish twins. *Neurology* 2005;64:600-607.

61 Pearson AJ, Chronicle EP, Maylor EA, Bruce LA. Cognitive function is not impaired in people with a long history of migraine: a blinded study. *Cephalalgia* 2006;26:74-80.

62 Sandor PS, Mascia A, Seidel L, De P, V, Schoenen J. Subclinical cerebellar impairment in the common types of migraine: a three-dimensional analysis of reaching movements. *Ann Neurol* 2001;49:668-672.

63 Teggi R, Colombo B, Bernasconi L, Bellini C, Comi G, Bussi M. Migrainous vertigo: results of caloric testing and stabilometric findings. *Headache* 2009;49:435-444.

64 Akdal G, Balci BD, Angin S, Ozturk V, Halmagyi GM. A longitudinal study of balance in migraineurs. *Acta Otolaryngol* 2012;132:27-32.

65 Calandre EP, Bembibre J, Arnedo ML, Becerra D. Cognitive disturbances and regional cerebral blood flow abnormalities in migraine patients: their relationship with the clinical manifestations of the illness. *Cephalalgia* 2002;22:291-302.

66 Mulder EJ, Linssen WH, Passchier J, Orlebeke JF, de Geus EJ. Interictal and postictal cognitive changes in migraine. *Cephalalgia* 1999;19:557-565.

67 Prins ND, van Dijk EJ, den Heijer T et al. Cerebral small-vessel disease and decline in information processing speed, executive function and memory. *Brain* 2005;128:2034-2041.

68 van den Heuvel DM, Ten Dam VH, de Craen AJ et al. Increase in periventricular white matter hyperintensities parallels decline in mental processing speed in a non-demented elderly population. *J Neurol Neurosurg Psychiatry* 2006;77:149-153.

69 Scher AI, Gudmundsson LS, Sigurdsson S et al. Migraine headache in middle age and late-life brain infarcts. *Jama* 2009;301:2563-2570.

70 Gerwig M, Rauschen L, Gaul C, Katsarava Z, Timmann D. Subclinical cerebellar dysfunction in patients with migraine: Evidence from eyeblink conditioning. *Cephalalgia* 2014.

71 Akdal G, Balci BD, Angin S, Ozturk V, Halmagyi GM. A longitudinal study of balance in migraineurs. *Acta Otolaryngol* 2012;132:27-32.

Part 1

Migraine and brain imaging

Chapter 2

Structural Brain Changes in Migraine

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Abstract

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 nonhigh 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

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]

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 (eg, 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 assesed by 1 rater, who was blinded to 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[17] which is a modified version of the Symbol Digit Modalities Test[18]; 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).

***e*Table 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.

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.

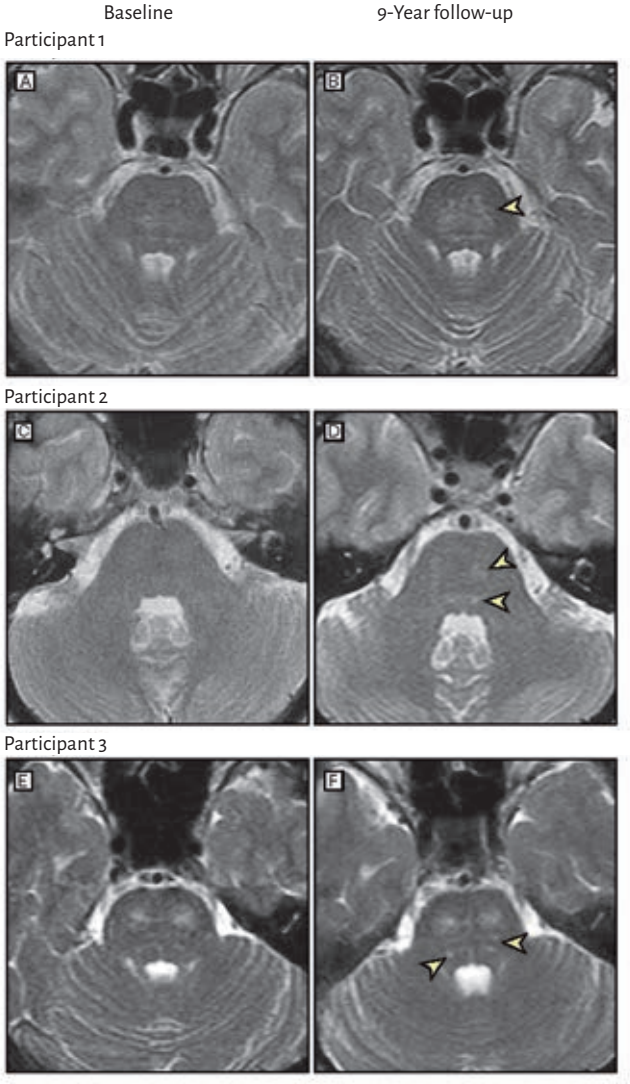

Figure 1. Brain Magnetic Resonance T2-Weighted Images at Baseline and Follow-up From 3 Representative Participants Showing Progression of Infratentorial Hyperintensities

Image B shows pontine hyperintensity (arrow head) 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).

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 packyears (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 semiquantitative 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).

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)

Table 1. continued

Characteristic	Total (n = 286)	Controls (n = 83)	Migraine (n = 203)	Migraine	
				No Aura (n = 89)	Aura (n = 114)
Alcohol use					
None during last 12 months	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 years	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

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).

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.

***e*Table 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 ≥ 29 yrs	1.8 [0.6-4.9] 1.2 [0.4-3.3]	P=.3	2.9 [1.3-6.7] 1.5 [0.7-3.2]	P=.06	3.3 [1.0-9.9] 1.6 [0.5-5.0]	P=.08	11.2 [1.4-90.1] 4.9 [0.6-41.8]	P=.1
low 25% high 25%	0.5 [0.1-1.6] 0.7 [0.3-2.0]	P=.8	0.9 [0.3-2.4] 0.3 [0.1-1.0]	P=.04	0.7 [0.2-2.2] 0.6 [0.2-1.8]	P=.5	2.1 [0.7-6.4] 0.5 [0.1-1.9]	P=.2
median (IQR) of those with lesions median (IQR) of those without	23 (11-39) 20 (0-34)	P*=.2	22 (7-34) 15 (0-36)	P*=.1	23 (16-38) 20 (0-34)	P*=.1	24 (15-37) 20 (0-34)	P*=.2
Migraine subtype								
without aura with aura	1.8 [0.7-5.1] 1.2 [0.4-3.2]	P=.3	2.9 [1.2-6.7] 1.7 [0.8-3.5]	P=.2	3.3 [1.1-9.9] 1.6 [0.5-5.0]	P=.1	11.5 [1.4-92.9] 5.0 [0.6-41.7]	P=.1
Number of headache attacks								
<median (lifetime) ≥median (lifetime)	1.7 [0.6-4.7] 1.3 [0.5-3.5]	P=.5	1.9 [0.9-4.2] 2.2 [1.0-4.9]	P=.9	2.8 [0.9-8.7] 1.9 [0.6-5.8]	P=.4	8.9 [1.1-73.3] 6.7 [0.8-55.0]	P=.5
median (IQR) of those with lesions median (IQR) of those without	271 (107-646) 264 (168-480)	P*=.9	274 (123-575) 252 (174-353)	P*=.4	263 (105-581) 274 (173-496)	P*=.6	284 (100-923) 264 (159-496)	P*=.9
<median (FU only) ≥median (FU only)	1.9 [0.7-5.5] 1.2 [0.4-3.3]	P=.3	2.1 [0.9-4.7] 2.2 [1.0-4.5]	P=.8	3.2 [1.0-9.9] 1.9 [0.6-5.6]	P=.2	12.3 [1.5-101.5] 5.3 [0.6-43.8]	P=.1
Mean attacks per month, median (IQR) of those with lesions of those without lesions	 0.7 (0.4-1.9) 0.9 (0.5-1.5)	P*=.7	 1.0 (0.5-1.6) 0.6 (0.4-1.0)	P*=.09	 0.8 (0.4-1.8) 0.9 (0.5-1.5)	P*=.8	 0.8 (0.5-2.2) 0.9 (0.4-1.5)	P*=.6
Headache activity status								
inactive at baseline active at baseline	3.4 [1.1-10.7] 1.1 [0.4-2.8]	P=.03	3.1 [1.0-9.5] 1.9 [0.9-3.8]	P=.4	5.3 [1.5-18.1] 1.7 [0.6-5.1]	P=.03	10.2 [1.1-93.1] 7.0 [0.9-55.6]	P=.6
inactive during 9 year FU active during 9 year FU	1.8 [0.6-5.0] 1.2 [0.4-3.4]	P=.5	2.9 [1.0-5.4] 1.9 [0.9-4.1]	P=.9	2.6 [0.8-8.1] 2.1 [0.7-6.3]	P=.7	5.7 [0.7-47.4] 10.6 [1.3-87.0]	P=.2

***e*Table 2.** continued

	High DWMH load at FU		Progression of DWMH load		High progression of DWMH load		Progression of IH	
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

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

	Controls (n = 83)	Migraine (n = 203)		Migraine Headache		
			P Value[A]	Without Aura (n = 89)	With Aura (n = 114)	*P* Value[A]
Deep white matter hyperintensities						
Men, No. (%)	26 (31)	58 (29)	.67	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

Table 2. continued

	Controls (n = 83)	Migraine (n = 203)		Migraine Headache		
			P Value[A]	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[13]	1 (4)	5(9)	.66	2(8)	3(9)	>.99
Women Prevalence	2(4)	30 (21)	.002	18 (28)	12(15)	.06
Progression[13]	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 (nonposterior 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. k 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 infractlike 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 Prevalence, No. (%)	2(4)	30 (21)		18 (28)	12(15)	
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).

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.

***e*Table 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]

Legends:
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

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 semiquantitative baseline reading of deep white matter hyperintensities and the current quantitative volume measurements that were not available for the nonresponders, 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.

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.

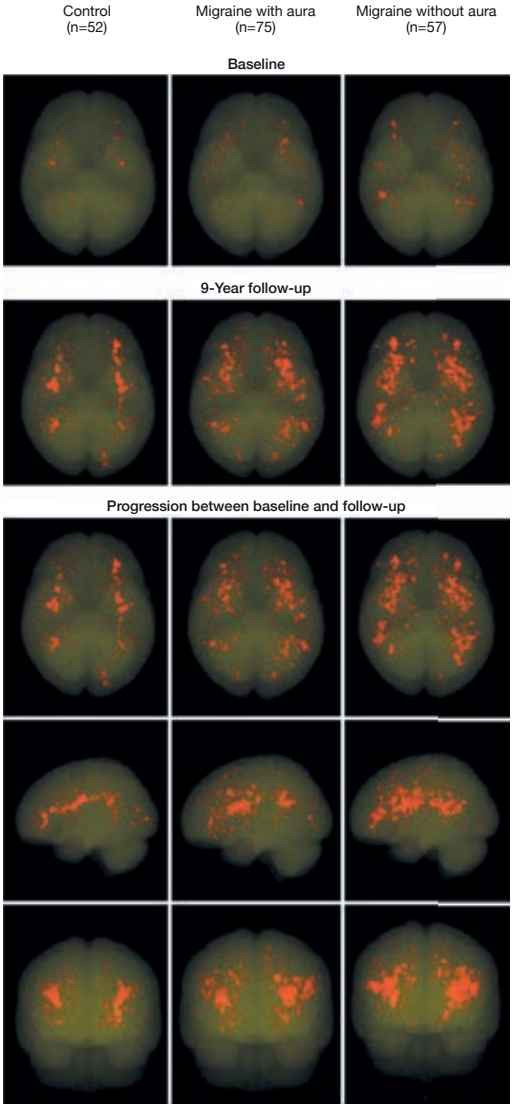

Figure 2. Geographical Location of All Individual Deep White Matter Hyperintensities Projected on Transparent 3-Dimensional Maps After Normalization of the Individual Magnetic Resonance Scans With Segmented Lesions to Standard Montreal Neurological Institute Space

The upper two rows display hyperintensities per study group at baseline and follow-up separately; the lower rows show the difference (ie, 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.

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References

1 Launer LJ, Terwindt GM, Ferrari MD. The prevalence and characteristics of migraine in a populationbased cohort: the GEM study. *Neurology*. 1999; 53(3):537-542.

2 Ferrari MD. Migraine. *Lancet*. 1998;351(9108): 1043-1051.

3 Headache Classification Committee of the International Headache Society. Classification and diagnostic criteria for headache disorders, cranial neuralgias and facial pain. *Cephalalgia*. 1988;8(suppl 7): 1-96.

4 Kruit MC, van Buchem MA, Hofman PA, et al. Migraine as a risk factor for subclinical brain lesions. *JAMA*. 2004;291(4):427-434.

5 Kruit MC, Launer LJ, Ferrari MD, van Buchem MA. Infarcts in the posterior circulation territory in migraine: the population-based MRI CAMERA study. *Brain*. 2005;128(Pt 9):2068-2077.

6 Kruit MC, Launer LJ, Ferrari MD, van Buchem MA. Brain stem and cerebellar hyperintense lesions in migraine. *Stroke*. 2006;37(4):1109-1112.

7 Kurth T, Mohamed S, Maillard P, et al. Headache, migraine, and structural brain lesions and function: population based Epidemiology of Vascular AgeingMRI study. *BMJ*. 2011;342:c7357.

8 Scher AI, Gudmundsson LS, Sigurdsson S, et al. Migraine headache in middle age and late-life brain infarcts. *JAMA*. 2009;301(24):2563-2570.

9 Dufouil C, de Kersaint-Gilly A, Besanc¸ on V, et al. Longitudinal study of blood pressure and white matter hyperintensities: the EVA MRI Cohort. *Neurology*. 2001;56(7):921-926.

10 Debette S, Markus HS. The clinical importance of white matter hyperintensities on brain magnetic resonance imaging: systematic review and meta-analysis. *BMJ*. 2010;341:c3666.

11 Buyck JF, Dufouil C, Mazoyer B, et al. Cerebral white matter lesions are associated with the risk of stroke but not with other vascular events: the 3-City Dijon Study. *Stroke*. 2009;40(7):2327-2331.

12 Vermeer SE, Hollander M, van Dijk EJ, Hofman A, Koudstaal PJ, Breteler MM; Rotterdam Scan Study. Silent brain infarcts and white matter lesions increase stroke risk in the general population: the Rotterdam Scan Study. *Stroke*. 2003;34(5):1126-1129.

13 van der Flier WM, van Straaten EC, Barkhof F, et al. Small vessel disease and general cognitive function in nondisabled elderly: the LADIS study. *Stroke*. 2005; 36(10):2116-2120.

14 Schürks M, Rist PM, Bigal ME, Buring JE, Lipton RB, Kurth T. Migraine and cardiovascular disease: systematic review and meta-analysis. *BMJ*. 2009; 339:b3914.

15 Rey A. *L'examin Clinique en Psychologie.* Paris, France: Presses Universitaires de France; 1985.

16 Stroop J. Studies of interference in serial verbal reactions. *J Exp Psychol*. 1935;18:643-662.

17 Miller E. Verbal fluency as a function of a measure of verbal intelligence and in relation to different types of cerebral pathology. *Br J Clin Psychol*. 1984; 23(pt 1):53-57.

18 Van der Elst W, Van Boxtel MP, Van Breukelen GJ, Jolles J. Normative data for the Animal, Profession and Letter M Naming verbal fluency tests for Dutch speaking participants and the effects of age, education, and sex. *J Int Neuropsychol Soc*. 2006;12(1):80-89.

19 Tiffin J, Asher EJ. The Purdue pegboard; norms and studies of reliability and validity. *J Appl Psychol*. 1948;32(3):234-247.

20 Wechsler D. *Manual for the Wechsler Adult Intelligence Scale-Revised*. New York, NY: Psychological Corp; 1981.

21 Kurth T, Diener HC. Current views of the risk of stroke for migraine with and migraine without aura. *Curr Pain Headache Rep*. 2006;10(3):214-220.

22 Wolf ME, Szabo K, Griebe M, et al. Clinical and MRI characteristics of acute migrainous infarction. *Neurology*. 2011;76(22):1911-1917.

23 Bigal ME, Kurth T, Santanello N, et al. Migraine and cardiovascular disease: a population-based study. *Neurology*. 2010;74(8):628-635.

24 Lee ST, Chu K, Jung KH, et al. Decreased number and function of endothelial progenitor cells in patients with migraine. *Neurology*. 2008;70(17): 1510-1517.

25 Tietjen GE, Herial NA, White L, Utley C, Kosmyna JM, Khuder SA. Migraine and biomarkers of endothelial activation in young women. *Stroke*. 2009; 40(9):2977-2982.

26 Schürks M, Rist PM, Kurth T. MTHFR 677C>T and ACE D/I polymorphisms in migraine: a systematic review and meta-analysis. *Headache*. 2010;50(4):588-599.

27 Scher AI, Terwindt GM, Verschuren WM, et al. Migraine and MTHFR C677T genotype in a populationbased sample. *Ann Neurol*. 2006;59(2):372-375.

28 Schwedt TJ, Demaerschalk BM, Dodick DW. Patent foramen ovale and migraine: a quantitative systematic review. *Cephalalgia*. 2008;28(5):531-540.

29 Longstreth WT Jr, Manolio TA, Arnold A, et al. Clinical correlates of white matter findings on cranial magnetic resonance imaging of 3301 elderly people. The Cardiovascular Health Study. *Stroke*. 1996; 27(8):1274-1282.

30 Prins ND, van Dijk EJ, den Heijer T, et al. Cerebral small-vessel disease and decline in information processing speed, executive function and memory. *Brain*. 2005;128(Pt 9):2034-2041.

31 Le Pira F, Lanaia F, Zappalà G, et al. Relationship between clinical variables and cognitive performances in migraineurs with and without aura. *Funct Neurol*. 2004;19(2):101-105.

32. Meyer JS, Thornby J, Crawford K, Rauch GM. Reversible cognitive decline accompanies migraine and cluster headaches. *Headache*. 2000;40(8):638-646.

33 Mulder EJ, Linssen WH, Passchier J, Orlebeke JF, de Geus EJ. Interictal and postictal cognitive changes in migraine. *Cephalalgia*. 1999;19(6):557-565, discussion 541.

34 Waldie KE, Hausmann M, Milne BJ, Poulton R. Migraine and cognitive function: a life-course study. *Neurology*. 2002;59(6):904-908.

35 O'Bryant SE, Marcus DA, Rains JC, Penzien DB. The neuropsychology of recurrent headache. *Headache*. 2006;46(9):1364-1376.

Part 2

Migraine and the heart

Chapter 3

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.

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 (= 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.

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 analyzed 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 1 Characteristics of study participants

				Migraine	
Characteristics	Total (n = 235)	Controls (n = 69)	Migraine (n = 166)	Aura (n = 96)	No aura (n = 70)
Age, y, mean (SD)	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 TIA[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)

Table 1 Continued

Characteristics	Total (n = 235)	Controls (n = 69)	Migraine (n = 166)	Migraine: Aura (n = 96)	Migraine: No aura (n = 70)
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 (0)	2 (2)	2 (3)	0 (0)
Hormonal substitution	3 (2)	1 (2)	2 (2)	2 (3)	0 (0)
ß-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 (0)
Migraine, y, mean (SD)	NA	NA	30 (12)	32 (12)	27 (12)[d]
Age at migraine onset, y, mean (SD)	NA	NA	22 (12)	21 (11)	22 (11)
Mean attack frequency per year	NA	NA	17 (22)	15 (24)	19 (21)
Ongoing recurrence of attacks	NA	NA	101 (61)	68 (71)	33 (47)

Abbreviations: ACE=angiotensin-converting enzyme; BM=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; $p = 0.01$.

Table 2 Prevalence of right-to-left shunt types

Right-to-left shunt	Controls (n = 69)	Migraine with aura (n = 96)	Migraine without aura (n = 70)	*p* Value (controls vs MA)	*p* Value (controls vs MO)	*p* Value (MA vs MO)
Spontaneous, n (%)	18 (26)	34 (35)	12 (17)	0.2	0.2	0.01
Small	7 (10)	16 (17)	11 (16)	0.2	0.3	0.9
Large	11 (16)	18 (19)	1 (1)	0.6	0.02	0.001
Total after provocation, n (%)	29 (42)	58 (60)	28 (40)	0.02	0.8	0.01
Small	10 (15)	15 (16)	14 (20)	0.8	0.4	0.5
Large	19 (28)	43 (45)	14 (20)	0.03	0.3	0.01

Abbreviations: MA=migraine with aura; MO=migraine without aura. Small shunt defined as passage of 1–9 microbubbles. Large shunt defined as passage of at least 10 microbubbles.

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 (%). Unless indicated otherwise, differences were not significant (p>0.05).
[a] p<0.05.

Table 4 and table e-1 also 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 subtype of right-to-left shunt

	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 silent brain infarct	23 (14)	7 (11)	0.6	13 (11)	17 (15)	0.3
Multiple silent brain infarcts	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 lesions	31 (19)	13 (21)	0.7	20 (17)	24 (22)	4

Abbreviation: RLS=right-to left shunts
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 lesions defined as upper 20th percentile. Data are expressed as n (%).
a p Value: no spontaneous RLS vs spontaneous RLS.
b p Value: no RLS vs RLS.

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.

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 clinicbased 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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References

1 Bigal ME, Kurth T, Santanello N, et al. Migraine and cardiovascular disease: a population-based study. Neurology 2010;74:628–635.

2 Kruit MC, van Buchem MA, Hofman PA, et al. Migraine as a risk factor for subclinical brain lesions. JAMA 2004; 291:427–434.

3 Palm-Meinders IH, Koppen H, Terwindt GM, et al. Structural brain changes in migraine. JAMA 2012;308: 1889–1897.

4 Anzola GP, Magoni M, Guindani M, Rozzini L, Dalla VG. Potential source of cerebral embolism in migraine with aura: a transcranial Doppler study. Neurology 1999; 52:1622–1625.

5 Scher AI, Gudmundsson LS, Sigurdsson S, et al. Migraine headache in middle age and late-life brain infarcts. JAMA 2009;301:2563–2570.

6 Del SM, Angeli S, Leandri M, et al. Migraine with aura and right-to-left shunt on transcranial Doppler: a casecontrol study. Cerebrovasc Dis 1998;8:327–330.

7 Kurth T, Schurks M, Logroscino G, Gaziano JM, Buring JE. Migraine, vascular risk, and cardiovascular events in women: prospective cohort study. BMJ 2008; 337:a636.

8 Cabanes L, Mas JL, Cohen A, et al. Atrial septal aneurysm and patent foramen ovale as risk factors for cryptogenic stroke in patients less than =5 years of age: a study using transesophageal echocardiography. Stroke 1993;24:1865–1873.

9 Hausmann D, Mugge A, Becht I, Daniel WG. Diagnosis of patent foramen ovale by transesophageal echocardiography and association with cerebral and peripheral embolic events. Am J Cardiol 1992;70:668–672.

10 Post MC, Thijs V, Herroelen L, Budts WI. Closure of a patent foramen ovale is associated with a decrease in prevalence of migraine. Neurology 2004;62:1439–1440.

11 Wilmshurst PT, Nightingale S, Walsh KP, Morrison WL. Effect on migraine of closure of cardiac right-to-left shunts to prevent recurrence of decompression illness or stroke or for haemodynamic reasons. Lancet 2000;356:1648–1651.

12 Reisman M, Christofferson RD, Jesurum J, et al. Migraine headache relief after transcatheter closure of patent foramen ovale. J Am Coll Cardiol 2005;45:493–495.

13 Dowson A, Mullen MJ, Peatfield R, et al. Migraine Intervention with STARFlex Technology (MIST) trial: a prospective, multicenter, double-blind, sham-controlled trial to evaluate the effectiveness of patent foramen ovale closure with STARFlex septal repair implant to resolve refractory migraine headache. Circulation 2008;117:1397–1404.

14 Spencer FA, Lopes LC, Kennedy SA, Guyatt G. Systematic review of percutaneous closure versus medical therapy in patients with cryptogenic stroke and patent foramen ovale. BMJ Open 2014;4:e004282.

15 Homma S, Sacco RL. Patent foramen ovale and stroke. Circulation 2005;112:1063–1072.

16 Nozari A, Dilekoz E, Sukhotinsky I, et al. Microemboli may link spreading depression, migraine aura, and patent foramen ovale. Ann Neurol 2010;67:221–229.

17 Sevgi EB, Erdener SE, Demirci M, Topcuoglu MA, Dalkara T. Paradoxical air microembolism induces cerebral bioelectrical abnormalities and occasionally headache in patent foramen ovale patients with migraine. J Am Heart Assoc 2012;1:e001735.

18 Eikermann-Haerter K, Negro A, Ayata C. Spreading depression and the clinical correlates of migraine. Rev Neurosci 2013;24:353–363.

19 Lipton RB, Stewart WF. The epidemiology of migraine. Eur Neurol 1994;34(suppl 2):6–11.

20 Headache Classification Committee of the International Headache Society. Classification and diagnostic criteria for headache disorders, cranial neuralgias, facial pain. Cephalalgia 1988;8(suppl 7):1–96.

21 Launer LJ, Terwindt GM, Ferrari MD. The prevalence and characteristics of migraine in a population-based cohort: the GEM study. Neurology 1999;53:537–542.

22 Lipton RB, Bigal ME, Diamond M, Freitag F, Reed ML, Stewart WF. Migraine prevalence, disease burden, and the need for preventive therapy. Neurology 2007;68:343–349.

23 Spencer MP, Moehring MA, Jesurum J, Gray WA, Olsen JV, Reisman M. Power m-mode transcranial Doppler for diagnosis of patent foramen ovale and assessing transcatheter closure. J Neuroimaging 2004;14:342–349.

24 De Cocker LJ, van Veluw SJ, Biessels GJ, et al. Ischaemic cavities in the cerebellum: an ex vivo 7-tesla MRI study with pathological correlation. Cerebrovasc Dis 2014;38: 17–23.

25 Rundek T, Elkind MS, Di Tullio MR, et al. Patent foramen ovale and migraine: a cross-sectional study from the Northern Manhattan Study (NOMAS). Circulation 2008; 118:1419–1424.

26 Kuper M, Rabe K, Holle D, et al. Prevalence of cardiac right left shunts in migraine: a population-based case-control study. Neurol Sci 2013;34:205–208.

27 Zito C, Dattilo G, Oreto G, et al. Patent foramen ovale: comparison among diagnostic strategies in cryptogenic stroke and migraine. Echocardiography 2009;26:495–503.

28 Droste DW, Silling K, Stypmann J, et al. Contrast transcranial Doppler ultrasound in the detection of right-to-left shunts: time window and threshold in microbubble numbers. Stroke 2000;31:1640–1645.

29 Guo S, Shalchian S, Gerard P, et al. Prevalence of right-to-left shunts on transcranial Doppler in chronic migraine and medication-overuse headache. Cephalalgia 2014;34:37–41.

30 Nahas SJ, Young WB, Terry R, et al. Right-to-left shunt is common in chronic migraine. Cephalalgia 2010;30:535–542.

31 Arquizan C, Coste J, Touboul PJ, Mas JL. Is patent foramen ovale a family trait? A transcranial Doppler sonographic study. Stroke 2001;32:1563–1566.

32 Wilmshurst P, Nightingale S. Relationship between migraine and cardiac and pulmonary right-to-left shunts. Clin Sci 2001;100:215–220.

33 Spencer BT, Qureshi Y, Sommer RJ. A retrospective review of clopidogrel as primary therapy for migraineurs with right to left shunt lesions. Cephalalgia 2014;34:933– 937.

34 Feurer R, Sadikovic S, Esposito L, et al. Lesion patterns in patients with cryptogenic stroke with and without right-toleft-shunt. Eur J Neurol 2009;16:1077–1082.

35 Adami A, Rossato G, Cerini R, et al. Right-to-left shunt does not increase white matter lesion load in migraine with aura patients. Neurology 2008;71:101–107.

36 Del SM, Dinia L, Bonzano L, et al. White matter lesions in migraine and right-to-left shunt: a conventional and diffusion MRI study. Cephalalgia 2008;28:376–382.

37 The International Classification Of Headache Disorders: 2nd edition. Cephalalgia 2004;24(suppl 1):9–160.

Chapter 4

Right-to-left shunts and micro-embolization in migraine

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Abstract

Purpose of review

The present review covers the latest studies on right-to-left shunts (RLSs) in migraine patients and different types of emboli capable of triggering migraine.

Recent findings

Although three recent studies found no increased RLS prevalence in migraine with aura patients, there remains ample evidence that the prevalence of RLS is increased in migraine with aura. Introduced emboli in the carotid artery of mice have been shown to cause cortical spreading depression, which has been considered the pathophysiological mechanism of migraine aura. In humans, iatrogenic introduced (micro)emboli can provoke migraine attacks; available evidence, however, is limited.

Summary

RLS and migraine with aura (but not without) are comorbid conditions, but the biological mechanism remains speculative. Specific emboli are probably able (although infrequently) to induce migraine symptoms. There is no convincing evidence that closure of a RLS alters migraine frequency; therefore, diagnosis or treatment of RLS in migraine has no place in daily clinical practice and should only take place in controlled studies.

Introduction

Since 1998, several studies have reported on the increased prevalence of right-to-left shunt (RLS) in patients with migraine with aura, but not in migraine without aura [1 – 4]. The biological mechanism linking RLS and migraine with aura remains speculative. There have been several retrospective and uncontrolled studies, also recently, indicating promising effects of closure [5 – 9], but a robust effect of shunt closure on migraine severity has not been shown in the single randomized controlled trial published back in 2008 [10].

Several questions remain. First, migraine with aura and a RLS are associated but is this a causal relation, and if so by what biological mechanism? Second, does closure of the RLS benefit the migraine patient? The aim of the current article is to answer these questions and comment on whether diagnosing RLS in migraine patients should be advised in clinical practice or not.

Background

A RLS is an abnormal communication between the right (venous) circulation and the left (arterial) circulation. Several structural abnormalities can cause right-to-left shunting; the most frequent cause is a patent foramen ovale (PFO) [11,12], a remnant from the fetal period that is located in the atrial septum of the heart. Other causes of RLS are atrial and ventricular septal defects and arteriovenous malformations or fistulae (PAVMs) at the pulmonary level [13]. When comparing publications on this subject, one should distinguish between the various types of RLS investigated. We will review the relationship between migraine and RLS, and more specifically PFO and PAVM.

Right-to-left shunt is more frequent in migraine with aura

Since 1998, several clinic-based case – control studies have been published, indicating a two to three times increased prevalence of RLS in migraine with aura patients compared with controls and migraine without aura patients using transcranial Doppler with aircontrast (TCD-c) [1 – 4,14]. This increased prevalence was also found specifically for PFO using cardiac echography [4]. A systematic review reported that PFO was more prevalent in migraine with aura patients than in the general population (pooled odds ratio 2.54, 95% confidence interval 2.01 – 3.08) [15]. Recently, two new case – control studies evaluating PFO prevalence were published. In the first, a population-based sample of mostly non-white participants from the North-

Manhattan study (NOMAS) was questioned about migraine and – as part of extensive cardiovascular evaluation – transthoracic echocardiography (TTE) was performed [16]. In this study evaluating 288 persons, the reported prevalence of PFO was similar in migraine with aura patients (16%), without aura (11%) and controls (15%). It was striking that as many as 79% of migraineurs were diagnosed with migraine with aura, whereas generally migraine with aura only makes up maximally 30% of migraineurs [17]. A great number of the migraine with aura patients perhaps were misdiagnosed and probably were migraine without aura patients in which the prevalence of RLS is known to be comparable with controls. Garg et al. [18] also found no differences in PFO prevalence among migraine with aura patients (27%), migraine without aura (26%) and age-matched and sex-matched controls (26%). The study used both TTE and TCD-c in 288 persons recruited from a headache center. Due to a very short evaluation time, pulmonary RLSs and small PFOs could have been missed. Finally, preliminary data from a large population-based Dutch study using TCD-c presented recently at a conference seems to confirm the increased prevalence of RLS among migraine with aura patients, and its publication is eagerly awaited.

A PAVM allows right-to-left shunting at the pulmonary level. Post et al. [19] studied 196 consecutive persons referred for screening of hereditary hemorrhagic telangiectasia (HHT) and showed that migraine with aura was present in 24% of these patients with a PAVM and only in 6% in patients without PAVM ($P = 0.001$). The prevalence of migraine without aura was not increased in individuals with a PAVM. A limitation of this study was that the migraine diagnosis was made only by reviewing returned questionnaires. Marziniak et al. [20] investigated 106 HHT patients and also showed that prevalence of migraine with aura in patients with PAVM (39%) was higher than that in patients without PAVM (10%); numbers of HHT patients with migraine with aura, however, were small ($n = 18$).

Only recently it was shown that, similar to PFO, the occurrence of PAVM is also relatively common in the general population. Woods et al. [12] described 104 healthy individuals (63% women) who were recruited to undergo TTE for RLS screening: 71% were found to have a RLS (38% had a PFO, 28% had a PAVM, 5% had evidence of both). In this study, any appearance of left-sided heart microcavitations was considered positive for a RLS, which is the lowest threshold possible and explains this very high prevalence of RLS. Before TTE, a 15-question migraine questionnaire was completed by participants, which was graded by a neurologist blinded for TTE results. Migraine with aura was diagnosed in 12% and migraine without aura in 29%. The prevalence of RLS in migraine with aura was 67%, which was not higher than that in migraine

without aura patients (77%) and controls (72%). Small or moderate PAVMs were also not associated with migraine, which was not broken down to migraine with and without aura. Results have to be evaluated with caution, as in this study only few large PFOs and no large PAVMs were found. Apart from the resulting power problem, one important limitation of this study is the limited questionnaire, which could have caused diagnostic bias.

In conclusion, a RLS is associated with migraine with aura. This is true for PFO, and probably also for PAVM. However, the prevalence of RLS in migraine with aura patients is increased probably less than two-fold to three-fold compared with controls, which was initially reported [1,2], as both PFO and PAVM are also common in the general population [12]. A causal relation between RLS and migraine with aura, as hypothesized by some, can only be shown by well designed randomized shamcontrolled RLS closure trials evaluating migraine frequency. While awaiting these studies, some recent publications have shown that there may be a reasonable linking biological mechanism, at least in animal studies.

Emboli triggering migraine attacks

For years, a mechanism linking RLS to migraine with aura was only speculative. One proposed mechanism was the transport through the RLS of unknown venous blood constituents that are normally not (or at decreased levels) present in the arterial circulation. Such postulated constituents were venous (paradoxical) emboli and serotonin [21]. The latest publications supporting the postulated embolic mechanism will be reviewed here. Nozari et al. [22] showed in mice that small particulate or air emboli injected into the carotid artery were able to evoke a cortical spreading depression (CSD) without causing ischemia, hereby linking emboli to migraine aura. It is unknown whether venous originated emboli (having passed through a RLS), as opposed to arterial originated emboli, also could cause CSD. If in humans it could also be demonstrated that small emboli are able to evoke a CSD, blood (vessel) abnormalities would then be acknowledged as a migraine trigger [23]. There are some clinical situations in humans that approximate these animal models. Four different types of emboli in humans will be discussed.

Air emboli causing migraine attacks

Migraine aura occurring during a TCD-c procedure has been reported as case reports [24,25] and recently the occurrence of migraine after a TCD-c procedure was studied prospectively. Caputi et al. [26] showed that among migraineurs with aura

immediately after TCD-c, migraine attacks were present in 8% of 159 participants; all of them had a permanent RLS. Sorensen et al. [27] prospectively questioned 445 individuals for the occurrence of different symptoms, including visual aura, after TCD-c in different patient groups (transient ischemic attack, cryptogenic stroke, migraine). TCD-associated symptoms such as migraine headache or ischemic symptoms were noted in 21% of participants. Occurrence of visual fortification aura occurred in 8% of migraine patients (n = 214) and in 0.4% of 231 nonmigraineurs (nonsignificant difference). Note that it was not reported whether the individuals experiencing specific symptoms had a RLS; generally it was concluded that any neurological symptom after TCD was more frequent in the RLS group (27%), compared with the non-RLS group (11%) ($P < 0.001$). Contrary to these studies [26,27], provoked migraine aura after aircontrast study seldom seems to occur in daily neurological practice. The relatively frequent occurrence of symptoms in these studies can also be explained by chance or other precipitating factors such as stress or the tight head frames used for TCD investigation. The nocebo effect, in which participants are (probably as a result of specific questioning) more likely to report side-effects, is also likely to play a role, especially when individuals can hear noise when emboli are detected by TCD.

Emboli after sclerotherapy

A second type of exogenous venous emboli occurs in sclerotherapy with the use of foam or liquids to treat varicose veins. Emboli in the middle cerebral artery (presumably after crossing a RLS) have been observed with TCD in the absence of neurological complications in up to 42% of patients undergoing foam sclerotherapy [28]. The composition of the emboli (e.g. gas, platelets or other compounds) is not known. A study using polidocanol (thought to cause smaller emboli) reported emboli during the sclerotherapy in as many as 89% of 61 participants with a RLS, but no neurological signs or symptoms [29]. A systematic review of cohort studies and randomized trials including 10 801 persons who underwent sclerotherapy reported the occurrence of visual disturbances (not considered to be a transient ischemic attack or stroke) in 84 persons (0.8%) [30]. Migraine (not further specified) occurred in 29 persons (0.3%) [30]. In these studies, percentages of individuals with a history of migraine were not reported and only in few of the included studies the RLS status in those experiencing migraine symptoms was known.

An alternative explanation for the occurrence of migraine attacks after sclerotherapy could be an increase of endothelin-1 following sclerotherapy, which has been shown in rats [31*]. Endothelin-1 is able to induce CSD in rats, linking endothelial

irritation following sclerotherapy to CSD [32]. In conclusion, individuals with RLS are at increased risk of micro-emboli after sclerotherapy, although clinical symptoms such as migraine aura attacks are infrequent. Future studies should report on RLS status and the history of migraine in participants.

Nitric oxide emboli

Third, in scuba diving, nitric oxide is released in the venous system and this gas is thought to cause neurologic decompression sickness [33]. Individuals with the largest RLS were at highest risk of neurological decompression illness (broadly defined as seizure, syncope, sensory, motor or visual unilateral symptoms) [34]. This suggests that nitric oxide from the venous system acts as a possible migraine aura trigger after passing through a RLS. The ability of nitric oxide (donors) to provoke migraine attacks has been clearly established before [35]; however, these are mainly migraine without aura attacks. In 83 scuba divers, a prospective (not randomized) study showed that closure of PFO significantly decreased major decompression illness during 5-year follow-up [36].

Fat emboli

The fourth type of venous originated emboli is fat emboli. After long bone fractures, the presence of semi-solid fat emboli in the venous system has been reported. Those emboli easily reach the cerebral circulation if a RLS is present and can give rise to (reversible) neurological symptoms [37]. In a study on 42 individuals with a femur shaft fracture who underwent daily detection of emboli, the presence of high micro-embolic signals in individuals with RLS was strongly predictive of the occurrence of neurological symptoms. Seventeen per cent of individuals developed neurological symptoms (cognitive or stroke symptoms), and all of those 17% had a RLS [38]. Aura symptoms were not reported and past migraine history was unknown. It seems that the fat globules inflict encephalopathy or focal defects but not aura phenomena, although based on the results of this study a link between fat emboli and migraine aura cannot be excluded.

Taken together, it seems that exogenous venous emboli (air, emboli following sclerotherapy and nitric oxide) in susceptible individuals can trigger migraine (aura) attacks. Theoretically, a RLS can be seen as a risk factor as it enables venous emboli to reach the arterial circulation. However, in most individuals with a RLS, these thousands of emboli entering the arterial circulation did not result in symptoms. The potential of micro-emboli to trigger a migraine attack is probably very limited, if present at all.

Emboli that are larger or more solid (and probably less present), such as fat emboli, have not been recognized as a trigger, although studies are scarce.

Other explanations for a causal relation between right-to-left shunt and migraine with aura

A causal mechanism linking RLS with a migraine attack could also be hemodynamic. Generally, RLS are of no hemodynamic significance, but some PFOs have been associated with the platypnea – orthodeoxia syndrome. In this syndrome, the patient complains of dyspnea only while sitting or standing, accompanied by arterial desaturation [39]. Furthermore, resting hypoxemia related to (left-to-right) shunting across a PFO has been reported [40]. Mild arterial desaturation due to a RLS, therefore, should be considered as a possible mechanism linking RLS with migraine, as hypoxia is a known trigger of migraine [41].

Migraine treatment as a cause of right-to-left shunt?

Increased pulmonary vascular resistance is associated with PFO [42]. It was shown that sildenafil decreased the RLS size, probably by decreasing pulmonary artery pressure [43]. The opposite occurs with 5HT1B agonists (e.g. triptans), which can cause pulmonary artery constriction [44]. The use of triptans, therefore, theoretically could enlarge or open a PFO by a transient increase of right-sided heart pressure. However, this does not explain that RLS prevalence is only increased in migraine with aura.

Are there proven beneficial effects of right-to-left shunt closure as prophylactic treatment of migraine?

Migraine patients have been referred to cardiologists for PFO closure, as migraine treatment [45]. Evidence for this therapy, however, is lacking, as the only randomized controlled study published so far is the Migraine Intervention with Starflex Technology (MIST) trial, which did not show an effect on the primary endpoint, cessation of migraine [10].

On the basis of (preliminary) findings of the MIST study, Diener et al. [46] in this journal concluded that there was insufficient evidence that PFO closure has a beneficial effect on migraine. Since then several observational (but no randomized) studies have been published [5 – 7,9]. Therefore, results from ongoing randomized PFO closure trials for migraine are eagerly awaited. Both the Stop pain, septal closure of PFO and the Escape trial (St. Jude, St. Paul, Minnesota, USA) have been terminated due to insufficient enrollment or ethical concerns. The Premium (sham controlled,

USA) and Prima (openlabel, Canada and Europe) trials, both by AGA Medical Corporation (St. Paul, Minnesota, USA) started in 2006, are still recruiting (http://www.con trolled-trials.com). A single-arm study on migraine prophylaxis is planned by Coherex, Salt Lake city, Utah, USA (http://clinicaltrials.gov).

Conclusion

There is reasonable evidence that migraine with aura is associated with RLS [15], and this is not altered by recent negative studies [12,16,18]; however, the difference might not be as marked as reported initially [1–4]. Significant gaps in our understanding of this association remain. In mice, it was demonstrated that arterial emboli were able to trigger CSD, which supports the hypothesized embolic mechanism linking RLS with migraine aura [22]. In humans, several kinds of emboli have been associated with migraine attacks. Reported frequencies vary widely, probably a nocebo effect of the aircontrast procedure plays an important role. There is insufficient evidence that RLS closure has a beneficial effect on migraine. Therefore, diagnosis or treatment of RLS in migraineurs has no place in current clinical practice and should as such only take place in controlled studies.

References

1 Anzola GP, Magoni M, Guindani M, et al. Potential source of cerebral embolism in migraine with aura: a transcranial Doppler study. Neurology 1999; 52:1622–1625.

2 Del Sette SM, Angeli S, Leandri M, et al. Migraine with aura and right-to-left shunt on transcranial Doppler: a case-control study. Cerebrovasc Dis 1998; 8:327 –330.

3 Carod-Artal FJ, da Silveira RL, Braga H, et al. Prevalence of patent foramen ovale in migraine patients with and without aura compared with stroke patients. A transcranial Doppler study. Cephalalgia 2006; 26:934 –939.

4 Schwerzmann M, Nedeltchev K, Lagger F, et al. Prevalence and size of directly detected patent foramen ovale in migraine with aura. Neurology 2005; 65:1415–1418.

5 Vigna C, Marchese N, Inchingolo V, et al. Improvement of migraine after patent foramen ovale percutaneous closure in patients with subclinical brain lesions: a case-control study. JACC Cardiovasc Interv 2009; 2:107–113.

6 Trabattoni D, Fabbiocchi F, Montorsi P, et al. Sustained long-term benefit of patent foramen ovale closure on migraine. Catheter Cardiovasc Interv 2011; 77:570–574.

7 Rigatelli G, Dell'avvocata F, Ronco F, et al. Primary transcatheter patent foramen ovale closure is effective in improving migraine in patients with highrisk anatomic and functional characteristics for paradoxical embolism. JACC Cardiovasc Interv 2010; 3:282 –287.

8 Wahl A, Praz F, Tai T, et al. Improvement of migraine headaches after percutaneous closure of patent foramen ovale for secondary prevention of paradoxical embolism. Heart 2010; 96:967–973.

9 Papa M, Gaspardone A, Fragasso G, et al. Usefulness of transcatheter patent foramen ovale closure in migraineurs with moderate to large right-to-left shunt and instrumental evidence of cerebrovascular damage. Am J Cardiol 2009; 104:434–439.

10 Dowson A, Mullen MJ, Peatfield R, et al. Migraine Intervention With STARFlex Technology (MIST) trial: a prospective, multicenter, double-blind, sham-controlled trial to evaluate the effectiveness of patent foramen ovale closure with STARFlex septal repair implant to resolve refractory migraine headache. Circulation 2008; 117:1397–1404.

11 Sarisoy S, Aydin OF, Sungur M, et al. The relationship between migraine and right-to-left shunt in children. Eur J Pediatr 2011; 170:365–370.

12 Woods TD, Harmann L, Purath T, et al. Smalland moderate-size right-to-left shunts identified by saline contrast echocardiography are normal and unrelated to migraine headache. Chest 2010; 138:264–269.

13 Pejhan S, Rahmanijoo N, Farzanegan R, Rahimi M. Surgically treatable pulmonary arteriovenous fistula. Ann Thorac Cardiovasc Surg 2012; 18:36 –38.

14 Tembl J, Lago A, Sevilla T, et al. Migraine, patent foramen ovale and migraine triggers. J Headache Pain 2007; 8:7–12.

15 Schwedt TJ, Demaerschalk BM, Dodick DW. Patent foramen ovale and migraine: a quantitative systematic review. Cephalalgia 2008; 28:531–540.

16 Rundek T, Elkind MS, Di Tullio MR, et al. Patent foramen ovale and migraine: a cross-sectional study from the Northern Manhattan Study (NOMAS). Circulation 2008; 118:1419–1424.

17 Launer LJ, Terwindt GM, Ferrari MD. The prevalence and characteristics of migraine in a population-based cohort: the GEM study. Neurology 1999; 53:537–542.

18 Garg P, Servoss SJ, Wu JC, et al. Lack of association between migraine headache and patent foramen ovale: results of a case-control study. Circulation 2010; 121:1406–1412.

19 Post MC, van Gent MW, Plokker HW, et al. Pulmonary arteriovenous malformations associated with migraine with aura. Eur Respir J 2009; 34:882–887.

20 Marziniak M, Jung A, Guralnik V, et al. An association of migraine with hereditary haemorrhagic telangiectasia independently of pulmonary rightto-left shunts. Cephalalgia 2009; 29:76 –81.

21 Wilmshurst P, Nightingale S. Relationship between migraine and cardiac and pulmonary right-to-left shunts. Clin Sci (Lond) 2001; 100:215–220.

22 Nozari A, Dilekoz E, Sukhotinsky I, et al. Microemboli may link spreading depression, migraine aura, and patent foramen ovale. Ann Neurol 2010; 67:221–229.

23 Dalkara T, Nozari A, Moskowitz MA. Migraine aura pathophysiology: the role of blood vessels and microembolisation. Lancet Neurol 2010; 9:309 –317.

24 Dinia L, Roccatagliata L, Bonzano L, et al. Diffusion MRI during migraine with aura attack associated with diagnostic microbubbles injection in subjects with large PFO. Headache 2007; 47:1455–1456.

25 Zaletel M, Zvan B, Kozelj M, et al. Migraine with aura induced by artificial microbubbles. Cephalalgia 2009; 29:480–483.

26 Caputi L, Usai S, Carriero MR, et al. Microembolic air load during contrast-transcranial Doppler: a trigger for migraine with aura? Headache 2010; 50:1320–1327.

27 Sorensen SG, Aguilar H, Reichert W, et al. Transient neurological symptoms during contrast transcranial Doppler right-to-left shunt testing in patients with cryptogenic neurological disease. J Interv Cardiol 2010; 23:284–290.

28 Morrison N, Neuhardt DL. Foam sclerotherapy: cardiac and cerebral monitoring. Phlebology 2009; 24:252 –259.

29 Regan JD, Gibson KD, Rush JE, et al. Clinical significance of cerebrovascular gas emboli during polidocanol endovenous ultra-low nitrogen microfoam ablation and correlation with magnetic resonance imaging in patients with right-to-left shunt. J Vasc Surg 2011; 53:131–137.

30 Sarvananthan T, She pherd AC, Willenberg T, Davies AH. Neurological complications of sclerotherapy for varicose veins. J Vasc Surg 2012;55:243–251.

31 Frullini A, Felice F, Burchielli S, Di SR. High production of endothelin after foam sclerotherapy: a new pathogenetic hypothesis for neurological and visual disturbances after sclerotherapy. Phlebology 2011; 26:203–208.

32 Dreier JP, Kleeberg J, Petzold G, et al. Endothelin-1 potently induces Leao's cortical spreading depression in vivo in the rat: a model for an endothelial trigger of migrainous aura? Brain 2002; 125:102–112.

33 Mollerlokken A, Gaustad SE, Havnes MB, et al. Venous gas embolism as a predictive tool for improving CNS decompression safety. Eur J Appl Physiol 2012; 112:401–409.

34 Wilmshurst P, Bryson P. Relationship between the clinical features of neurological decompression illness and its causes. Clin Sci (Lond) 2000; 99:65 –75.

35 Olesen J, Iversen HK, Thomsen LL. Nitric oxide supersensitivity: a possible molecular mechanism of migraine pain. Neuroreport 1993; 4:1027–1030.

36 Billinger M, Zbinden R, Mordasini R, et al. Patent foramen ovale closure in recreational divers: effect on decompression illness and ischaemic brain lesions during long-term follow-up. Heart 2011; 97:1932–1937.

37 Riding G, Daly K, Hutchinson S, et al. Paradoxical cerebral embolisation. An explanation for fat embolism syndrome. J Bone Joint Surg Br 2004; 86:95 –98.

38 Forteza AM, Koch S, Campo-Bustillo I, et al. Transcranial Doppler detection of cerebral fat emboli and relation to paradoxical embolism: a pilot study. Circulation 2011; 123:1947–1952.

39 Pierce CW. Platypnea-orthodeoxia syndrome in an elderly woman with a patent foramen ovale. Can J Cardiol 2010; 26:213–214.

40 Naqvi TZ, Rafie R, Daneshvar S. Original investigations. Potential faces of patent foramen ovale (PFO PFO). Echocardiography 2010; 27:897–907

41 Schoonman GG, Sandor PS, Agosti RM, et al. Normobaric hypoxia and nitroglycerin as trigger factors for migraine. Cephalalgia 2006;26: 816–819.

42 Dear WE, Chen P, Barasch E, et al. Sixty-eight-year-old woman with intermittent hypoxemia. Circulation 1995; 91:2284–2289.

43 Sallustio F, Di LS, Diomedi M, Stanzione P. Effect of a single oral dose of sildenafil on right-to-left shunt. Cerebrovasc Dis 2011; 32:296–297.

44 MacLean MR, Dempsie Y. The serotonin hypothesis of pulmonary hypertension revisited. Adv Exp Med Biol 2010; 661:309–322.

45 Dao CN, Tobis JM. PFO and paradoxical embolism producing events other than stroke. Catheter Cardiovasc Interv 2011; 77:903–909.

46 Diener HC, Kurth T, Dodick D. Patent foramen ovale, stroke, and cardiovascular disease in migraine. Curr Opin Neurol 2007; 20:310–319.

Chapter 5

Aortic root pathology in Marfan syndrome increases the risk of migraine with aura

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Abstract

Aim

To assess the lifetime prevalence of migraine in patients with Marfan syndrome (MFS) and to investigate a history of aortic root replacement (AR) as a possible risk factor.

Methods

In a multicentre study 123 MFS patients (n = 52 with AR, n = 71 without AR), 82 age and sex-matched controls and 51 patients with AR but without MFS, were interviewed using a semi-structured headache questionnaire. A multinomial logistic regression model was used to investigate risk factors for migraine with and without aura, adjusting for age and gender.

Results

Lifetime migraine prevalence was increased in female MFS patients (51%) compared to healthy female controls (29%), p = 0.017. In males lifetime migraine prevalence among MFS patients was only numerically increased. Lifetime prevalence of migraine with aura was increased among MFS patients compared to healthy controls both in males (19% vs.3%, p = 0.048) and females (30% vs. 14%, p = 0.049). A history of AR, independently from MFS, gender and age, increased the lifetime prevalence of migraine with aura (OR 3.1 [1.2–8.0]). In all but one patient migraine started before the AR.

Conclusions

The lifetime prevalence of migraine with aura, but not migraine without aura, is increased in patients with MFS. This association is driven by a history of AR. The replacement procedure itself is unlikely to be causally associated with migraine as in nearly all subjects, migraine started before the procedure. However this study adds to the evidence that underlying vessel wall pathology may be involved in migraine with aura.

Introduction

Migraine is a disabling neurovascular disorder with a lifetime prevalence of 13% in men and 33% in women (1). Approximately 70% of migraineurs suffer from migraine without aura and 30% from migraine with aura (1). The aetiology of migraine with and without aura are considered to be multifactorial due to a combination of genetic and environmental factors (2,3). Migraine with aura has been associated with cardiac shunts (4,5), non-shunting congenital heart defects (6,7), congenital abnormalities of the aorta (8), pulmonary arteriovenous malformation (9) and connective tissue disorders such as Ehlers–Danlos and Marfan syndrome (10,11). Marfan syndrome (MFS) is an autosomal-dominant multisystem disorder with specific cardiovascular, ocular and skeletal symptoms caused by a mutation in the fibrillin-1 gene (12). Aortic root dilatation or aortic dissection are considered major criteria for the diagnosis of MFS (13) and can be found in approximately half of patients (14). Aortic root replacement (AR) is a common procedure in severe MFS. In the present study we investigated (i) whether migraine prevalence is increased in patients with MFS, (ii) whether the effect is stronger in MFS patients who had severe aorta root dilatation requiring AR as a measure of disease severity, (iii) whether migraine prevalence is increased in non-MFS patients who underwent AR.

Materials and methods

Patients and procedures

MFS patients were recruited from two sites. MFS diagnosis on both sites was made according to the Ghent nosology (13). Danish recruitment took place in 2000 among members of the Danish Marfan patients' organisation (Landsforeningen of Marfan's syndrome) with re-interviewing in 2009 to register the specific history of AR.

The second site was the cardiology outpatient clinic of the Academic Medical Centre in 2008 (Amsterdam, the Netherlands). All eligible MFS patients were invited to participate. History of aortic root pathology was obtained from the database of the cardiology outpatient clinic. When AR had been performed, the indication was registered, which could either be prophylactic because of progressive aortic root dilatation, or acute following acute type-A aortic dissection. Two types of AR could have been performed and were registered, a Bentall procedure or a valve-sparing AR (David procedure).

All control subjects were recruited among acquaintances of Dutch MFS patients, specifically excluding family members. Patients were asked to supply the name of an acquaintance in the same age range and of the same gender as the patient who could serve as a control, before specifying the study goal. By this means, specific selection according to headache history of controls and patients was minimised.

To investigate the specific contribution of AR, non-MFS patients with a history of AR were recruited among patients attending the cardiothoracic surgery outpatient clinic of the Academic Medical Centre in 2008 (Amsterdam, the Netherlands). Indications for AR in this group were heterogeneous, ranging from aortic root or aortic ascendens dilatation with concomitant bicuspid aortic valve to aortic coarctation, aortic valve stenosis, severe aortic regurgitation, or systemic hypertension.

Subjects were asked to participate in a general health interview in order to reduce selection bias towards headache sufferers. The study was conducted in accordance with the revised Declaration of Helsinki (1998) and in agreement with the guidelines of the Danish and AMC Amsterdam ethics committees.

Migraine diagnosis

Danish MFS patients returned a questionnaire and then participated in a semi-structured telephone interview (10), migraine diagnosis was made according to ICHD-1 criteria (15). The Dutch participants (Marfan patients, non-Marfan patients with AR and controls) were interviewed in two stages. First three screening questions were asked. Screen positive for migraine headache was defined as those who had at least five moderate or severe headaches (excluding those due to hangover or sinus infection), or the participant was previously diagnosed with migraine by a physician. This first step screener was adapted from the GEM study and has a high sensitivity but a moderate specificity (1). Those fulfilling these screen-positive criteria proceeded in the same contact with a semi-structured telephone interview that focused on signs and symptoms of migraine headache and aura as outlined in ICHD-II (16). Those who screened negative did not proceed to the second stage of the interview, and were classified as having no migraine. An experienced headache neurologist, who was blinded to a subject's medical files and diagnoses, evaluated all the recorded individual interview results and made the migraine diagnosis, resulting in lifetime prevalence of migraine. No specific migraine diagnostic tool was used. A high lifetime attack frequency was defined as having had 4 or more attacks per months any time during life.

In one-third of initially screened positive subjects, final diagnosis was no migraine. These subjects were diagnosed with cluster headache, tension-type headache, and medication overuse headache.

Statistical analyses

Descriptive statistics were used to describe demographic and migraine characteristics. Comparisons between groups were analysed by a Student's t-test for continuous variables and the chi-square test for nominal variables. Multinomial logistic regression analysis was used to determine risk factors for migraine. Migraine with aura, migraine without aura and no migraine were used as dependent, no migraine was set as reference. As independent variables MFS, AR and gender were used, adjusting for age. P-values <0.05 were considered statistically significant. All analyses were performed using SPSS 16.0 (SPSS Inc., Chicago, IL).

Results

Table 1. Demographic characteristics

	MFS N = 123	Healthy controls N = 82	Non-MFS with AR N = 51
Age, mean (SD)	42 (14)	43 (15)	53 (15)[a]
Male gender (%)	53 (43)	31 (38)	39 (77)[a]
Aortic root replacement (%)	52 (42)	0 (0)	51 (100)
Mean age at AR (SD)	30 (12), n = 52	Na	51 (15)[a]

AR: aortic root replacement; MFS: Marfan syndrome; Non-MFS with AR: non-Marfan syndrome with aortic root replacement; na: not applicable. Comparisons: Marfan syndrome vs. healthy controls and non MFS with AR vs. controls. Mean age at AR comparison Marfan syndrome vs. non MFS with AR.
[a] $p < 0.001$.

Table 2. Lifetime migraine prevalence for different diagnostic groups

	MFS		Healthy controls		Non-MFS with AR	
	Male	Female	Male	Female	Male	Female
	N = 53	N = 70	N = 31	N = 51	N = 39	N = 12
Migraine (%)	14 (26)	36 (51)[a]	6 (19)	15 (29)	7 (18)	6 (50)
Migraine without aura (%)	4 (8)	15 (21)	5 (16)	8 (16)	4 (10)	2 (17)
Migraine with aura (%)	10 (19)[a]	21 (30)[a]	1 (3)	7 (14)	4 (10)	4 (33)

MFS: Marfan syndrome; non-MFS with AR: non-Marfan syndrome with aortic root replacement. Comparisons: Marfan syndrome males vs. healthy male controls. Same comparisons for females separately. Comparison non-MFS with AR to controls, also stratified for gender.
Chi-square. [a] $p < 0.05$.

Table 3. Risk factors for migraine

Variables	Migraine without aura OR (95% CI)	*p*-value	Migraine with aura OR (95% CI)	*p*-value	No migraine
Aortic root replacement (n = 103)	2.8 (0.9–8.5)	0.07	3.1 (1.2–8.0)	0.02	1.0 (referent)
Marfan syndrome (n = 123)	2.5 (0.7–8.8)	0.2	2.5 (0.9–7.1)	0.08	1.0 (referent)
Female gender (n = 133)	4.7 (1.7–13.3)	0.003	3.6 (1.6–8.2)	0.03	1.0 (referent)

The predictors for migraine without aura and migraine with aura, adjusted for age using a multinomial logistic regression model using aortic root replacement, Marfan syndrome and gender as independent variables. No migraine was set as referent.
OR: odds ratio, 95% CI: 95% confidence interval.

A total of 117 Dutch MFS patients were invited to participate in a general health interview and 47 MFS patients in Copenhagen were re-invited to participate in an interview on AR. A total of 123 of 164 invited MFS patients participated (response rate 75%, n = 33 Danish, n = 90 Dutch). A total of 60 non-MFS patients with AR were invited and of these 51 participated (response rate 85%). Eighty-two controls were provided by MFS patients and all 82 controls participated.
The demographic characteristics of the study population are summarised in Table 1. MFS patients with AR were slightly older than MFS patients without AR. Age when AR was performed was lower in MFS patients when compared to non-MFS patients.

Lifetime migraine prevalence was increased in female MFS patients (51%) compared to healthy female controls (29%), p = 0.017 (Table 2). In males lifetime migraine prevalence was only numerically increased. Lifetime migraine with aura prevalence was increased among MFS patients compared to healthy controls both in males (19% vs. 3%, p = 0.048) and females (30% vs. 14%, p = 0.049). Migraine without aura prevalence was not increased in Marfan patients. In non-MFS patients with AR, migraine prevalence compared to healthy controls was not significantly increased.

Table 4. Characteristics of migraineurs among groups, stratified for aortic root surgery

	Aortic root surgery		No aortic root surgery	
Variables	MFS (*n* = 27)	Non-MFS (n = 13)	MFS (*n* = 23)	Controls (*n* = 21)
Mean age at onset migraine (SD)	20 (11)	18 (17)	17 (6)	21 (12)
Mean age at onset migraine with aura (SD)	19 (10)	19 (18)	16 (5)	18 (5)
Visual aura duration, minutes (SD)	24 (8)	52 (46)	63 (105)	33 (22)
Lifetime high attack frequency (%)	8 (29)	4 (31)	11 (48)	10 (51)

MFS: Marfan syndrome; non-MFS: non-Marfan syndrome with aortic root replacement; SD: standard deviation. Values are presented as means (SD). Lifetime high attack frequency > 3 attacks/ month.

To analyze the effect of AR in MFS patients on the prevalence of different migraine types, and to be able to make necessary adjustments for age and gender, a multinomial logistic regression model was used. As expected female gender was a risk factor for both migraine with and without aura (Table 3). AR was a risk factor for migraine with aura (OR 3.1 [1.2–8.0]) but not for migraine without aura. Independent from AR, MFS was not significantly associated with migraine with aura.

As AR was the driver in the increased prevalence of migraine with aura, Table 4 shows migraine characteristics between the study groups stratified for AR. None of these migraine characteristics differed. In all but one of the MFS patients with migraine, onset of migraine was before AR. MFS patients without AR but with dilatation not yet requiring AR had no increased risk for migraine with aura.

Of only 41/123 (33%) of MFS patients the presence or absence of dural ectasias was known by spinal imaging. Migraine with aura was found in 24% of patients with dural ectasias compared to 13% of those without dural ectasias (OR 2.2 [0.2–21.1]).

Discussion

In the present, largest ever, study on the association between migraine and MFS patients we confirmed earlier reports from two smaller cohorts (10,11) that MFS is associated with an increased lifetime migraine prevalence both compared to contemporary and historical controls (1,17). Thanks to the large number of participants, we could in addition determine that MFS only increased the risk of migraine with aura and not of migraine without aura. Moreover, we showed that aorta root pathology requiring AR was, independently from MFS, associated with an increased risk of migraine with aura, whereas MFS, independently from AR, was not significantly associated with migraine with aura. History of an AR thus was the main driver in the increased prevalence of migraine with aura. The underlying mechanism for this association is unknown but seems to point at systemic vessel wall pathology. Further research is warranted to unveil potential mechanisms.

There is increasing evidence that migraine is linked with impaired systemic endovascular function. Migraine has been associated with diseases considered to be related to extracellular matrix disorder like cervical artery dissection (18,19). The activity of elastases, enzymes capable of degrading elastic fibres and regulating enzymes of the extracellular matrix, has been associated with migraine with aura. A higher level of extracellular matrix degradation can explain both dissection as well as

atherosclerotic lesions (20). MFS is caused by mutations in the gene encoding for the extracellular matrix protein fibrillin-1. Contrary to diseases with vascular dilatation, recently it was found that the aortic rigidity measured by aortic pulse wave velocity in migraine is increased (21), whereas it has also been shown that compliance of brachial and femoral artery were decreased in migraineurs compared with controls (22).

A possible effect of these abnormalities found in the systemic blood vessels is a reaction from the endothelial cells, which secrete vasoactive mediators like vasodilator nitric oxide and vasoconstrictor endothelin-1. Several studies have found increased levels of these mediators to be present in migraineurs. These mediators are in turn thought to be able to produce cortical spreading depression. Another possibility is the presence of micro-emboli in the affected aortic root, which can act as a trigger for cortical spreading depression and was recently shown by Nozari et al. in mice (23). The use of specific vasoactive drugs in MFS patients with a dilating aortic root should also be considered, but was not investigated in this study. However most commonly used medications in MFS probably have a prophylactic rather than a migraine enhancing effect.

In our subjects the AR operation itself was not associated with the presence of migraine, as in all but one subject, migraine started many years before the operation. Surgical repair of the dilated aortic root/ ascending aorta for MFS patients to prevent a dissection, is usually performed at a threshold of an external aortic diameter of 50 mm (24). It is feasible to think that thus the dilatation would be associated with the increased migraine prevalence, however in MFS patients without AR but with dilatation not yet requiring operation no increased prevalence of migraine with aura was found. Possibly this non-operated MFS group is more benign and displays a different vascular phenotype.

Previously, one of us hypothesised that the dural ectasias frequently found in MFS could be an explanation for the increased headache prevalence (10). However, in the 42 patients in whom results of spinal imaging were known, we failed to find an association between migraine with aura and dural ectasias.

Strengths and limitations

As Marfan prevalence is low, numbers of migraineurs in the study are small, especially after gender stratification. The use of a telephone semi-structured interview aids diagnostic accuracy, whereas the study by Vis et al. (11) investigating partly the same

MFS patients only used filled in questionnaires by post, introducing possible diagnostic inaccuracy and response bias. For the Dutch study sample, a specially trained student who performed the telephone interviews was blinded for AR status (but not for MFS diagnosis); however the final migraine diagnosis was made by a headache neurologist blinded for all clinical characteristics. Migraine with aura prevalence could have been slightly underestimated, as the interview was only continued after the first screening step if participants had suffered at least five headache attacks. According to the ICHD-II criteria, for migraine without aura five attacks are needed, but only two attacks are necessary to fulfil migraine with aura criteria (16). Both MFS patients and aortic root patients without MFS were identified using hospital-based databases, whereas controls were not hospital based. Controls were selected by the Marfan patients, which could have introduced selection bias. This might have caused some disparity for unknown factors. If migraine activity altered due to the aortic root operation, this could not be investigated by this study, but a prospective study answering this question is highly interesting.

Aorta root pathology requiring AR was found to be a risk factor for migraine with aura. MFS independent from aortic root operation was no risk factor for migraine with aura. This study adds to the evidence that underlying vessel wall pathology might play a role in migraine with aura.

References

1 Launer LJ, Terwindt GM and Ferrari MD. The prevalence and characteristics of migraine in a populationbased cohort: the GEM study. Neurology 1999; 53: 537–542.

2 Russell MB and Olesen J. Increased familial risk and evidence of genetic factor in migraine. BMJ 1995; 311: 541–544.

3 Russell MB, Iselius L and Olesen J. Inheritance of migraine investigated by complex segregation analysis. Hum Genet 1995; 96: 726–730.

4 Schwerzmann M, Nedeltchev K, Lagger F, et al. Prevalence and size of directly detected patent foramen ovale in migraine with aura. Neurology 2005; 65: 1415–1418.

5 Del Sette SM, Angeli S, Leandri M, et al. Migraine with aura and right-to-left shunt on transcranial Doppler: a case-control study. Cerebrovasc Dis 1998; 8: 327–330.

6 Hermans H, Post MC, Thijs V, et al. Increased prevalence of migraine in adult congenital heart disease. Heart 2007; 93: 361–362.

7 Shahar E, Borenstein A and Filk D. Severe migraine associated with coarctation of aorta: complete recovery following balloon dilation. J Child Neurol 2000; 15: 826–827.

8 Truong T, Slavin L, Kashani R, et al. Prevalence of migraine headaches in patients with congenital heart disease. Am J Cardiol 2008; 101: 396–400.

9 Post MC, van Gent MW, Plokker HW, et al. Pulmonary arteriovenous malformations associated with migraine with aura. Eur Respir J 2009; 34: 882–887.

10 Knudsen S and Russell MB. Increased risk of migraine in Marfan's syndrome? Acta Neurol Scand 2006; 114: 281–286.

11 Vis JC, Timmermans J, Post MC, et al. Increased prevalence of migraine in Marfan syndrome. Int J Cardiol 2009; 136: 330–334.

12 Judge DP and Dietz HC. Marfan's syndrome. Lancet 2005; 366: 1965–1976.

13 De Paepe A, Devereux RB, Dietz HC, et al. Revised diagnostic criteria for the Marfan syndrome. Am J Med Genet 1996; 62: 417–426.

14 Rand-Hendriksen S, Lundby R, Tjeldhorn L, et al. Prevalence data on all Ghent features in a cross-sectional study of 87 adults with proven Marfan syndrome. Eur J Hum Genet 2009; 17: 1222–1230.

15 Headache Classification Subcommittee of the International Headache Society. Classification and diagnostic criteria for headache disorders, cranial neuralgias and facial pain. Cephalalgia 1988; 8(Suppl 7): 1–96.

16 Headache Classification Subcommittee of the International Headache Society. The International Classification of Headache Disorders: 2nd edition. Cephalalgia 2004; 24(Suppl 1): 9–160.

17 Russell MB, Rasmussen BK, Fenger K, et al. Migraine without aura and migraine with aura are distinct clinical entities: a study of four hundred and eighty-four male and female migraineurs from the general population. Cephalalgia 1996; 16: 239–245.

18 Tzourio C, Benslamia L, Guillon B, et al. Migraine and the risk of cervical artery dissection: a case-control study. Neurology 2002; 59: 435–437.

19 Pezzini A, Granella F, Grassi M, et al. History of migraine and the risk of spontaneous cervical artery dissection. Cephalalgia 2005; 25: 575–580.

20 Tzourio C, El AM, Robert L, et al. Serum elastase activity is elevated in migraine. Ann Neurol 2000; 47: 648–651.

21 Schillaci G, Sarchielli P, Corbelli I, et al. Aortic stiffness and pulse wave reflection in young subjects with migraine: A case-control study. Neurology 2010; 75: 960–966.

22 Vanmolkot FH, Van Bortel LM and de Hoon JN. Altered arterial function in migraine of recent onset. Neurology 2007; 68: 1563–1570.

23 Nozari A, Dilekoz E, Sukhotinsky I, et al. Microemboli may link spreading depression, migraine aura, and patent foramen ovale. Ann Neurol 2010; 67: 221–229.

24 Hiratzka LF, Bakris GL, Beckman JA, et al. 2010 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/ SVM guidelines for the diagnosis and management of patients with Thoracic Aortic Disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, American Association for Thoracic Surgery, American College of Radiology, American Stroke Association, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of Thoracic Surgeons, and Society for Vascular Medicine. Circulation 2010; 121: e266–e369.

CHAPTER 6

Cardiac monitoring of high dose verapamil in cluster headache - An international Delphi study

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Abstract

Background

In many patients, high dose verapamil (HDV) is the only effective prophylactic treatment for cluster headache and is also used in familial hemiplegic migraine. Although cardiac adverse events and EKG abnormalities are relatively common, evidence-based guidelines for screening and monitoring patients on HDV are lacking.

Goal and methods

Using the Delphi approach, we interviewed 22 international clinical experts in cardiac rhythm disorders to formulate EKG guidelines for the pretreatment screening and monitoring of cluster headache patients using HDV.

Results

The panel only agreed on performing pretreatment EKG to screen for pre-existing cardiac arrhythmia. Pretreatment EKG was deemed not necessary by most panel members for patients who did not have cardiac adverse events during a previous period of cluster headache attacks treated with HDV. Half the panel advised Holter EKG for patients on verapamil ≥ 480 mg/day. The highest recommended daily doses varied between 240 and 960 mg. Contra-indications for use of verapamil largely followed FDA guidelines.

Discussion

Experts in cardiac rhythm disorders agreed on pre- treatment EKG monitoring, but no consensus was reached on EKG monitoring during HDV treatment and around dose adjustments. .

Introduction

Cluster headache is a highly disabling brain disorder characterized by recurrent attacks of intense unilateral headache and facial autonomic features for 30-180 minutes. [1] Attacks typically strike several times a day, in most patients clustered in periods of several weeks to months alternating with attack-free periods of months to years (episodic cluster headache).[1] Up to 20% of patients may have *chronic* cluster headache without attack-free periods. To prevent attacks, treatment guidelines recommend verapamil in doses which usually exceed those generally used in cardiovascular disease.[2,3] Adverse events of high dose verapamil (HDV) may include cardiac arrhythmia, heart failure, and pulmonary edema.[4] Consequently, patients with AV blocks, ventricular dysfunction, hypotension, or certain forms of atrial fibrillation are usually excluded.[4] Evidence-based guidelines on how to prescreen and monitor cardiac safety in cluster headache patients treated with HDV are, however, lacking.[2,5] In clinical practice this may cause sub-optimal treatment results of HDV in some patients.

The goal of the present study was to define guidelines for safe use and electrocardiogram (EKG) monitoring of HDV in cluster headache. To this end we interviewed cardiologists who are experts in cardiac rhythm disorders and used the Delphi approach to arrive at consensus.

Methods

We randomly identified 40 cardiologists from the membership list of the Heart Rhythm Society who were invited to participate. Cardiologists were eligible if they had been first or last author of at least five publications on cardiac rhythm disorders in peer reviewed medical journal in the last 10 years. Twenty-two (55%) responded and completed the questionnaires. (participants see e-table 1)

A case vignette was presented in which a patient with cluster headache and no cardiac medical history was prescribed with verapamil 240 mg/day. We used the Delphi approach[6] to arrive at consensus about the EKG protocol and which EKG findings were considered contraindications for continuation of verapamil. The first round included questions about possible EKG protocols using a five point Likert scale. Consensus was defined as answers 'strongly agree' and 'agree' added up to ≥ 80%. When no consensus was reached, propositions were taken to the second

round. (Questions e-table 2.). For continuous variables, mean values with ranges and standard deviations (SD) are presented, using SPSS, version 20, SPSS Inc., Chicago, IL, USA, for Windows.

Results

Panel members reached consensus on one of six proposals (table 1) as 82% agreed that an EKG should be made prior to the first dose of verapamil. Half the panel recommended to make EKGs during stable doses at set times, especially with mean daily doses of ≥ 330 mg (range: ≥ 120 - 480 mg). EKG *before* dose increase was recommended by 50% while 60% advised an EKG *after* dose increase. In total 45% recommended EKG both before and after dose increase. Those who advised EKG monitoring *after* dose increase, recommended doing this after an average of 5 days (range 1-14 days, SD 3.8). If patients were using ≥ 480 mg verapamil per day, ambulatory EKG Holter-monitor registration was recommended by 50% of the panel members. Most panel members deemed pretreatment EKG not necessary in patients who had had no cardiac adverse events while on verapamil during a previous period of cluster headache attacks.

Absolute contra-indications for continuation of verapamil treatment included: (1) bradycardia < 40 bpm (92% agreement); (2) 3rd degree AV block (86%); and (3) 2nd degree AV block Mobitz type (86%) (table 1). A 1st degree AV block (> 250 ms; was regarded as relative contra-indication (92%). For bradycardia <50 bpm and 2nd degree AV block Wenckebach type near consensus as relative contra-indications was reached (75% agreement).

Seventeen respondents recommended a mean maximal daily dose of 550 mg (range 240-960 mg). There was no preference for sustained- or regular-release formulations. (table 1).

Cardiologists from Europe and the United States did not differ with respect to their answers.

Table 1. Results of Delphi questionnaire

Propositions **Need for EKG**	Agreement by cardiologists
1. Prior to start of verapamil	82%
2. At set times during stable dose	50%
If not necessary at all doses, cut off dose(mean)	330 mg/day
3. Prior to dose increase	50%
4. After dose increase	60%
5. Holter EKG ≥ 480 mg/day verapamil	50%
6. Before restart when previously no side effects	23%
EKG absolute contra-indications	
Bradycardia < 40 bpm (asymptomatic)	92% *
3rd degree AV block	86%
2nd degree AV block, Mobitz type	86%
Sinus pause > 3 seconds	69% *
2nd degree AV block Wenckebach type	69% *
Sick sinus syndrome	46% *
1st degree AV block but < 250 ms	31% *
Re-entrant tachycardia	23% *
Asymptomatic bradycardia < 50 bpm	8 % *
EKG relative contra-indications	
1st degree AV block > 250 ms	92% *
New junctional rhythm	77% *
Asymptomatic bradycardia < 50 bpm	75% *
2nd degree AV block, Wenckebach type	75% *
Bradycardia < 40 bpm (asymptomatic)	50% *
New bundle branch Block	31% *
Verapamil	
Sustained release preferred	52%
Highest daily dose to prescribe (mean)[&]	550 mg (range 240-960)

*Percentage of agreement in second Delphi round.
[&] Only answered by n=17.
Answers with 5% agreement or lower not included in table

Discussion

We used the Delphi approach to define recommendations from cardiologists specialized in rhythm disorders for safe use and EKG monitoring of HDV in cluster headache. The panel members agreed on performing a pretreatment EKG in patients using verapamil for the first time. Pretreatment EKG was deemed not necessary in patients who did not have cardiac adverse events during a previous period of cluster

headache treated with verapamil. No consensus was reached on EKG monitoring during verapamil treatment and dose adjustments. For verapamil doses of ≥ 480 mg/day, half the panel advised ambulatory EKG Holter-monitor registration. Consensus about absolute and relative contraindications for continuing HDV largely followed FDA recommendations. There was no preference among the panel members for either sustained- or regular-released formulations of verapamil.

Although cardiac arrhythmias and bradycardia have been reported in up to 40% of patients using HDV,[7,8] published recommendations on EKG monitoring are remarkably limited, highly variable, and solely based on expert opinions.[2,5,9,10] The protocols range from: (i) starting with 240 mg verapamil daily after pretreatment EKG and increasing the dose with 80 mg every two weeks, each time preceded by an EKG, until attacks have subsided, or side effects have become too serious, or a maximum dose of 960 mg/day is reached[11] to (ii) starting with a pretreatment EKG (without specified starting dose and titration scheme) followed by (a) repeated EKGs before and 10 days after each dose increase[3]; (b) repeated EKGs only at doses above 480 mg/day[12]; or (c) repeated EKGs with each dose increase (without specifying whether this is before or after dose increase) and every three months when on a stable dose[13].

The recommendations of the panel members were similarly divergent. They only reached consensus about performing a pretreatment EKG and near consensus about that pretreatment EKG was not necessary in patients who had not experienced cardiac adverse events during a previous cluster period treated with verapamil. No consensus was reached on EKG monitoring during treatment and around dose adjustments. Most panel members, however, did recommend repeated EKG five days after each verapamil dose increase, in line with the time it takes to reach steady state plasma levels after increasing the dose.[4] Interestingly, half the panel members recommended Holter EKG for doses ≥ 480 mg/day, which is not mentioned in any cluster headache treatment review or guideline.

FDA considers second and third degree AV block, sick-sinus syndrome without pacemaker, and atrial flutter/fibrillation with accessory bypass tract hard contra-indications for use of verapamil. Panel members felt that a 2nd degree AV block Wenckebach type only is a relative contra-indication and did not reach consensus about whether sick sinus syndrome and atrial flutter/fibrillation were absolute contraindications.

Verapamil is available in regular or extended release formulations with different time-to-peak-concentrations and half-life times.[4] The three available efficacy studies on verapamil in cluster headache were conducted with either sustained,[9] regular

release[14] or not specified.[10] Most cluster headache guidelines do not specify the formulation. The panel did not favor any particular formulation.

The highest recommended daily doses of verapamil ranged from 240mg to 960 mg (mean 550 mg) which is consistent with the doses used in the efficacy studies (on average 354-360 mg/day in episodic cluster headache[9,13] and 574 mg/day in chronic cluster[9]). In review articles and guidelines, doses up to 1200 mg are sometimes advised.[11,13]

Recommendations

Based on the results of our study, we recommend performing a pretreatment EKG before initiating verapamil therapy but this is not necessary in patients who did not experience adverse events during previous treatment with verapamil. No consensus-based recommendations on EKG monitoring during verapamil treatment and around dose increases can be given although, based on the literature EKG prior and after every dose increase would be a logical recommendation. It goes without saying that individual patient characteristics always have to be taken into account. Future studies should compare different EKG regimes prospectively.

Clinical implications:

Experts agreed on performing pretreatment EKG when prescribing Verapamil Pretreatment EKG was deemed not necessary for patients who did not have cardiac adverse events during a previous period of cluster headache attacks treated with Verapamil.

E-Table 1. Panellists

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E-table 2.

Questionaires first and second Delphi round.

Delphi study: 'EKG control with Verapamil use for cluster headache'

Currently the best preventive treatment of cluster headache (CH) is verapamil as it reduces attack frequency and the need for attack treatment in the majority of patients. Verapamil is used in doses up to 960 mg/day, which is much more than used for most cardiovascular indications. These doses increase the risk for cardiac toxicity (eg. atrioventricular block and bradycardia).

Because of the risk of cardiac side effects, electrocardiogram (EKG) screening is advised in CH patients using verapamil. Evidence based guidelines for EKG screening, however, are not available.

The aim of this study is to provide a practice guideline for verapamil use in CH based on expert opinion by means of the Delphi method. The Delphi method is a well known method for consensus-building by using a series of questionnaires to collect data from a panel of selected experts. Questionnaires will be sent to 30 selected internationally well know cardiologists, specialized in heart rhythm disorders.

The goal of the study is to achieve consensus on EKG control and dosing regime for CH patients using verapamil. The selected cardiologists will fill in the questionnaires in two or three separate stages.

Questionaire 1:

The questions are about your clinical practice.

Case vignette.
A cluster headache patient without cardiac history, with normal blood pressure and heart rate. No cardiac complaints. No cardiovascular co-medication. There is an indication for preventive treatment with verapamil. The dose is adjusted to the clinical efficacy.

Please mark your answers by making the answer bold or underline.

1. An EKG should be made prior to a first verapamil prescription of 80 mg 3dd1.
   Strongly disagree Disagree Neutral Agree Strongly agree

2. Regular EKG checks at set times should be done when on a stable dose of verapamil.
   Strongly disagree Disagree Neutral Agree Strongly agree

2a. If so, is this necessary for all doses? (high and low)
   Strongly disagree Disagree Neutral Agree Strongly agree

2b. If not necessary for all doses, what is the cut-off dose (in mg/day) to do regular EKG checks at set times ? / day

3. An EKG should be repeated prior to any dose increase of verapamil.
   Strongly disagree Disagree Neutral Agree Strongly agree

4. An EKG should be repeated after any dose increase of verapamil.
   Strongly disagree Disagree Neutral Agree Strongly agree

4a. If so, within how many days after the increase?
   ..... days after dose increase

5. Which EKG abnormalities are absolute criteria for discontinuation of verapamil?

   .....

6. Which EKG abnormalities are relative criteria for discontinuation of verapamil?

   .....

7. What is the maximum daily dose of verapamil to prescribe in the given case?
   240 mg / 320 mg/ 400 mg/ 480 mg/ 560 mg/ 640 mg / 720 mg/ 800 mg/ 880 mg/ 960 mg / 1040 mg/ 1120 mg

8. Verapamil controlled release (retard, sustained release) should be used instead of normal (short acting) verapamil
   Strongly disagree Disagree Neutral Agree Strongly agree

9. When on a verapamil dose of 480 mg/day (or higher), a 24-hour holter EKG is to prefer over an normal EKG.
   Strongly disagree Disagree Neutral Agree Strongly agree

10. In the given case, after 3 months of daily dose of 480 mg Verapamil, the current cluster headache episode has ended and Verapamil could be discontinued. After six months, however, cluster attacks recurred resulting in a new indication for verapamil (start dose 80 mg 3dd1).
    Should a EKG be made prior to restart (considering that all previous EKGs were normal)?
    Strongly disagree Disagree Neutral Agree Strongly agree

11. Additional comments (if any):

    .....

12. Do you use a local or national guideline on verapamil use?
    Yes / No
    If Yes: Local or National

Summary of consensus reached in first Delphi round:

An EKG should be made prior to a first verapamil prescription of 80 mg 3dd1
81,8% agreed
Which EKG abnormalities are absolute criteria for discontinuation of verapamil? (open question)
AV III was answered by 86,4%
AV II Mobitz was answered by: 86,4 %
For the remaining answers no consensus (defined as least 80 % agreement) was reached.

Please answer questions of this second Delphi questionnaire round.

Again the same case vignette applies to all questions:
Case vignette.
A cluster headache patient without cardiac history, with normal blood pressure.
No cardiac complaints (asymptomatic patient) . No cardiovascular co-medication. There is an indication for cluster headache treatment with verapamil.

- AV II Wenkenbach block is an absolute contra-indication for start or continuation of verapamil
  Strongly disagree Disagree Neutral Agree Strongly agree

- Asymptomatic bradycardia of 50 bpm or less is an absolute contra-indication for start or continuation of verapamil
  Strongly disagree Disagree Neutral Agree Strongly agree

- Asymptomatic bradycardia of 40 bpm or less is an absolute contra-indication for start or continuation of verapamil
  Strongly disagree Disagree Neutral Agree Strongly agree

- Sinuspause > 3 seconds is an absolute contra-indication for start or continuation of verapamil
  Strongly disagree Disagree Neutral Agree Strongly agree

- Sicksinus syndrome is an absolute contra-indication for start or continuation of verapamil
  Strongly disagree Disagree Neutral Agree Strongly agree

- Atrioventricular re-entrant tachycardias (AVRT) syndromes are an absolute contra-indication for start or continuation of verapamil
  Strongly disagree Disagree Neutral Agree Strongly agree

Following questions are about relative contraindications;

- The presence of a first degree AV block < 250 ms is a relative contra-indication for start or continuation of verapamil
  Strongly disagree Disagree Neutral Agree Strongly agree
- The presence of a first degree AV block > 250 ms is a relative contra-indication for start or continuation of verapamil
  Strongly disagree Disagree Neutral Agree Strongly agree
- AV II Wenkebach block is a relative contra-indication for start or continuation of verapamil
  Strongly disagree Disagree Neutral Agree Strongly agree
- Asymptomatic bradycardia of 50 bpm or less is a relative contra-indication for continuation of verapamil
  Strongly disagree Disagree Neutral Agree Strongly agree
- Asymptomatic bradycardia of 40 bpm or less is a relative contra-indication for continuation of verapamil
  Strongly disagree Disagree Neutral Agree Strongly agree
- A new bundle branch block is a relative contra-indication for continuation of verapamil
  Strongly disagree Disagree Neutral Agree Strongly agree
- New junctional rhytm is a relative contra-indication for continuation of verapamil
  Strongly disagree Disagree Neutral Agree Strongly agree

Reference List

1 The International Classification of Headache Disorders, 3rd edition (beta version). *Cephalalgia* 2013 Jul;33:629-808.

2 May A, Leone M, Afra J, et al. EFNS guidelines on the treatment of cluster headache and other trigeminal-autonomic cephalalgias. *Eur J Neurol* 2006 Oct;13:1066-1077.

3 Nesbitt AD, Goadsby PJ. Cluster headache. *BMJ* 2012;344:e2407.

4 Greenwood village CTHA. Drugdex system (Micromedex 2.0). Drugdex 2014

5 Francis GJ, Becker WJ, Pringsheim TM. Acute and preventive pharmacologic treatment of cluster headache. *Neurology* 2010 Aug 3;75:463-473.

6 Falzarano M, Pinto ZG. Seeking consensus through the use of the Delphi technique in health sciences research. *J Allied Health* 2013;42:99-105.

7 Cohen AS, Matharu MS, Goadsby PJ. Electrocardiographic abnormalities in patients with cluster headache on verapamil therapy. *Neurology* 2007 Aug 14;69:668-675.

8 Lanteri-Minet M, Silhol F, Piano V, Donnet A. Cardiac safety in cluster headache patients using the very high dose of verapamil (>/=720 mg/day). *J Headache Pain* 2011 Apr;12:173-176.

9 Gabai IJ, Spierings EL. Prophylactic treatment of cluster headache with verapamil. *Headache* 1989 Mar;29:167-168.

10 Bussone G, Leone M, Peccarisi C, et al. Double blind comparison of lithium and verapamil in cluster headache prophylaxis. *Headache* 1990 Jun;30:411-417.

11 Matharu MS, Goadsby PJ. Trigeminal autonomic cephalgias. *J Neurol Neurosurg Psychiatry* 2002 Jun;72 Suppl 2:ii19-ii26.

12 Stillman M.J. Treatment of trigeminal autonomic cephalalgias and other primary headaches., *The ClevelandClinic Manual of Headache Therapy New York:* ed 2011.

13 Ashkenazi A, Schwedt T. Cluster headache--acute and prophylactic therapy. *Headache* 2011 Feb;51:272-286.

14 Leone M, D'Amico D, Frediani F, et al. Verapamil in the prophylaxis of episodic cluster headache: a double-blind study versus placebo. *Neurology* 2000 Mar 28;54:1382-1385.

Part 3

Migraine and brain function

Chapter 7

Cerebellar function and ischemic brain lesions in migraine patients from the general population

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Abstract

Objective

The objective of this article is to obtain detailed quantitative assessment of cerebellar function and structure in unselected migraine patients and controls from the general population.

Methods

A total of 282 clinically well-defined participants (migraine with aura n=111; migraine without aura n = 89; non-migraine controls n= 82; age range 43–72; 72% female) from a population-based study were subjected to a range of sensitive and validated cerebellar tests that cover functions of all main parts of the cerebellar cortex, including cerebrocerebellum, spinocerebellum, and vestibulocerebellum. In addition, all participants underwent magnetic resonance imaging (MRI) of the brain to screen for cerebellar lesions. As a positive control, the same cerebellar tests were conducted in 13 patients with familial hemiplegic migraine type 1 (FHM1; age range 19–64; 69% female) all carrying a CACNA1A mutation known to affect cerebellar function.

Results

MRI revealed cerebellar ischemic lesions in 17/196 (8.5%) migraine patients and 3/79 (4%) controls, which were always located in the posterior lobe except for one control. With regard to the cerebellar tests, there were no differences between migraine patients with aura, migraine patients without aura, and controls for the: (i) Purdue-pegboard test for fine motor skills (assembly scores p= 0.1); (ii) block-design test for visuospatial ability (mean scaled scores p= 0.2); (iii) prism-adaptation task for limb learning (shift scores p= 0.8); (iv) eyeblink-conditioning task for learningdependent timing (peak-time p= 0.1); and (v) body-sway test for balance capabilities (pitch velocity score under two-legs stance condition p= 0.5). Among migraine patients, those with cerebellar ischaemic lesions performed worse than those without lesions on the assembly scores of the pegboard task ($p < 0.005$), but not on the primary outcome measures of the other tasks. Compared with controls and non-hemiplegic migraine patients, FHM1 patients showed substantially more deficits on all primary outcomes, including Purdue-peg assembly ($p < 0.05$), block-design scaled score ($p < 0.001$), shift in prism-adaptation ($p < 0.001$), peak-time of conditioned eyeblink responses ($p < 0.05$) and pitch-velocity score during stance-sway test ($p < 0.001$).

Conclusions

Unselected migraine patients from the general population show normal cerebellar functions despite having increased prevalence of ischaemic lesions in the cerebellar posterior lobe. Except for an impaired pegboard test revealing deficits in fine motor skills, these lesions appear to have little functional impact. In contrast, all cerebellar functions were significantly impaired in participants with FHM1.

Background

A range of clinical neurophysiological and functional imaging studies have suggested that migraine might be associated with cerebellar dysfunction (1–10). However, these studies were all conducted in patients who were selected from headache clinics and thus likely are on the more severe end of the clinical spectrum. Moreover, tests were not analysed blinded for diagnosis, and most migraine patients were using antimigraine medications potentially interfering with cerebellar function. Therefore, it is still uncertain whether migraine is associated with cerebellar dysfunction, and, if so, to what extent and why? Is cerebellar dysfunction due to the increased prevalence of cerebellar ischaemic lesions in migraine patients or is there a more functional explanation similar to what's seen in familial hemiplegic migraine type 1 (FHM1) (11,12)? Although a systematic quantitative assessment of cerebellar function in FHM has never been conducted, many FHM1 patients have signs of cerebellar ataxia on clinical examination (13). In the present study we systematically and quantitatively assessed in detail (i) motor and non-motor cerebellar function, (ii) presence and distribution of ischaemic lesions in the cerebellum and other parts of the brain, and (iii) the relationship between cerebellar lesions and dysfunction in 200 unselected patients with migraine with or without aura from the general population. The results were analysed blinded for diagnosis and compared with those obtained in 82 non-migraine control individuals and, as a positive control, 13 patients with genetically proven FHM1.

Methods

Participants

Individuals with migraine with aura (n =111, MA) or without aura (n=89,MO) and non-migraine controls (n=82) were all participants from the population based Cerebral Abnormalities in Migraine, an Epidemiological Risk Analysis Cohort (CAMERA II) study, which was primarily aimed at assessing longitudinal progression of brain lesions on magnetic resonance imaging (MRI) (14). All participants were invited to undergo cerebellar functions tests on the day MRI was performed. Participants were allowed to complete some or all tests, according to available time on the test occasion. No specific selection criteria were used. The study individuals were not informed about the specific goals of each test to avoid selection bias. Fifteen patients with

genetically proven FHM1 were invited as positive controls, 13 of whom (mean age 42 years, range 19–64; 69% female) agreed to participate.

All individuals with migraine were investigated in between attacks (at least two days after a previous and before a next attack). Thus, participants who developed an attack within 48 hours following data collection were retested later. All participants were interviewed on the use of medication, alcohol, or sedatives in the 24 hours prior to examination. Informed consent was obtained according to the Declaration of Helsinki. The Human Research and Review committee at the Leiden University Medical Center approved study procedures.

Neurological examination

All clinical examinations, tests, and data-processing were conducted by HK and IPM, who remained blinded for the individual diagnoses and clinical characteristics of the participants throughout the study (Table 1).

MRI

Whole-brain MR images were acquired using a 1.0T system in Doetinchem (Magnetom Harmony; Siemens AG, Erlangen, Germany) and 1.5T scanner in Maastricht (ACS-NT; Philips Medical Systems, Best, The Netherlands). For additional information see supplemental information at the end of this chapter.

Cerebellar tests

The cerebellar tests we used assess functions mediated by cerebrocerebellum, spinocerebellum, and vestibulocerebellum. The Purdue pegboard test is a specific test of fine motor skills (15), the Wechsler Adult Intelligence Scale, third edition (WAIS-III) block-design test assesses visuospatial ability to rotate objects mentally (16), the prism adaptation task tests subconscious arm movement learning (17), the eyeblink conditioning task tests acquisition of conditioned responses and learningdependent timing of these responses (18,19) and the body-sway test evaluates balance capabilities (20–22). For additional information on all separate cerebellar tests, see supplemental methods and e-Figure 1 at the end of this chapter.

Statistical analyses

Participants with MA, MO, controls and FHM1 patients were averaged as separate groups and analysed in a comparative fashion off-line. Characteristics and neurological examination dichotomous variables were analysed with Chi square, and

continuous variables with one-way analysis of variance (ANOVA). For the pegboard, block-design, prism adaptation test and bodysway task, one-way ANOVA was used. For comparison of latencies to peak-time in the valid trials between groups during eyeblink conditioning, we used the Kruskal-Wallis analysis, as data were not normally distributed (with post-hoc analysis between two groups). For conditioned response (CR) onset, CR peak-amplitudes, and percentage of CRs in the valid trials between groups, we used a one-way ANOVA. For the body-sway test roll angle and angular velocity as well as pitch angle and angular velocity were analysed using the 90% range automatically produced by Swaystar software. For Swaystar analysis linear regression was used to adjust for age and body mass index (BMI). For analysis of cerebellar tests vs ischaemic lesions, groups (with and without ischaemic lesions) were compared using Chi square or one-way ANOVA. Analyses were performed using SPSS 20.0 with significance levels set at 0.05. In addition, we used conservative p value for multiple comparisons applying Bonferroni correction for multiple comparisons set at $p < 0.01$.

Results

Neurological examination and MRI

Migraine and control individuals did not differ on baseline characteristics and physical neurological examination. Participants with FHM1 were on average younger and more frequently left-handed, and more frequently showed limb hypermetria and other signs of ataxia (Table 1).

In total 20 participants had cerebellar ischaemic lesions: 11/110 (10%) of those with MA, 6/86 (7%) of those with MO, and 3/79 (4%) of the controls (Supplemental table). Examples of different sizes of cerebellar silent infarcts in migraineur subjects are shown in Figure 1. Recent MRI was available in only three participants with FHM1 and no cerebellar infarcts were present. Except in one control, these lesions were always located in the posterior lobe in the cerebellar hemispheres and paravermal region; no lesions were observed in the vermis or vestibulocerebellum (Supplemental table). Participants with cerebellar ischaemic lesions more frequently were left-handed compared to those without such lesions (5/20 (25%) vs 15/251 (6%); $p=0.01$; handedness unknown in four participants), but otherwise comparable for age, educational level and neurological examination.

Table 1. Characteristics and physical examination.

Characteristics	Controls (n=82)	MA (n=111)	MO (n=89)	FHM1 (n=13)
Mean age (SD)	55 (7.5)	57 (8.1)	58 (7.5)	42 (13.3)
Female gender	72%	72%	71%	67%
Right-handedness	91%	93%	94%	100%
Mean attacks per year (SD; range)	Na	14 (20; 1–170)	19 (19; 2–105)	7 (14; 1–52)
Cerebellar lesion on MRI	4%	10%	7%	0%
Medication:				
Migraine prophylaxis	NA	5%	1%	23%
Triptans	NA	14%	8%	8%
Sedatives	5%	8%	10%	8%
Physical examination				
Limb hypermetria/ataxia	4%	2%	3%	15%
Dysdiadochokinesis	3%	4%	2%	8%
Hypermetric eye movements	3%	2%	1%	0%

Physical examination is available in 282 +12. MRI is available in 275 +2 participants. MA: migraine with aura; MO: migraine without aura; FHM1: familial hemiplegic migraine type 1; MRI: magnetic resonance imaging; NA: not applicable; SD: standard deviation.

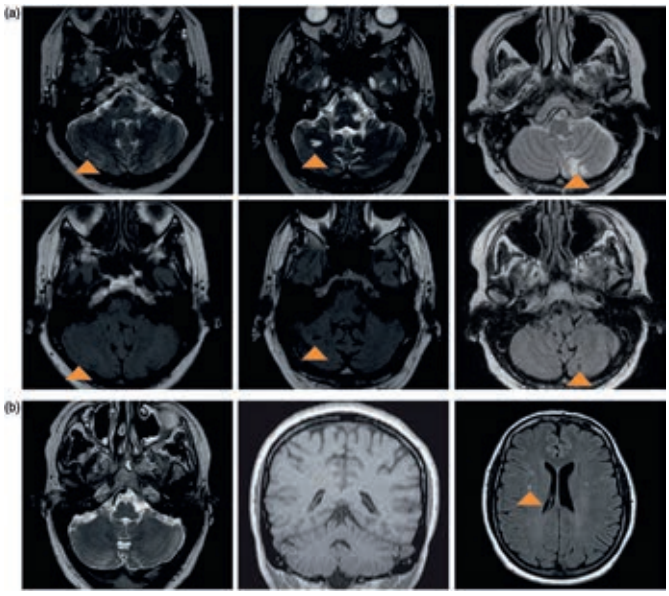


Figure 1. (a) Three examples of cerebellar infarcts in patients with migraine with aura. In the upper row T2-weighted images (infarcts appear as hyperintense parenchymal defects, indicated with arrowheads) and in the lower row corresponding FLAIR images. From left to right: female, 66 years old, with a small infarct in the right cerebellar hemisphere; male, 62 years old, with a medium-sized infarct in the right cerebellar hemisphere; and male, 54 years old, with multiple large infarcts in the left paravermal region. (b) MRI images from a 40-year-old male FHM1 patient, without cerebellar infarct or evidence of cerebellar or vermian atrophy; in the supratentorial white matter some nonspecific white-matter hyperintense lesions (arrowhead) are present (left image: transverse T2weighted image; middle image: coronal T1-weighted image; right image: transverse FLAIR image). FLAIR: fluid-attenuated inversion recovery; MRI: magnetic resonance imaging; FHM1: familial hemiplegic migraine type 1.

Cerebellar tests

Purdue pegboard task. A total of 282 participants (111 MA, 89 MO, and 82 controls) underwent Purdue pegboard investigation. There were no differences between the three groups on the assembly task or any of the other outcome measures (Table 2). The 20 individuals with a cerebellar ischaemic lesion performed significantly worse on most pegboard tasks (assembly task 5.9 vs 7.3, p= 0.002; number of pegs with right hand 12.4 vs 13.6 in non-infarct group, p= 0.03; and number of pegs with both hands 9.4 vs 10.8, p= 0.001) (Supplemental table). Among migraine patients the 17 with cerebellar ischaemic lesions on average performed worse than the 183 migraine patients without such lesions (assembly task 5.9 vs 7.3, respectively, p=0.005; number of pegs with right hand 11.8 vs 13.5, p=0.003; and number of pegs with both hands 9.5 vs 10.9, p= 0.006) (Supplemental table and Table 2). Participants with FHM1 (n =12) performed significantly worse on the assembly score (p= 0.04) and right-handed tasks (p= 0.03), but not on the other pegboard scores (Table 2).

Table 2. Participant characteristics and outcomes of Purdue pegboard investigation.

	Controls (n=82)	MA (n=111)	MO (n=89)	*p* value three groups	FHM1 (n=12)	*p* value four groups
Participant characteristics						
Mean age (SD)	55 (7.5)	57 (8.1)	58 (7.5)		42 (13.3)	
Female gender	72%	72%	71%		67%	
Right handedness	91%	93%	100%		100%	
Mean attacks per year (SD; range)	NA	14 (20; 1–170)	19 (19; 2–105)		7 (14; 1–52)	
Cerebellar lesion MRI	4%	10%	7%		NA	
Medication:						
Migraine prophylaxis	NA	5%	1%		25%	
Triptans	NA	14%	8%		0%	
Sedatives	5%	8%	10%		8%	
Outcomes Purdue pegboard						
Assembly task	7.3 (1.9)	6.8 (1.9)	7.3 (1.9)	0.1	6.0 (1.3)	0.04[a]
Right-handed task	13.7 (2.3)	13.6 (2.1)	13.1 (2.3)	0.1	12.0 (2.0)	0.03[a]
Left-handed task	13.2 (2.2)	13.3(2.2)	13.1 (2.4)	0.9	12.8 (2.3)	0.9
Both-handed task	10.5 (1.8)	10.8 (2.0)	10.8 (1.9)	0.6	10.5 (2.4)	0.8
Sum score	37.5 (5.4)	37.5 (5.5)	37.0 (5.7)	0.8	35.0 (4.9)	0.5

Tabled values represent the group means and standard deviations (SD), except for the variable gender, right handedness, medication and cerebellar lesions. Handedness data were taken from 278 +12 participants; MRI participants with pegboard from 275. Pegboard tasks are displayed as mean pegs during 30 seconds (SD). Range right-handed task covers 5–19 pegs, range sum score covers 16–50 pegs, and range assembly task 2–12 pegs. aBonferroni post-hoc analysis all <0.05 for FHM1 vs controls, FHM1 vs MA and FHM1 vs MO.
MA: migraine with aura; MO: migraine without aura; FHM1: familial hemiplegic migraine type 1; MRI: magnetic resonance imaging; NA: not applicable; SD: standard deviation.

Block-design test. A total of 202/282 (72%) participants (82 MA, 62 MO, and 58 controls) underwent the block-design test. The scaled score (primary endpoint) as well as the raw score and percentage within the highest tertile of scaled score (secondary endpoints) were not significantly different between migraine patients with or without aura and controls (Table 3). Participants with cerebellar ischaemic lesions (n= 9) did not perform worse than those without (Supplemental table). Participants with FMH1 (n=12) obtained significantly lower scores on the block-design test than the other three study groups. None of the participants with FHM1 was in the highest tertile of scaled scores (Table 3).

Table 3. Participant characteristics and outcomes of block design test.

	Controls (n= 58)	MA (n=82)	MO (n=62)	p value three groups	FHM1 (n=12)	p value four groups
Participant characteristics						
Mean age (SD)	55 (7.3)	57 (8.2)	58 (7.4)		42 (13.3)	
Female gender	64%	70%	76%		67%	
Right-handedness (%)	91%	95%	94%		100%	
Mean attacks per year (SD; range)	NA	17 (26; 1–170)	17 (17; 2–105)		7 (14; 1–52)	
Cerebellar lesion MRI	2%	8%	3%		NA	
Medication:						
Migraine prophylaxis	NA	0%	0%		25%	
Triptans	NA	11%	8%		0%	
Sedatives	2%	10%	8%		8%	
Outcomes block design test						
Mean scaled score (SD)	9.8 (3.2)	10.7 (3.6)	9.7 (3.3)	0.2	4.0 (3.0)	<0.001[a]
Scaled score, high	11 (19%)	27 (33%)	15 (24%)	0.2	0 (0%)	0.047
Mean raw score (SD)	30.3 (14.6)	33.5 (15.9)	29.5 (13.9)	0.2	13.4 (11.3)	<0.001[a]

Handedness known for 198 +12 participants. Neurological examination for 200+12 participants. MRI for 199 participants. High education defined as university of professional education or higher; block-design test scaled score was recoded in tertiles (low, medium, high), low 4–7, medium 8–12, high 13–19; analysis of variance (ANOVA) post hoc aBonferroni all <0.001.

MA: migraine with aura; MO: migraine without aura; FHM1: familial hemiplegic migraine type 1; MRI: magnetic resonance imaging; NA: not applicable; SD: standard deviation.

Prism adaptation test. A total of 132/282 (47%) individuals (49 MA, 44 MO, and 39 controls) participated in the prism goggles adaptation test (Table 4). Accurate goal-directed hand movements towards the target were similar in all three study groups. No significant differences between groups in prism-induced hand movement adaptation (primary endpoint; phase five vs phase two) or movement variability (Figure 2; Table 4) were found. Of 128 participants in the prism adaptation test who also underwent MRI, seven had cerebellar ischaemic lesions, five of whom had MA. No differences were found between these small sub-groups (Supplemental table).

In the 12 participants with FHM1 the prism-induced hand movement adaptation was greatly reduced compared to the other groups, both with regard to the general adaption (phase five vs phase two) and mean horizontal shift of task five (in both cases, four group comparison $p<0.001$; Table 4).

Table 4. Participant characteristics and outcomes of prism adaptation test.

	Controls (n=39)	MA (n=49)	MO (n=44)	p value three groups	FHM1 (n = 12)	p value four groups
Participant characteristics						
Mean age (SD)	55 (7)	58 (8)	57 (7)		42 (13)	
Female gender	62%	78%	77%		75%	
Right-handedness	87%	94%	96%		100%	
Mean attacks per year (SD; range)	NA	14 (15; 1–105)	18 (20; 2–105)		7 (14; 1–52)	
Cerebellar lesion MRI	3%	11%	2%		NA	
Medication:						
Migraine prophylaxis	NA	2%	0%		25%	
Triptans	NA	15%	9%		0%	
Sedatives	2%	10%	8%		8%	
Outcomes prism adaptation						
Adaptation in cm (SD)	3.5 (1.8)	3.1 (1.6)	3.6 (1.7)	0.8	–1.0 (3.4)	<0.001[a]
Mean horizontal shift task 4 in cm (SD)	0.9 (3.1)	1.2 (2.7)	1.2 (2.6)	0.8	0.2 (0.9)	0.5
Mean horizontal shift task 5 in cm (SD)	–4.3 (2.5)	–3.7 (1.8)	–3.9 (2.2)	0.8	–0.3 (2.1)	<0.001[a]

Mean horizontal shift task 4; horizontal shift with prism goggles and with feedback. Mean horizontal shift task 5; horizontal shift after prism goggles being removed, negative values indicate leftward shift. Adaptation; defined as mean x-coordinate task 5 minus mean x-coordinated task 2. aBonferroni post-hoc analysis all <0.001 for FHM1 vs controls, FHM1 vs migraine with aura and FHM1 vs migraine without aura.
MA: migraine with aura; MO: migraine without aura; FHM1: familial hemiplegic migraine type 1; MRI: magnetic resonance imaging; NA: not applicable; SD: standard deviation.

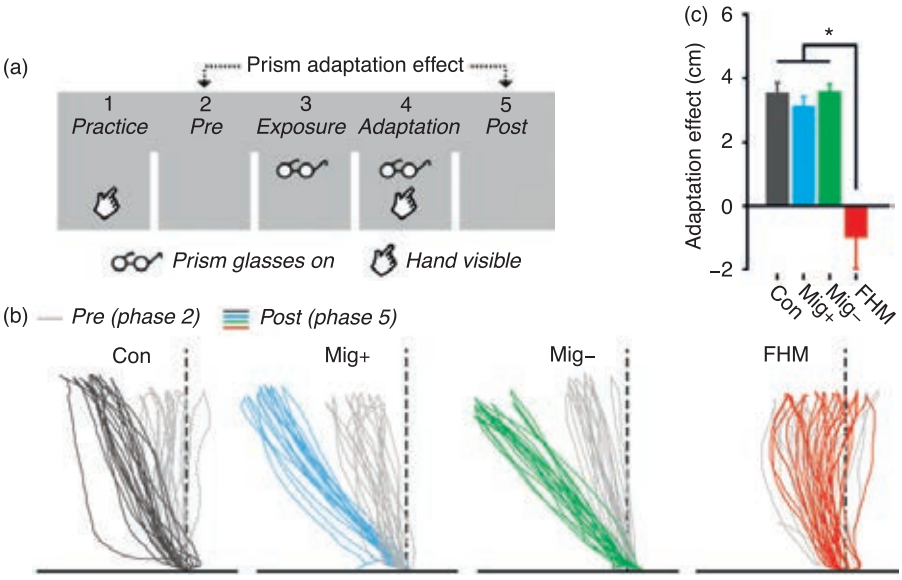


Figure 2. Prism adaptation task in non-migraine controls, migraine patients with or without aura, and patients with FHM1. (a) The prism adaption experiment consisted of five phases in which participants had to move their hand to a visible target with or without visible feedback of their hand and with or without wearing prism glasses. In the adaptation phase (phase 4) participants learned to align their hand movements to the target that was visually shifted due to the prism glasses. (b) Individual raw hand movements in phase 2 (pre-adaptation) and phase 5 (post-adaptation) of four participants show that wearing prism glasses induces changes in hand movements, except for the FHM1 patient. (c) Overall, the prism adaptation effect was present in the control group and both groups of migraine patients, whereas the FHM1 group showed no prism adaptation effect. FHM1: familial hemiplegic migraine type 1.

Eyeblink conditioning. We performed eyeblink conditioning in 104/282 (37%) participants (38 MA, 35 MO, and 31 controls). Latency to onset, latency to peak-time, peak-amplitude, and percentage of conditioned responses did not differ between the three study groups (Figure 3 d-g; Table 5). Adjusting for gender and age did not alter these findings. Cerebellar ischaemic lesions were found in 6/103 of the participants who also underwent MRI; three with MA, two with MO, and one control. Four of these lesions were located in the posterior paravermis and two in the posterior hemisphere, but none in the critical eyeblink region HVI (10,23) (see also supplemental table). No differences in latency to peak-time (p= 0.5) or peakamplitude (p=0.1) of the conditioned responses were found between participants with and without cerebellar ischaemic lesions. In participants with FHM1 (n=11) mean latency to onset and peak-time of conditioned responses deviated significantly (p=0.001 and p=0.01, respectively) from the other study groups; both time points occurred earlier,

preventing optimal closure of the eyelid when the unconditioned stimulus was about to occur (Figure 3c–e). In addition, the mean peak-amplitude of participants with FHM1 was significantly smaller ($p = 0.045$) than the amplitudes in the other three study groups (Figure 3c-f). When looking at percentage of CRs before (block 1) and after training (maximum percentage in block 6, 7 or 8), all three study groups showed a similar significant increase (before training between groups $p=0.9$, one-way ANOVA; after training between groups $p=0.8$, one-way ANOVA; before training vs after training p all groups <0.001, paired t-test) (Figure 3g). Together these data show no difference in conditioning between controls and participants with migraine. On the other hand, participants with FHM1 learn to make the association between conditioned and unconditioned stimulus (similar CR percentages), but are unable to produce a strong, properly timed eyeblink (Table 5).

Body-sway task. In total 177/282 (63%) participants (71 MA, 53 MO, and 53 controls) completed the bodysway task. Most subjects completed the two-legged stance condition 155/177 (88%), compared to 136 participants (77%) for walking condition and 77 participants (44%) who completed the one-legged stance step condition. The proportions of participants who could complete the separate conditions did not differ among the three study groups; neither did the other body-sway parameters such as roll angle, roll velocity, pitch angle, and pitch velocity (Table 6). This remained so after adjusting for age and BMI.

Brain imaging was available for 174/177 (98%) participants, eight of whom (seven with migraine) had a cerebellar ischaemic lesion. These performed equally well on all sub-tasks of the body-sway test as the participants without such a lesion (data not shown).

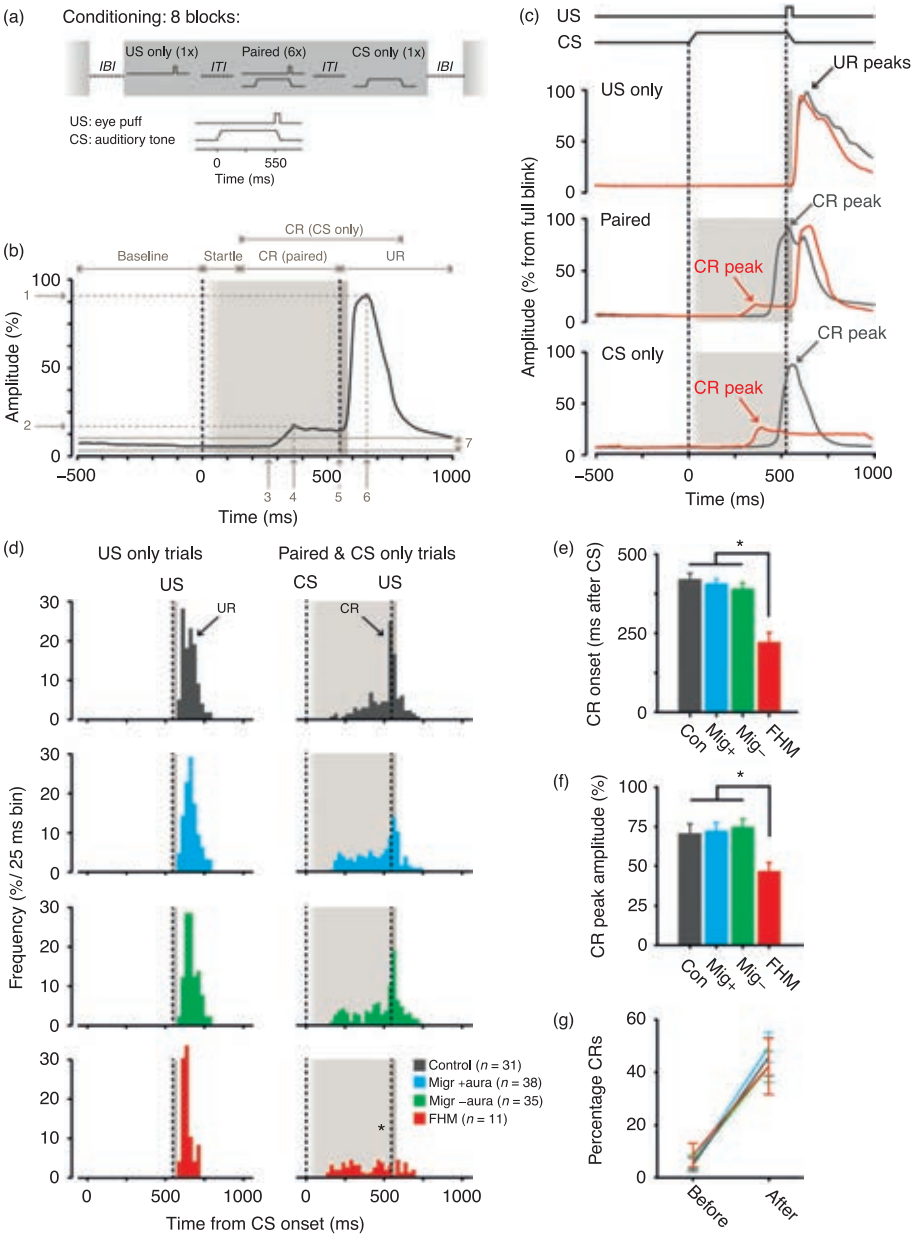


Figure 3. Eyeblink conditioning in non-migraine controls, migraine patients with or without aura, and patients with FHM1. (a) Experimental paradigm for the eyeblink conditioning task. The unconditioned stimulus (US) was a mild air puff (30 ms), which was applied to the left eye and elicited a reflexive eyeblink. The conditioned stimulus (CS) was a clearly audible tone (1 kHz, 70–80 dB, duration 580 ms), presented via headphones. Each training session consisted of eight blocks, separated by an inter-block interval (IBI) of 120 ± 20 s. Each block in turn consisted of eight trials separated by an inter-trial interval (ITI) of 30 ± 10 s. CS and US were presented in a delay paradigm, in which the interval between CSand US-onset was 550 ms. (b) Analysis of raw data traces. Eyelid

movements larger than the 2 x SD of the 500 ms pre-CS period were considered as significant and further categorised into auditory startle response (latency to peak 10–150 ms) and cerebellar conditioned responses (CRs; latency to peak 150-600 ms). The peakamplitude for all responses was expressed as the percentage of the averaged peak-amplitude in all US-only trials for that participant. Arrows indicate: 1 unconditioned response (UR) peak-amplitude, 2 CR peak-amplitude, 3 CR onset, 4 CR peak-time, 5 UR onset, 6 UR peak-time, and 7 2 x SD of 500 ms pre-CS baseline period. (c) Examples of raw data traces obtained from a control (anthracite line) and FMH1 patient (red line). In US-only trials (upper panel) controls and FMH patients show a normal reflexive eyelid closure. In paired (middle panel) and CS-only trials (lower panel) controls show large amplitude and perfectly timed CRs, i.e. the peak of the CR is exactly at the point where the US is delivered. FHM1 patients show CRs, but those CRs have much smaller amplitudes. In addition, the timing of their CRs is severely impaired in that they start too early and therefore reach the maximum eyelid closure too early. (d) Right panels. Peak timing of CRs over all eight training blocks per group. Controls, and migraine patients with and without aura show a clear preference in the peak-time of their CR around the US onset. FHM1 patients completely lack this timing aspect in their CRs (asterisk). Left panels. For comparison we plotted the peak timing of URs over all eight training blocks in US-only trials, in which no difference was found between the four groups. (E) CR onset over all eight training blocks per group. FHM1 patients have CRs that started significantly earlier than CRs in controls, migraine patients with and without aura. (f) CR peak-amplitude over all eight training blocks per group. FHM1 patients have significantly smaller CR amplitudes than controls and migraine patients with and without aura. (g) No difference was found between groups in the CR percentage before training (block 1) and after training (maximum percentage in either block 6, 7 or 8). FHM1: familial hemiplegic migraine type 1.

When including participants with FHM1 in a fourgroup comparison with controls and participants with migraine with or without aura, pitch angle velocity ($F(3,164) = 24.1$, $p < 0.001$) and pitch angle ($F(3,164) = 13.3$, $p < 0.001$) were significantly different. Post hoc analysis using the Bonferroni-test showed that for the two-legged stance condition the mean pitch angle velocity (4.2; SD 2.2) and pitch angle (2.2; SD 0.8) for participants with FHM1 were significantly higher than those in controls and participants with migraine with or without aura (Figure 4). These differences remained so after adjustments for BMI and age (see Model 1 in Table 6). None of the participants with FHM1 could complete the one-legged stance step condition. When evaluating all six individual tasks of this test separately, sway measurements were significantly increased in both pitch and roll directions in participants with FHM1 compared to the other groups (Table 6). During the walking condition post hoc comparisons using the Bonferroni-test indicated that the mean pitch velocity for participants with FHM1 (40.6 degrees per sec, SD 7.7) was significantly higher compared to controls (31.9 degrees per sec, SD 9.4) and participants with migraine (30.2 degrees per sec, SD 8.6) or without aura (28.2 degrees per sec, SD 8.8). These differences remained significant after adjusting for age and BMI.

Table 5. Participant characteristics and outcomes of eyeblink conditioning test.

	Controls (*n*=31)	MA (*n*=38)	MO (*n*=35)	*p* value three groups	FHM1 (*n*=11)	*p* value four groups
Characteristics						
Mean age (SD)	54 (7.0)	57 (8.4)	56 (6.8)		40 (12.9)	
Female gender	58%	58%	77%		73%	
Right-handedness	93%	92%	91%		100%	
Mean attacks per year (SD; range)	NA	14 (26; 1–170)	16 (19; 3–105)		7 (15; 1–52)	
Cerebellar lesion MRI	3%	8%	6%		NA	
Medication:						
Migraine prophylaxis	NA	3%	0%		27%	
Triptans	NA	13%	8%		9%	
Sedatives	0%	10%	7%		9%	
Outcomes						
Latency to CR peak time (ms)	554 (85.6)	520 (89.8)	501 (100.3)	0.3	420 (92.5)	0.01[a]
Latency to CR onset (ms)	421 (90.6)	405 (84.9)	387 (87.1)	0.4	224 (94.7)	<0.001[b]
Peak amplitude CR (% from full UR)	72.3 (30.3)	72.9 (30.7)	74.2 (26.9)	0.98	46.2 (16.9)	0.045[c]
Percentage CR before training	5 (13)	6 (15)	6 (14)	0.9	9 (14)	0.9
Percentage CR after training	46 (36)	50 (33)	42 (33)	0.7	42 (34)	0.8

MRI n =103; all eyeblink conditioning values are expressed as mean ±SD. a*p* value for four-group comparison Kruskal-Wallis test; post hoc; MA vs FHM1 p=0.01, MO vs FHM1 *p* =0.03, Control vs. FHM1 *p*= 0.001. b*p* value four-group comparison one-way analysis of variance (ANOVA), post hoc all comparison <0.001. c*p* value for four-group comparison ANOVA); post hoc; MA vs FHM1 *p*= 0.02, MO vs FHM1 *p*= 0.005, Control vs. FHM1 *p*=0.014. All peak-time and onset values of conditioned responses (CRs) expressed as latency in milliseconds after onset of conditioned stimulus (CS); CR amplitude expressed as percentage from full eyelid closure. When looking at CR percentage before (block 1) and after training (maximum percentage in block 6, 7 or 8), all groups showed a significant increase (*p* all groups <0.001).

MA: migraine with aura; MO: migraine without aura; FHM1: familial hemiplegic migraine type 1; MRI: magnetic resonance imaging; NA: not applicable; SD: standard deviation.

Table 6. Participant characteristics and outcomes of body sway test.

	Controls (*n* = 53)	MA (*n*= 71)	MO (*n* = 53)	three groups	*p* value model 1	FHMI (*n*=13)	four groups	*p* value model 1
Participant characteristics								
Mean age (SD)	55 (7.3)	58 (8.1)	58 (7.3)			42(13)		
Female gender	62%	72%	72%			69%		
Body mass index (SD)	26 (3.6)	26 (3.9)	25 (3.4)			25 (3.8)		
Alcohol use last 12 hours	10%	1%	4%			0%		
Mean attacks per year ((SD; range)	NA	17 (27; 1-170)	1 17 (17; 2-105)			7 (14; 1-52)		
Cerebellar lesion MRI	2%	7%	4%			NA		
Medication:								
Migraine prophylaxis	NA	0%	0%			23%		
Triptans	NA	10%	8%			8%		
Sedatives	2%	10%	8%			8%		
Outcomes								
Two-legs stance condition								
Completed	n = 44 (83%)	n = 63 (89%)	n = 48 (91%)	0,5	NA	n= 12 (92%)	0,6	NA
Roll angle	0.8 (0.3)	0.8 (0.3)	0.8 (0.4)	0,9	0,7	1.0 (0.7)	0,2	0,2
Roll velocity	1.5 (0.8)	1.4 (0.6)	1.4 (0.6)	0,8	0,5	2.1 (1.4)	0,02	0,1
Pitch angle	1.4 (0.3)	1.4 (0.4)	1.5 (0.5)	0,7	0,6	2.2 (0.8)	<0.001	0,001
Pitch velocity	2.1 (0.7)	2.0 (0.5)	2.1 (0.7)	0,5	0,2	4.2 (2.2)	<0.001	<0.001
One-leg stance step condition								
Completed	n = 20 (38%)	n = 33 (47%)	n = 24 (45%)	0,6	NA	n = 0 (0%)	0,01	Na
Roll angle	8.0 (2.2)	7.6 (2.2)	8.2 (2.7)	0,6	0,6	NA	NA	NA
Roll velocity	22.7 (6.0)	20.2 (5.5)	22.6 (7.3)	0,3	0,1	NA	NA	NA
Pitch angle	6.1 (1.3)	5.9 (1.4)	6.3 (2.3)	0,8	0,4	NA	NA	NA
Pitch velocity	39.3 (10.9)	34.0 (8.1)	34.5(9.5)	0,2	0,03	NA	NA	NA
Walking condition								
Completed	n = 39 (78%)	n = 58 (83%)	n = 39 (75%)	0,6	NA	n= 12 (92%)	0,5	NA
Roll angle	8.5 (3.3)	7.9 (3.6)	7.4 (3.02)	0,4	0,2	6.8 (3.3)	0,4	0,4
Roll velocity	28.7 (6.7)	26.4 (7.2)	27.4 (8.2)	0,3	0,1	31.7 (7.9)	0,1	0,03
Pitch angle	8.1 (3.2)	8.0 (3.1)	6.9 (2.4)	0,1	0,3	7.1 (1.6)	0,2	0,3
Pitch velocity	31.9 (9.4)	30.2 (8.6)	28.2 (8.8)	0,2	0,3	40.6 (7.7)	<0.001	0,02

Data represent mean (SD), or numbers (percentage in parenthesis). MRI is available in 174 participants. Medication use indicates current users. Completed: participant performed on all separate tasks of the condition for at least five seconds. Number of participants differs between two-leg stance, one-leg stance stepping condition and walking condition, as participants had to complete all separate tasks of a particular condition. Number of individuals participating in walking task was 185, as five patients refused. P value Model 1 = p value using linear regression with adjustment for BMI and age. Post-hoc comparisons are given in text.
MA: migraine with aura; MO: migraine without aura; FHM1: familial hemiplegic migraine type 1; MRI: magnetic resonance imaging; BMI: body mass index; NA: not applicable; SD: standard deviation.

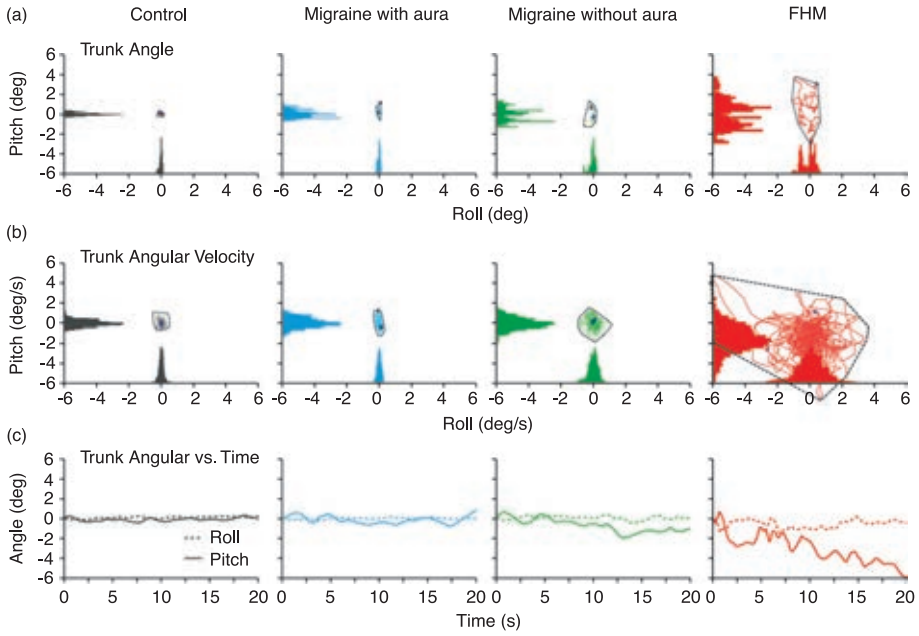


Figure 4. Body-sway measurements during one task of two-legged stance condition (two legs with eyes closed on foam) for individual participants. Panels show pitch angle vs roll angle (top row), pitch angle velocity vs roll angle velocity (middle row), and angles for roll and pitch over time (bottom row) for a healthy control, migraineur with aura, migraineur without aura and FHM1 patient, from left to right, respectively. Note that for all parameters controls and migraine patients are similar, whereas the FHM1 patient stands out showing deviations and instability. FHM1: familial hemiplegic migraine type 1.

Discussion

We tested the hypotheses (i) that migraine is associated with cerebellar dysfunction and (ii) that this might be due to increased prevalence of cerebellar ischaemic lesions. To this end we systematically assessed motor and non-motor cerebellar function of unselected but well-defined migraine patients with or without aura from the general population by using an array of sensitive and validated tests covering all main functions of the cerebellar cortex. In addition, all participants underwent brain MRI to screen for cerebellar lesions. Results were compared with those obtained in non-migraine controls and, as a positive control, participants with genetically proven FHM1. Whereas participants with FHM1 performed worse compared both to controls and participants with non-hemiplegic migraine on the primary outcomes of all behavioural tests, participants with non-hemiplegic migraine did not differ from non-

migraine controls for: (i) fine motor speed and coordination as evaluated with the Purdue pegboard task; (ii) perceptual intelligence and motor function as evaluated with the WAIS-III block-design test; (iii) cerebellar motor coordination and learning of limb movements as evaluated with the prism adaptation test; (iv) associative cerebellar motor learning evaluated with the eyeblink conditioning paradigm; and (v) vestibular motor coordination and adaptation as evaluated with the body-sway test. Participants with migraine who had cerebellar ischaemic lesions performed worse on some parameters of the pegboard task, but not on the other cerebellar motor tasks.

Cerebellar function in migraine patients from the general population

The present study is the first to assess cerebellar function in detail over a wide range of modalities in a large and unselected but clinically well-characterised group of migraine patients from the general population. Whereas previous studies suggested subclinical cerebellar dysfunction in migraine patients who were drawn from headache clinics (1,6,10), we failed to find any evidence of impaired cerebellar function in the 'average migraine patient' from the general population despite using a diverse set of highly sensitive clinical tests.

We employed a wide array of tests, which together cover functions of all main parts of the cerebellar cortex including cerebrocerebellum (hemispheres; e.g. Purdue pegboard task, block-design test and eyeblink conditioning), spinocerebellum (vermis and paravermis; e.g. prism adaptation test and eyeblink conditioning) and vestibulocerebellum (flocculus and nodulus; e.g. bodysway test) (23–30). The cerebrocerebellum receives input from the cerebral cortex and mainly controls planning of movements, while the spinocerebellum and vestibulocerebellum receive inputs from spinal cord and brainstem regions involved in sensory proprioceptive, vestibular and visual processing and mainly control execution of limb, eye and head movements (31–33). Moreover, the tests probably also cover functions of both the anterior and posterior lobe (25,26,28–30). The posterior lobe may differ from the anterior lobe in that it may be more prominently involved in non-motor cognitive and autonomic functions (31,34–37), and/or visuomotor planning (32).

Our results diverge from those obtained in other studies (1,2,6,10). These studies were small and included migraine patients who were all selected from headache clinics. As a consequence, many of these patients most likely were on the more severe end of the clinical migraine spectrum and were using antimigraine medications potentially interfering with cerebellar functions. Moreover, the researchers in these studies were not blinded for diagnosis while using only single test paradigms such

as the pointing paradigm or posturographic measures of sway (1,6), which are potentially open for bias. We don't believe the contrasting findings were due to use of different tests. The pointing paradigm resembles the prism paradigm we used in that it also compares motor output of the forelimbs before and after manipulating visual feedback and the posturographic measures of sway were similar to our body-sway test (1,6). Conditioned eyeblink responses measured with the use of electromyography (EMG) (10), can be readily repeated with the more sensitive Magnetic Distance Measurement Technique (MDT) method used in the current study (19). Finally, as we did find significant differences in a relatively small group of FHM1 patients with the same set of tests, we are reassured that the tests we employed were sufficiently sensitive to detect differences. Thus, in contrast to previous findings (1,7,8,38), our findings argue against the hypothesis that cerebellar function is altered in the average migraine patient. Moreover the results of our study underline the importance of including unbiased study populations and ensuring that investigators are blinded for clinical diagnosis.

The effect of cerebellar ischaemic lesions on cerebellar function

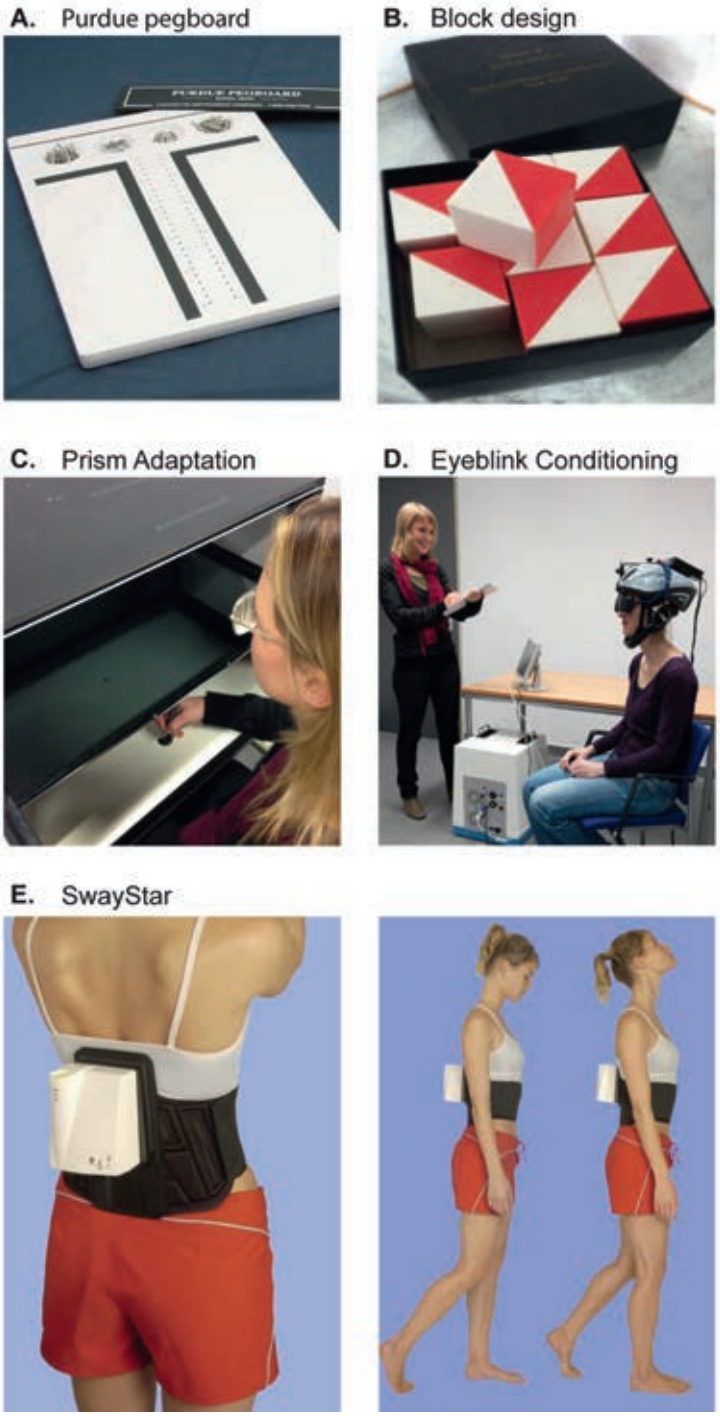
A conspicuous advantage of our study was that virtually all migraine patients and controls (275/282; 98%) were subjected to detailed brain MRI as part of the CAMERA-2 study. In total 20/275 (7%) individuals,17 with migraine and three controls, showed cerebellar ischaemic lesions, eight had an isolated cerebellar ischaemic lesion. Migraine patients with cerebellar ischaemic lesions performed significantly worse on multiple outcomes of the pegboard task including the assembly score, number of pegs with right hand and number of pegs with both hands. However, outcome parameters of all other cerebellar tests were not affected.

Why we detected deficits only with the pegboard test remains elusive. Possibly the cerebellar ischaemic lesions were accidently selectively localised in the cerebellar lobules involved in pegboard performance, but not the other tests. Such an explanation would be in line with the finding that the patients with impaired pegboard performance all showed larger lesions mainly in the posterior lobules (Supplemental table), which is the cerebellar region presumably responsible for this task (29,31,34). The anterior lobe can also contribute to limb movements (39). However, as indicated by several studies (29,31,34) the fine finger movements, as tested intensely by the pegboard test, rely mainly heavily on the loop between the posterior cerebellum and cerebral cortex. Alternatively, performance of the pegboard task might also depend on cerebral cortical function (29), and the

individuals suffering from impaired pegboard performance might accidently show ischaemic lesions in both the cerebellum and supratentorial regions (possibly even including whitematter lesions). Such a hypothesis would be compatible with findings by Brighina and colleagues (7), who found in MA patients a significant deficit in cerebellar inhibition of cerebral cortical processing following conditioning with transcranial magnetic stimulation. However, several of the migraine patients with both cerebellar and supratentorial lesions had a good score on the pegboard task (supplemental table), whereas many with a bad score had no signs of cerebral cortical lesions. Studies at even higher MRI resolution and including even larger numbers of patients with possibly even more specific tests and multivariate lesion symptom mapping approaches might help to resolve this issue (40).

Cerebellar function in FHM1

In contrast to migraine patients, FHM1 patients showed impaired cerebellar function with significant differences for all primary and most secondary outcome measures of all five cerebellar function tests. As our group of FHM1 patients was small (n=13) and their average age was about 15 years younger (Table 1), the differences we found are likely to underestimate the true difference with non-hemiplegic migraine patients and controls. Our test findings were in line with the findings on physical examination and are in agreement with other studies on figural memory and executive function in FHM1 patients (41). Body-sway in FHM1 patients was particularly increased in the anterior-posterior direction, which is in line with findings in spinocerebellar ataxia patients (42). The symptoms of impaired motor and non-motor cerebellar function in FHM1 patients probably initially result directly from a different calcium influx in their Purkinje cells, the simple spike output of which is highly irregular early on (43,44). These electrophysiological aberrations have been shown to be sufficient to cause ataxia (43,45,46), but they will also induce changes in energy consumption and contribute to cerebellar degeneration over time (47,48). Thus, the combination of these pathophysiological mechanisms following the FHM1 CACNA1A mutation increasingly affects the capabilities for motor learning and consolidation, and ultimately leads to motor performance problems and overt signs of ataxia (45). However, as we did not have (recent) MRI imaging of most FHM1 patients, any effect of possible macroscopical structural lesions on cerebellar function can also not be ruled out.


A. Purdue pegboard
B. Block design
C. Prism Adaptation
D. Eyeblink Conditioning
E. SwayStar

E-figure 1.

Supplemental methods

MRI

We acquired 48 contiguous 3-mm axial slices (field of view 22 cm; matrix, 190-205 x 256) using combined proton density and T2-weighted fast spin-echo (repetition time/echo time, 3000/14-85 for Magnetom Harmony and 3000/27-120 for ACS-NT) and fluid-attenuated inversion-recovery (FLAIR; repetition time/echo time/inversion time 8000/105/2000 for Magnetom Harmony and 8000/100/2000 for ACS-NT) sequences to cover the whole brain. (Silent) ischaemic lesions were defined as non-mass parenchymal defects with a vascular distribution and iso-intense to cerebrospinal fluid signal on all sequences (Bokura *et al.*, 1998; Kruit *et al.*, 2004). Infratentorial lesions were evaluated as hyperintense on T2- and proton-density-weighted and not hypo-intense on FLAIR images. Location and vascular territory of new and pre-existing infarct-like lesions were analyzed by two neuroradiologists, blinded for diagnosis (κ=0.87, p<0.001). Detailed cerebellar topography of found infarct-like lesions was provided using cerebellar territories described by Ye (2010). All sequences of baseline and follow-up scans were presented side-by-side (angulation-corrected and position-linked).

Cerebellar tests

The Purdue pegboard (Lafayette instrument company, model 32020) is made of a board with two vertical lines penetrated at equal distances with 25 holes (Supplementary figure 1A) (Loras *et al.*, 2013). In the first part of the test participants are given 30 seconds to place as many pins (i.e. pegs) in the right-hand column of holes as possible. Pins may only be placed with the right hand and must be inserted in order. In the second part, this process is repeated using the left hand and column. In the third part, participants have 30 seconds to place pins into both columns at the same time; they must use the right hand for the right column and the left hand for the left column. In the final part of the test, called the assembly test, the participant must pick up a pin and insert it into a hole with the right hand and then pick up a washer and place it over the pin with the left hand. Subsequently, participants must pick up a collar with the right hand and place it over the pin on top of the washer, and then place a final washer on top of the collar with the left hand. Participants should complete as many assemblies as possible within 60 seconds. The primary endpoint of the pegboard test was the number of assemblies during the assembly task (Table 2). Secondary outcome measures were number of placed pegs during tasks 1, 2 and 3,

and combined sum score of pegs during these tasks. The assembly task is adjusted for handedness by reversing pins and washers for left handed participants.

The block-design test was assessed following the manual for WAIS III (Kaufman and Lichtenberg, 1999). The participant is required to arrange a set of blocks to reproduce a displayed pattern printed on cardboard (3 by 4 inches) (Supplementary figure 1B). The items start simple, but get more difficult with each next item. The size of the designs varies from 4 to 16 blocks. The time needed to assess these designs is recorded, and points are given according to cut off values for the time used for each design. The time allowed to complete an item varies from 20 sec (4 blocks) to 120 sec (16 blocks). The discontinue criterion is four successive scores of zero. Scores from the different items are added to form the rough score (minimum 0, maximum 68 points). The mean scaled score (adjusted for age) was the primary endpoint (Table 3). Secondary endpoints were the raw score and the percentage within the highest tertile of scaled scores.

During the prism adaptation task repetitive pointing of the arm to visual targets seen with optical prisms normally induces a bias pointing in the opposite direction following prism removal (Van der Geest *et al.*, 2005; Werner *et al.*, 2010; Krab *et al.*, 2011). Participants are seated in front of a digitalizing tablet (Intuos 4 XL DTP, Wacom Europe GmbH, Krefeld, Germany) and a black dotted target is projected from above by a see-through mirror, while their hand is visible. Putting an opaque plate below the mirror blocks visual feedback of hand position, while the target is still visible through the mirror (Supplementary figure 1C). The experiment consists of four phases (Fig. 2A). In all phases the subject has to move the pen a number of times from a starting position at the bottom of the tablet towards the position of the target over a distance of 20 cm. In phase one (practice) the subject has to move the pen towards the target 10 times, while they can see their hand (visual feedback). In phase two (pre-test) the subject has to move the pen 10 times without visual feedback. In phase three (prism exposure) the subject wears prism glasses that shift the visual world 10° to the right, without visual feedback of the hand movement. Subjects have to move the pen 10 times to the target. In phase four (adaptation) they can see their hand again, so that the position of hand and target can be visually (re-)aligned. Just before the final phase five (post-test), the glasses are removed and subjects have to move the pen 10 times without visual feedback. The average x-coordinate and y-coordinate of the endpoints of the hand movements are calculated for each phase of the experiment for a single participant (Table 4). Primary outcome was the shift in mean x-coordinates between the post-test and pre-test phases (prism induced hand movement adaptation: phase

five minus phase two). Secondary outcome was the individual spread of x coordinates observed when there was no visual feedback of the hand (movement variability; phase two).

During classical Pavlovian eyeblink conditioning an eyeblink eliciting unconditioned stimulus (US; e.g. an air puff) is repeatedly preceded by a conditioned stimulus (CS; e.g. an auditory tone), ultimately inducing a conditioned response (CR) on the CS alone (Koekkoek *et al.*, 2003; Koekkoek *et al.*, 2005) (Fig. 3A). Participants are equipped with a headphone, video goggles (Logitech, USA) and an air puff nozzle connected to it. The 580 ms tone CS (1 kHz, 70-90 dB) is delivered via the headphone, while the 30 ms air puff US is applied to the left cornea via the nozzle, creating a CS-US interval of 550 ms. The experiment consists of 8 blocks, each consisting of 1 US-only, 6 paired CS-US, and 1 CS-only trial (Fig. 3A). Eyelid movements are recorded with the Magnetic Distance Measurement Technique (MDMT) (Koekkoek *et al.*, 2005; Smit *et al.*, 2008). Individual eyeblink traces are analyzed offline with custom computer software (LabVIEW®) by an experienced researcher, blinded for participant characteristics. Eyelid movements larger than 2 x SD of the 500 ms pre-CS period are considered as significant and further categorized into auditory startle response (latency to peak 10-150 ms) and cerebellar CRs (latency to onset 150-500 ms and latency to peak 150-600 ms) (Fig. 3B). As primary outcome measures for this test of learning-dependent timing we used the adaptive timing of eyeblink CRs as represented by the mean latency to CR onset and mean latency to CR peak-time (Table 5). As secondary outcome measures we used the peak-amplitude of the CRs per session, expressed as percentage of the mean URs in US-only trials, and the percentage of CRs of paired trials before and after conditioning, applying a 2 SD criterion for eyelid position to pass baseline and an attention check for the final blocks (using a 5 SD criterion did not result in additional significant differences among groups; data not shown). CR peak-amplitude and CR peak-time were only calculated for trials in which a CR was present and auditory startle responses were not further analyzed.

The body-sway task measures balance abnormalities during stance and gait tasks by quantifying body-sway using body-worn gyroscopes measuring angular velocity (Allum and Carpenter, 2005; Horlings *et al.*, 2008; Kung *et al.*, 2009). The equipment consists of 1) a foam support (density of 25 kg/m^3) with a height, width and length of 10 cm, 44 cm and 102 cm, respectively, on which the subjects have to stand and walk; 2) two digital angular velocity transducers with low drift (less than 6°/h) that are attached to the lower back at L1-L3 level using a special belt (Supplementary figure 1E) (Swaystar system, Balance International Innovations GmbH Switzerland); and 3)

a computer connected to the gyroscopes by Bluetooth® (Horlings *et al.*, 2008). Body-sway in the mediolateral (roll) and anterior-posterior (pitch) plane is measured using the two gyroscopes under three different protocols, including a two-legged stance condition, a one-legged stance step condition, and a walking condition. As primary outcome measure for the body-sway test we used the pitch and roll velocity score under the two-legged stance condition (Table 6). As secondary outcome measures we used pitch and roll angle under two-legged stance condition, pitch and roll velocity under one-legged stance step condition, pitch and roll angle under one-legged stance step condition, pitch and roll velocity under walking condition, and pitch and roll angle under walking condition. To complete a condition was defined as a participant could perform all seperate body-sway measurements included in that condition for at least 5 seconds.

Supplemental table. Overview of main outcomes of structural MRI

Subject	Age, gender, migraine	Amount of cerebellar ischemic lesions	Cerebellar ischemic region and size	Supratentorial infarct-like lesion	Infratentorial hyperintense lesion (pontine)	Peg Assembly score	Block design scaled score	Prism adaptation (cm)	Eyeblink peaktime (ms)	Eyeblink normalized peak-amplitude#	Body-sway Two-legs stance condition roll angle	Neurological examination
Total group*, Impact of lesions						N=275 Mean 5.9 vs 7.3 *P* = 0.002	N=199 Mean 10.2 vs 10.2 *P*=0.97	N=128 Mean 3.6 vs 3.4 *P*=0.8	N=103 Mean 502 vs 542 ms. *P*=0.5	N=103 Mean 54.0 vs 75.6 *P*=0.1	N=155 Mean 0.8 vs 0.9 P=0.7	
1	64, M,MO	1	PPV-large	None	None	2	Na	Na	509	69	0.77	Gait width abnormal
2	62, F, MO	4	PPV-large PPV,medium PH-small (2)	Yes	Yes	6	Na	Na	Na	Na	Na	Sensory limb ataxia
3	53, M, MA	4	PPV-large (2), PH-large PH-small	Yes	Yes	3	Na	Na	Na	Na	Na	Pyramidal signs
4	61, M, MA	1	PH-medium	Yes	None	5	8	3,9	440	23	Na	Tandem side steps
5	65, F, MA	2	PH-medium PPV-medium	Yes	None	6	Na	Na	Na	Na	Na	None
6	66, M, MA	4	PH-medium PH-small (2) PPV-small	Yes	Yes	7	13	4,7	439	45	Na	None
7	66, F, MO	4	PPV-medium (4)	None	None	6	Na	Na	Na	Na	Na	None
8	50, F,MO	1	PPV-medium	None	None	8	13	5,0	615	110	0.66	None
9	61, F, MA	2	PPV-small PH-small	Yes	None	7	Na	Na	Na	Na	Na	None
10	71, M,MA	2	PH-small (2)	None	None	5	5	2,2	Na	Na	1.14	None
11	70, F,CO	1	APV-small	None	None	5	Na	Na	Na	Na	Na	None

12	54, F, CO	1	PH-small	Yes	Yes	7	Na	Na	Na	Na	Na	None
13	75, F, MA	1	PH-small	Yes	None	7	14	4,6	Na	Na	0.59	None
14	72, F,MO	3	PH-medium (1); small (2)	Yes	None	5	6	Na	Na	Na	Na	None
15	51, F,MA	1	PH-small	None	None	8	14	3.5	Na	Na	0.65	None
16	57, FCO	1	PH-small	Yes	None	6	8	1,1	604	50	1.34	None
17	60, F,MO	1	PH-small	None	None	5	Na	Na	Na	Na	Na	None
18	66, M,MA	1	PH-small	Yes	None	8	11	Na	410	27	0.82	Tandem side steps
19	64,F,MA	2	PPV-small; PH-small	Yes	None	5	Na	Na	Na	Na	Na	Dysdiado-chokinesis
20	62,M,MA	1	PH-small	None	None	7	Na	Na	Na	Na	Na	None

References

1. Sandor PS, Mascia A, Seidel L, et al. Subclinical cerebellar impairment in the common types of migraine: A threedimensional analysis of reaching movements. Ann Neurol 2001; 49: 668–672.
2. Ishizaki K, Mori N, Takeshima T, et al. Static stabilometry in patients with migraine and tension-type headache during a headache-free period. Psychiatry Clin Neurosci 2002; 56: 85–90.
3. Harno H, Hirvonen T, Kaunisto MA, et al. Subclinical vestibulocerebellar dysfunction in migraine with and without aura. Neurology 2003; 61: 1748–1752.
4. Furman JM, Sparto PJ, Soso M, et al. Vestibular function in migraine-related dizziness: A pilot study. J Vestib Res 2005; 15: 327–332.
5. Dodick DW and Roarke MC. Crossed cerebellar diaschisis during migraine with prolonged aura: A possible mechanism for cerebellar infarctions. Cephalalgia 2008; 28: 83–86.
6. Akdal G, Donmez B, Ozturk V, et al. Is balance normal in migraineurs without history of vertigo? Headache 2009; 49: 419–425.
7. Brighina F, Palermo A, Panetta ML, et al. Reduced cerebellar inhibition in migraine with aura: A TMS study. Cerebellum 2009; 8: 260–266.
8. Kassab M, Bakhtar O, Wack D, et al. Resting brain glucose uptake in headache-free migraineurs. Headache 2009; 49: 90–97.
9. Teggi R, Colombo B, Bernasconi L, et al. Migrainous vertigo: Results of caloric testing and stabilometric findings. Headache 2009; 49: 435–444.
10. Gerwig M, Rauschen L, Gaul C, et al. Subclinical cerebellar dysfunction in patients with migraine: Evidence from eyeblink conditioning. Cephalalgia 2014; 34: 904–913.
11. Kruit MC, van Buchem MA, Hofman PA, et al. Migraine as a risk factor for subclinical brain lesions. JAMA 2004; 291: 427–434.
12. Scher AI, Gudmundsson LS, Sigurdsson S, et al. Migraine headache in middle age and late-life brain infarcts. JAMA 2009; 301: 2563–2570.
13. Ducros A, Denier C, Joutel A, et al. The clinical spectrum of familial hemiplegic migraine associated with mutations in a neuronal calcium channel. N Engl J Med 2001; 345: 17–24.
14. Palm-Meinders IH, Koppen H, Terwindt GM, et al. Structural brain changes in migraine. JAMA 2012; 308: 1889–1897.
15. Lorå s H, Stensdotter AK, Ö hberg F, et al. Individual differences in motor timing and its relation to cognitive and fine motor skills. PLoS One 2013; 8: e69353.
16. Bernard JA and Seidler RD. Cerebellar contributions to visuomotor adaptation and motor sequence learning: An ALE meta-analysis. Front Hum Neurosci 2013; 7: 27.
17. Krab LC, de Goede-Bolder A, Aarsen FK, et al. Motor learning in children with neurofibromatosis type I. Cerebellum 2011; 10: 14–21.
18. Koekkoek SK, Hulscher HC, Dortland BR, et al. Cerebellar LTD and learning-dependent timing of conditioned eyelid responses. Science 2003; 301: 1736–1739.
19. Koekkoek SK, Yamaguchi K, Milojkovic BA, et al. Deletion of FMR1 in Purkinje cells enhances parallel fiber LTD, enlarges spines, and attenuates cerebellar eyelid conditioning in Fragile X syndrome. Neuron 2005; 47: 339–352.
20. Allum JH and Carpenter MG. A speedy solution for balance and gait analysis: Angular velocity measured at the centre of body mass. Curr Opin Neurol 2005; 18: 15–21.
21. Horlings CG, Kung UM, Bloem BR, et al. Identifying deficits in balance control following vestibular or proprioceptive loss using posturographic analysis of stance tasks. Clin Neurophysiol 2008; 119: 2338–2346.
22. Kung UM, Horlings CG, Honegger F, et al. Postural instability in cerebellar ataxia: Correlations of knee, arm and trunk movements to center of mass velocity. Neuroscience 2009; 159: 390–404.
23. Timmann D, Brandauer B, Hermsdorfer J, et al. Lesion-symptom mapping of the human cerebellum. Cerebellum 2008; 7: 602–606.

24. Diener HC, Dichgans J, Bacher M, et al. Quantification of postural sway in normals and patients with cerebellar diseases. Electroencephalogr Clin Neurophysiol 1984; 57: 134–142.
25. Yeo CH and Hesslow G. Cerebellum and conditioned reflexes. Trends Cogn Sci 1998; 2: 322–330.
26. Mostofi A, Holtzman T, Grout AS, et al. Electrophysiological localization of eyeblink-related microzones in rabbit cerebellar cortex. J Neurosci 2010; 30: 8920–8934.
27. Ye BS, Kim YD, Nam HS, et al. Clinical manifestations of cerebellar infarction according to specific lobular involvement. Cerebellum 2010; 9: 571–579.
28. Norris SA, Hathaway EN, Taylor JA, et al. Cerebellar inactivation impairs memory of learned prism gaze-reach calibrations. J Neurophysiol 2011; 105: 2248–2259.
29. Kuhn S, Romanowski A, Schilling C, et al. Manual dexterity correlating with right lobule VI volume in righthanded 14-year-olds. Neuroimage 2012; 59: 1615–1621.
30. Thieme A, Thurling M, Galuba J, et al. Storage of a naturally acquired conditioned response is impaired in patients with cerebellar degeneration. Brain 2013; 136(Pt 7): 2063–2076.
31. Dietrichs E. Clinical manifestation of focal cerebellar disease as related to the organization of neural pathways. Acta Neurol Scand Suppl 2008; 188: 6–11.
32. Glickstein M, Sultan F and Voogd J. Functional localization in the cerebellum. Cortex 2011; 47: 59–80.
33. Voogd J, Schraa-Tam CK, van der Geest JN, et al. Visuomotor cerebellum in human and nonhuman primates. Cerebellum 2012; 11: 392–410.
34. Schmahmann JD and Sherman JC. The cerebellar cognitive affective syndrome. Brain 1998; 121(Pt 4): 561–579.
35. Stoodley CJ and Schmahmann JD. Functional topography in the human cerebellum: A meta-analysis of neuroimaging studies. Neuroimage 2009; 44: 489–501.
36. Strick PL, Dum RP and Fiez JA. Cerebellum and nonmotor function. Annu Rev Neurosci 2009; 32: 413–434.
37. Buckner RL, Krienen FM, Castellanos A, et al. The organization of the human cerebellum estimated by intrinsic functional connectivity. J Neurophysiol 2011; 106: 2322–2345.
38. Vincent M and Hadjikhani N. The cerebellum and migraine. Headache 2007; 47: 820–833.
39. Hoogland TM, De Gruijl JR, Witter L, et al. Role of synchronous activation of cerebellar Purkinje cell ensembles in multi-joint movement control. Curr Biol 2015; 25: 1157–1165.
40. Zhang Y, Kimberg DY, Coslett HB, et al. Support vector regression based multivariate lesion-symptom mapping. Conf Proc IEEE Eng Med Biol Soc 2014; 2014: 5599–5602.
41. Karner E, Delazer M, Benke T, et al. Cognitive functions, emotional behavior, and quality of life in familial hemiplegic migraine. Cogn Behav Neurol 2010; 23: 106–111.
42. van de Warrenburg BP, Bakker M, Kremer BP, et al. Trunk sway in patients with spinocerebellar ataxia. Mov Disord 2005; 20: 1006–1013.
43. Hoebeek FE, Stahl JS, van Alphen AM, et al. Increased noise level of Purkinje cell activities minimizes impact of their modulation during sensorimotor control. Neuron 2005; 45: 953–965.
44. Gao Z, Todorov B, Barrett CF, et al. Cerebellar ataxia by enhanced Ca(V)2.1 currents is alleviated by Ca2+-dependent K+-channel activators in Cacna1a(S218L) mutant mice. J Neurosci 2012; 32: 15533–15546.
45. De Zeeuw CI, Hoebeek FE, Bosman LW, et al. Spatiotemporal firing patterns in the cerebellum. Nat Rev Neurosci 2011; 12: 327–344.
46. Todorov B, Kros L, Shyti R, et al. Purkinje cell-specific ablation of Cav2.1 channels is sufficient to cause cerebellar ataxia in mice. Cerebellum 2012; 11: 246–258.
47. Uncini A, Lodi R, Di Muzio A, et al. Abnormal brain and muscle energy metabolism shown by 31P-MRS in familial hemiplegic migraine. J Neurol Sci 1995; 129: 214–222.
48. Elliott MA, Peroutka SJ, Welch S, et al. Familial hemiplegic migraine, nystagmus, and cerebellar atrophy. Ann Neurol 1996; 39: 100–106.

Chapter 8

The impact of a migraine attack and its after-effects on perceptual organization, attention, and working memory

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Abstract

Introduction

Many migraine patients report cognitive complaints during the first hours or days following a migraine attack. The aim of this study was to assess whether and which cognitive (perceptual, attentional, or memory) processes are impaired during the first 48 hours after a migraine attack.

Methods

Three different cognitive tasks (global-local task, the attentional network task, and N-back task) were administered to 16 migraine patients (13 migraine without aura; mean age 58 years, 15 female) and 18 controls (59 years,
15 female), matched on age, gender, and educational level. Tasks were administered at three time points; during the first headache free day following a migraine attack (first session), 24 hours later (second session), and 12 days after the attack (third session).

Results

The attentional network and N-back tasks showed no significant differences between migraineurs and controls. In the global-local task, controls showed faster reaction times to global than to local stimuli, which is the standard globalprecedence effect. This effect was absent in the migraineurs in all three sessions, especially if they used prophylaxis. Conclusion: Migraineurs had no impaired attentional or working-memory functioning in the 2 days after an attack. They did show impairments in the processing of global visual features compared with controls, both between and immediately after an attack.

Introduction

Many migraine patients report mild cognitive complaints, such as slowing of reaction and memory problems, during both the ictaland the post-ictal phase (1,2). Studies comparing cognitive functioning of migraine patients in the inter-ictal phase with controls are abundant but showed inconsistent findings. Some studies reported inter-ictal cognitive deficits in the domains of psychomotor speed (1,3), executive function (4), language (5), visual processing (6), attention (2,3), and memory (2,7), while other studies demonstrated no differences in cognitive functioning between migraineurs and controls (8-10).

However studies of specific after-effects of a migraine attack on cognitive functioning are scarce. One study investigating after-effects of a migraine attack failed to find differences in cognitive function, even though patients did report subjective impairments (2). However, there is some evidence for post-ictal physiological alterations, like altered regional cerebral bloodflow (11) and reduced alpha activity in the electroencephalograph (12), which might suggest temporary cognitive deficits. The available findings suggest a number of candidate processes but a systematic model of the impact of migraine on human information processing is lacking. Therefore, we chose a number of theoretically motivated, well-understood cognitive tasks that investigated the complete process from perception and attention to working memory.

The aim of the present study was to identify specific cognitive processes (perceptual, attentional, or memory) that might be impaired by migraine attacks during the first 48 hours after the attack, as compared to an inter-ictal baseline.

Methods

Participants

Sixteen migraine patients diagnosed according to the International Headache Society (ICHD) II criteria (13) were recruited from the neurology headache outpatient clinic databases of the Leiden University Medical Center, Leiden, the Netherlands. Eighteen healthy controls were matched on age, gender, and educational level. Controls without a history of headache attacks were recruited among relatives of investigators and patients. Excluded were subjects who were: suffering from depression, illiterate, had a history of stroke or other brain injuries, or had more than 10 migraine days per

month. Approval for the study was obtained from the local medical ethics committee of the Leiden University Medical Center; all participants provided informed consent.

Design

If patients agreed to participate, they were instructed to contact the study coordinator at the end of a migraine attack on the first headache-free morning after a migraine attack. It was required that patients were headache-free, had had a good night sleep, and did not use attack medication during the last night to ensure testing was not influenced by pain, tiredness, or medication effects. Patients were then visited at home the same day to obtain the cognitive tests during the first session. The cognitive tests were repeated 24 hours later (second session) and 12 days post attack (third session). Within each participant the second and third session were on the same hour of the day as the first session. If a new migraine attack had occurred in between sessions 2 and 3, the third session had to be at least 3 days after the new attack. Session 3 was not allowed to take place during the prodromal phase of a following attack. To limit the time between the baseline and two post-attack sessions, a design was chosen in which the first test session was always the first day after the attack and, consequently, the second and third session were also in a fixed order. To control for any learning effect as a result of this repeated testing, control participants without migraine history were tested with the same protocols on three sessions with the same time intervals in between. Participants were tested by four specially trained students. All participants received the same instructions. Participants were tested by the same student during all three sessions. Participants were seated in front of a laptop monitor (Dell Latitude D-600, screen size 14.1 inch, resolution 1024 x 768, luminance 99.1 cd/m^2, 85 Hz) and performed all tests under the same quiet circumstances. Participants were instructed to keep caffeine or nicotine use before the second and the third session at the same level as before the first session, so that the intra-individual consumption was likely to be constant over the three sessions. Before cognitive testing started, questionnaire data were obtained on general migraine characteristics, preceding migraine attack characteristics, general history, and medication use. Instructions for each test were according to protocol: they were read aloud by the investigator and were also shown on the computer monitor.

Neuropsychological testing

The tasks were constructed with E-prime software. The three following computerized different tests were administered during a 60-minute session at three different time points.

Perceptual organization (global-local) task

Perceptual organization capabilities were assessed by means of a global-local task (14). Participants were presented with hierarchically organized visual figures, in which a larger (global) letter was composed of smaller (local) letters. Letters used were H, S, and O. Stimuli could be congruent (if the local letters were identical to the global letter), incongruent (if the local letter and the global letter were different), or neutral (if a large or small O was presented).

Before the presentation of each stimulus, the participant was instructed to identify the global letter or the local letter, which always was an H or an S, and to press the respective response key on the keyboard. The letter at the to-be-ignored level could be an H, S, or O. This resulted in a total of 12 different letter combinations, which could be categorized in terms of global vs. local level (of the relevant stimulus) and congruent vs. incongruent vs. neutral relationship between the stimulus at the relevant level, and the stimulus at the irrelevant level.

One session consisted of 10 mini-blocks of 12 stimuli, presented in random order each. The visual instruction to respond to the local or global letter was presented for 2000 ms, followed by a 1000 ms blank screen and the stimulus, which was presented for 8000 ms or until a response was being made. Each stimulus measured 2 x 4 cm and was seen from a distance of about 60 cm. Each global letter consisted of 44 local letters. Reaction time and the accuracy of responses were recorded, with reaction times for correct responses being the main dependent variable.

Attention task (ANT)

The Attentional Network Task developed by Fan and colleagues (15) assesses three separable attentional functions (and, presumably, the underlying neural networks): alertness, orienting, and executive control of attention. The task is a combination of a flanker task (16) and a spatial cueing task (17). In each trial, participants are facing a visual cue followed by a visual target stimulus, which they respond to by pressing a left or right keyboard button.

The target stimulus consists of a horizontal row of five symbols, and participants are to respond to the central symbol, which is an arrowhead pointing to the left or

right (calling for a left or right button press, respectively). The central arrow is flanked by four irrelevant symbols, two on either side. These flankers can be either congruent (arrowheads pointing into the same direction as the target, e.g. >>> > >), incongruent (arrowheads pointing into the opposite direction, e.g. < < > < <), or neutral (e.g. - -> - -). The row of symbols randomly appears at the top or bottom of the screen and it may or may not be preceded by a cue informing about target location. In particular, there are four cue conditions: the no-cue condition, where the cue is omitted, the centre-cue condition, in which an asterisk appears at the centre of the screen, the double-cue condition, where two asterisks appear at the centre of the possible target-stimulus locations, and the spatial-cue condition, where just one asterisk appears at the location where the target stimulus will be appearing.

The combinations of the three flanker conditions and four cue conditions provide the data base for calculating three indices of theoretical relevance (alertness, orientation, and executive control) (15).

Each trial would begin with the presentation of a cue, except in the no-cue condition, for 100 ms. After a blank interval of 400 ms, the target was presented for 1700 ms or until a response was being made. Three blocks of 96 randomly determined trials were presented. Target and flankers were presented in black on a white background. Each symbol measured about 5 x 7 mm, seen from a distance of about 60 cm. Before each session, a 2-minute training block was included in the protocol. Reaction time and accuracy were recorded, the primary dependent variable being reaction time for correct responses.

Working memory (N-back) task

The N-back task requires the monitoring, updating, and manipulation of remembered information and places great demands on working memory. The participant is required to monitor a series of letters shown on the screen and to respond whenever a stimulus appears that is the same as the one presented in trials before. In our study the n was 0, 1, 2, or 3. The 0-back condition served as a kind of control or baseline condition, the target letter was the letter 'X' and participants were to respond to any 'X' they would see by pressing the space bar of the computer keyboard. In the three remaining conditions, the target letter was defined as any letter that was identical to the one presented in the preceding trial (1-back, that is), two trials before (2-back), or three trials before (3-back).

There was a block for each of the four levels. Each block consisted of 60 stimuli of which 12 were target stimuli, that is, the probability of a target stimulus was 20%.

Letters appeared in black on a white background, measured 3 x 3 cm and were seen from a distance of about 60 cm. Each letter was shown for 1000 ms, followed by 1000 ms blank. Reaction time to target letters and percentage of correct responses were recorded, with accuracy being the main dependent variable.

Patient characteristics

During a face-to-face interview, migraine characteristics were evaluated for the preceding attack as well as migraine history and general health. The visual analogue scale was used by participants to report the pain experienced during the preceding attack, with a value of 0 implying no pain and a value of 10 implying agonizing pain. Furthermore, preceding migraine severity was assessed by a 4-point scale; no pain, mild pain, moderate pain, or severe pain. Educational level was dichotomized to low (primary school) vs. higher.

Statistical analysis

Baseline characteristics were analysed using t-tests for continuous variables and chi-squared/Fisher exact tests for dichotomous variables. Reaction time and percentage correct for all computerized tasks were analysed using analysis of variance (ANOVA) for repeated measurements. For the omnibus analysis of the global-local task, a 3 x 2 x 2 x 2 ANOVA was used with session (3), level (global/local, 2), and congruence (2) as within subject factors and group (migraine vs. control) as between-subject factor. The paired sample t-test was used for comparing the global-local effect in each group. For the omnibus analysis of each of the three indicators of the ANT, 3 x 2 x 2 ANOVAs were used with session (3) and condition (2) as within-subjects factors and group (migraine vs. control) as between subjects factor. For the omnibus analysis of the N-back task a 3 x 4 x 2 design was used with session (3) and level (4: 0, 1, 2, or 3) as within-subjects factors and group (migraine vs. control) as between-subject factor. t-tests were used for more detailed comparisons. The significance level was set to $p = 0.05$ for all statistical tests.

Results

Demographics of migraine patients and controls did not differ significantly, as shown in Table 1. Mean age of patients was 58 years and 13 (81%) had migraine without aura. The characteristics of the attack preceding the first test are shown in Table 2. None

of the three migraineurs with aura actually had an attack with aura preceding the study. Mean duration between the end of the attack and first testing was 17 hours (SD 6.9, range 5–27). The second test session took place 23.3 hours (SD 2.1, range 21–30) after the first, and the third session 12 days (SD 14, range 3–70) after the second. Two participants suffered another migraine attack before the third visit, causing the third visit to be postponed.

Perceptual organization (global-local) task

Mean reaction times for the global-local task are shown in Table 3. Reaction times decreased with each session in both migraineurs and controls [$F(2,27) = 16.94$, $p < 0.0001$] and congruence between the letters at the two levels (global and local) yielded faster responses than incongruence [$F(1,28) = 81.56$, $p < 0.0001$]. Neither Migraine group vs. controls nor global vs. local produced a main effect [$F(1,28) < 1$]. There was a migraine vs. controls-by-global vs. local interaction [$F(1,28)4.99$, $p = 0.034$]. The source of this interaction is shown in Figure 1: controls showed faster reaction time when responding to global than to local stimuli [$t(1,15) = 3.86$, $p = 0.035$ (one-tailed)], a replication of the standard global-precedence effect (14). Migraineurs actually showed a trend towards the opposite pattern with longer reaction times to global than to local stimuli, but this difference did not reach significance ($p = 0.12$). In other words, the standard globalprecedence effect was eliminated in migraine patients. Even though the figure suggests a modulation by session, there was no three-way interaction ($p = 0.26$) of global vs. local, migraine vs. controls, and session, suggesting that the difference between migraineurs and controls was statistically comparable across sessions. Interestingly, the interaction of group and level approached significance if only the prophylaxis-using migraineurs were considered ($p=0.055$) but was far from significance if non-prophylaxis users were compared with controls ($p=0.2$).

The one participant not using triptans did not perform differently compared to triptan users on the global-local test.

Table 1. Characteristics of participants

	Migraine patients (n=16)	Controls (n=18)	*p*-value
Female gender	15 (94)	15 (83)	0.6
Age (years)	58 ± 9.1	59 ± 7.4	0.7
Education moderate/high	9 (56)	11 (61)	0.8
History of depression	4 (25)	2 (11)	0.4
Current antidepressive use	2 (13)	2 (11)	1.0
Migraine without aura	13 (81)	-	NA

Values are n (%) or mean ± standard deviation. NA, not applicable.

Table 2. Characteristics of preceding migraine attack

Characteristic	Migraine patients (n=16)
Attack duration (hours)	39 ± 35
Visual analogue scale	6 ± 1.9
Moderate or severe attack	13 (81)
Aura accompanied attack	0 (0)
Nausea 10 (63) Vomiting	3 (19)
Photophobia	10 (63)
Phonophobia	10 (63)
Triptans used	15 (94)
Migraine prophylaxis use	9 (56)

Values are n (%) or mean ± standard deviation.

Table 3. Global-local reaction time (ms) according to condition

Session	Condition	Migraine patients (n=16)	Controls (n=18)
1 (day 1 post attack)	Total	1199 ± 93	1137 ± 87
	Global	1226 ± 94	1100 ± 88
	Local	1173 ± 95	1174 ± 89
	Congruent	1078 ± 88	1062 ± 82
	Incongruent	1321 ± 103	1211 ± 96
2 (day 2 post attack)	Total	989 ± 74	914 ± 69
	Global	993 ± 83	907 ± 77
	Local	986 ± 69	922 ± 64
	Congruent	933 ± 68	839 ± 63
	Incongruent	1046 ± 82	990 ± 76
3 (interictal, baseline)	Total	959 ± 68	862 ± 64
	Global	973 ± 75	839 ± 70
	Local	945 ± 64	887 ± 60
	Congruent	871 ± 66	802 ± 62
	Incongruent	1048 ± 72	924 ± 67

Values are mean ± standard error of the mean. Reaction time for correct responses is shown. Total, mean reaction time over all conditions (global or local level and congruent or incongruent).

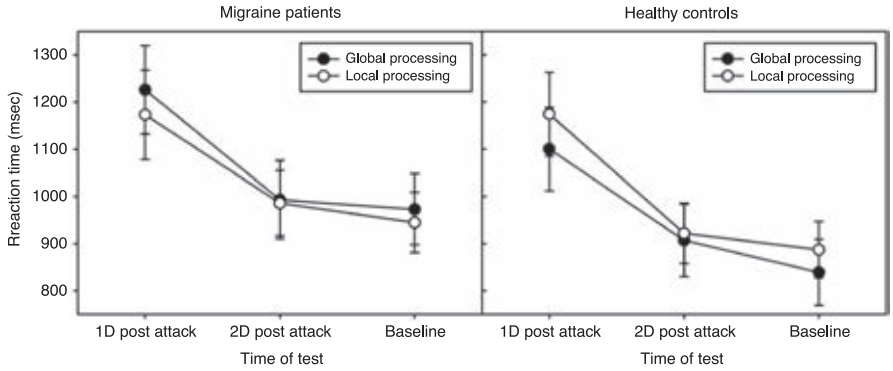

Figure 1. Plot of reaction time for the perceptual organization task for migraine patients and healthy controls.

Attention task (ANT)

Alerting. Main effects of session [F(2,58) =15.21, $p < 0.0001$] and warning cue (present/not present) [F(1,29) = 53.99, $p < 0.0001$] indicated that reaction time decreased over sessions and was faster with an alerting cue. Thus the standard alerting effect was replicated (18). However, no significant effect was found for group [F(1,29) < 1] or any interaction involving group [F(1,29 < 1]. The ANOVA of the error rates yielded no reliable effect, only a trend towards a group-by-cue interaction showing that migraineurs had a higher percentage of correct responses [F(1,32)=3.55, p= 0.069].

Orienting. Main effects of session [F(2,58) = 20.6, $p < 0.0001$] and warning cue (spatial vs. neutral) [F(1,29) = 291.2, $p < 0.0001$] indicated that reaction time decreased over sessions and was faster with spatial than with neutral cues. That is, the standard benefit of spatial orienting was replicated (17). However, no significant effect was observed for the group variable [F(1,29) < 1] or any interaction involving it. There was an advantage of spatial over neutral cues in both groups in the error-rate analysis [F(1,32) = 9.88, p = 0.004].

Executive control. Main effects of session [F(2,58) =18,57, $p < 0.0001$] and flanker congruency [F(1,29) = 207,2, $p < 0.0001$] showed reaction time decreased over sessions and was faster with congruent than with incongruent flankers. That is, the standard flanker-congruency effect was replicated (16). However, no significant effect was observed for the migraine vs. control variable [F(1,29) < 1] or any interaction involving it. The error rate analysis showed an effect on flanker congruency [F(2,58)= 6.13, p= 0.004], indicating that incongruent flankers induced more errors. Reaction times according to flanker type are presented in Table 4.

Table 4. ANT reaction time (ms) according to flanker type

Session	Flanker type	Migraine patients ($n = 16$)	Controls ($n = 18$)
1 (day 1 post attack)	Congruent	653 ± 29	648 ± 35
	Incongruent	781 ± 32	782 ± 42
	Neutral	657 ± 28	647 ± 33
2 (day 2 post attack)	Congruent	643 ± 29	611 ± 27
	Incongruent	747 ± 32	731 ± 33
	Neutral	639 ± 26	600 ± 24
3 (interictal, baseline)	Congruent	607 ± 20	596 ± 26
	Incongruent	707 ± 24	711 ± 32
	Neutral	601 ± 18	587 ± 26

Values are mean ± standard error of the mean.

Table 5. N-back reaction time (ms) according to n-level

Session	Level	Migraine patients ($n = 16$)	Controls ($n = 18$)
1 (day 1 post attack)	0	436.6 ± 22.6	452.4 ± 20.3
	1	468.0 ± 24.6	520.6 ± 22.1
	2	580.1 ± 30.2	611.3 ± 27.2
	3	666.2 ± 23.0	649.2 ± 20.6
2 (day 2 post attack)	0	417.4 ± 20.0	432.7 ± 18.0
	1	480.0 ± 24.6	502.3 ± 22.1
	2	561.8 ± 28.9	569.4 ± 26.1
	3	629.2 ± 24.7	643.3 ± 22.3
3 (interictal, baseline)	0	407.5 ± 13.7	437.8 ± 12.4
	1	457.4 ± 19.3	475.3 ± 17.4
	2	545.6 ± 23.3	554.4 ± 21.0
	3	600.6 ± 22.1	637.6 ± 20.0

Values are mean ± standard error of the mean.

Working memory (N-back) task

Mean reaction times decreased over session [$F(2,54) = 4.54$, $p = 0.015$] and increased with level [$F(3,81) = 113.09$, $p < 0.0001$], thus replicating the standard N-back effect (19). However, all effects involving migraine group vs. control were far from significant [F's < 1]. Error rates decreased with session [$F(2,64) = 25.68$, $p < 0.0001$] and decreased with lower levels of difficulty [$F(3,96) = 104.46$, $p < 0.0001$]. Reaction times for each session are presented in Table 5.

Discussion

Migraineurs often complain about cognitive impairment shortly after a migraine attack. Studies showed evidence of profound post-ictal effects on cognitive tests after epileptic attacks, however this has not been demonstrated after migraine attacks. The aim of this study was to assess the degree to which a recent migraine attack affects cognitive functions at different processing levels. We tested migraineurs in various, theoretically motivated experimental tasks at three points in time post-ictally and compared their performance with healthy controls. Three results of this study are particularly noteworthy.

First, we did not find evidence for any reliable changes in cognitive performance during the postattack phase, as indicated by the absence of any interaction between session, group, and cognitive measures. In other words, no temporal negative effect on cognitive function after the attack was found. This observation is in line with the one previous study reporting no negative influence during the post-ictal phase of a migraine attack (2). However, while Mulder et al. (2) tested participants who still had mild headache during testing, we defined the post-ictal phase by the absence of headache. Moreover, while Mulder et al. (2) recruited their participants from a student population, we recruited migraine patients from the outpatient headache, which resulted in a higher mean age.

Second, reliable and stable differences between migraine patients and controls were observed with respect to the organization of local and global visual stimuli. The controls showed the standard global precedence effect (14) with better performance on global than on local stimulus features (trend). Interestingly, this standard global precedence effect was not present in migraineurs. The fact that this difficulty did not change across sessions suggests that it is not caused by, or associated with, the migraine attack per se but, rather, seems to be associated with the (enduring) migraine disposition.

Third, none of the remaining measures (N-back, ANT) showed any hint of an interaction with group (migraineurs vs. controls). Even though null effects need to be interpreted with the necessary caution, it is important to point out that the tasks as such worked very well i.e., we were able to replicate all the standard effects and yet we found no association between migraine and alerting, orientation, executive control, and working memory measures. Thus, even though more systematic research on this issue is required, we tentatively conclude that alerting, orientation, executive control, and working memory do not play a role in, and do not seem to be impaired

by, migraine. This leaves the global-local task, investigating organization of local and global visual stimuli, as the test differing between migraineurs and controls, a finding which is consistent with the previous observation that migraineurs have higher perceptual thresholds for the recognition of global shape (20).

The global-local task was developed by Navon (14) and taps into the organization of visual information into coherent objects or Gestalts and assesses this performance by presenting participants with hierarchically organized visual stimuli, such as a global letter that is made of a number of local letters. Healthy humans have a strong preference to perceive the global letter first and faster, suggesting that they organize the local information into a coherent global whole the so-called global precedence effect (14). The first evidence for specific dysfunction in migraineurs comes from two recent studies (20,21) showing that migraineurs did not differ from healthy controls in a visual task tapping into very early sensory processes (presumably performed by brain area V1) but have higher thresholds than controls for the perception of global shape (presumably performed by the extrastriate area V4). This suggests a locus in the cortical information-processing stream later than visual stages (V1) but earlier than at encoding into working memory, which implies higher visual areas that are either directly involved in feature integration or that provide integration processes with global information. As demonstrated by Badcock and colleagues (23), the global precedence effect can be eliminated by filtering out low-spatial frequency information in Navon-type stimuli. It is thus possible that in migraineurs the processing through low-spatial frequency tuned visual channels is impaired. This would fit with the observation that channels that prefer higher flicker rates (commonly tuned to lower spatial frequency ranges) can have lower sensitivity in migraineurs during their inter-ictal period (24). Hence, patients may not be able to process or to integrate more global features into perceptual representations of objects and events.

The organization of perceptual information is followed by attentional selection processes, in which no difference was found in our study between migraineurs and controls by ANT test. Human attention is thought to fall into a least three different abilities, which are handled by three neurally dissociable networks (15): alerting (activating the system in response to the presence of a relevant stimulus), orienting (selecting a particular stimulus or location for further processing), and executive control (biasing response selection towards appropriate responses). Not one of these abilities seems to be impaired by migraine.

The outcome of attentional selection processes are thought to be transferred to working memory, which organizes further processing or storage of the selected

information. To assess the impact of migraine on working memory efficiency, we employed the well established N-back task (for an overview, see Kane et al. (19)), which requires participants to hold information and continuously update this information based on new incoming stimuli. In this study, however, no difference in N-back task was found between migraineurs and controls.

Several caveats are in order and some limitations apply. It is possible that migraine-specific prophylaxis played a role in producing the observed elimination of the global-local effect in migraineurs. Various adverse effects of prophylaxis on cognition have been reported (22) and a direct effect of the prophylactic medication can be suggested. Migraine characteristics between prophylaxis users and non-users as age of migraine onset, total migraine years, current attack frequency, current attack duration, and current presence of photophobia or phonophopia did not differ. However this does not rule out that some clinical characteristics before the start of prophylaxis were in fact different (for example attack frequency) compared to the non-prophylaxis using group. The types of prophylaxes used by our participants were too heterogeneous to correct for their respective type-specific potential effects.

The absence of a post-attack effect could be explained by the high percentage of triptan users in our study, 94% of the participants used triptan during the attack preceding the tests. Possibly the use of triptans prevented the development of cognitive complaints, and differences would probably be easier to detect after untreated attacks. However, participants willing to skip their attack treatment will probably lead to the inclusion of less severely affected migraineurs. Another explanation for the absence of a post-attack effect is the long time which passed between the end of the attack and actual testing. However, testing sooner would invite possible artefacts, such as side effects of headache, mood, medication, and exhaustion. A fatigue score in each participant before each session was not obtained, and therefore adjusting for this possible important factor was not possible.

Another caveat relates to testing procedures. With regard to the fact that we tested participants repeatedly, it is important to point out that there were pronounced session effects, i.e. learning improved performance considerably. This underscores the need for a control group in studies investigating post-attack changes, as this permits the correction for learning effects, which might be particularly strong if participants are relatively old and not used to computerized testing. Even though the examiners were not blinded for diagnosis, all the relevant tests were computerized and the sequence of trials was fully randomized which should have prevented systematic biases.

Moreover, recruiting patients for tests on cognitive functioning might bias the study towards patients with a higher education and, indeed, in our study the educational level was above average. Furthermore, migraineurs recognizing cognitive decline themselves (after an attack) might be more likely to participate in a study focusing on (post-attack) cognitive effects.

Finally, due to the rather high demands posed by our experimental protocol and the relatively selective recruiting procedure, only a limited number of patients could be tested. In addition, the requirement to match the members of the control group to the patients created a sample that was considerably more heterogeneous than the student samples that have been used to develop the tasks we employed. All this is likely to have increased the error variance and made our statistical tests relatively conservative. Therefore, the absence of statistically significant effects, such as with the numerically reversed global precedence effect in migraineurs or the interaction between group and session, should be interpreted with caution. In any case, the strength of the present study is the design with matched controls that were tested within the same time intervals and the exclusion of effects of the actual headache phase by delaying post-ictal testing until the first headache free day. Future studies on post-ictal cognitive functioning should probably exclude prophylaxis users and consider starting testing somewhat sooner after the (untreated) attack. While in previous studies on cognitive function in migraineurs, specific differences were found between migraineurs with aura and migraineurs without aura, in future studies groups of both migraine with aura and without aura should be reasonable large to make comparisons between these groups.

In conclusion, no evidence for temporary changes in cognitive performance could be found during the postictal phase (on average 17 hours after the end of the attack) in migraineurs on attentional function, working memory, or perceptual organization capabilities using this study design. However we found that the normal global precedence was absent in migraineurs, specifically in prophylaxis users a deficit that is likely to impair the processing of the visual context and Gestalts.

References

1. Calandre EP, Bembibre J, Arnedo ML and Becerra D. Cognitive disturbances and regional cerebral blood flow abnormalities in migraine patients: their relationship with the clinical manifestations of the illness. Cephalalgia 2002; 22(4): 291–302.
2. Mulder EJ, Linssen WH, Passchier J, Orlebeke JF and de Geus EJ. Interictal and postictal cognitive changes in migraine. Cephalalgia 1999; 19(6): 557–565.
3. Hooker WD and Raskin NH. Neuropsychologic alterations in classic and common migraine. Arch Neurol 1986; 43(7): 709–712.
4. Camarda C, Monastero R, Pipia C, Recca D and Camarda R. Interictal executive dysfunction in migraineurs without aura: relationship with duration and intensity of attacks. Cephalalgia 2007; 27(10): 1094–1100.
5. Waldie KE, Hausmann M, Milne BJ and Poulton R. Migraine and cognitive function: a life-course study. Neurology 2002; 59(6): 904–908.
6. Coleston DM, Chronicle E, Ruddock KH and Kennard C. Precortical dysfunction of spatial and temporal visual processing in migraine. J Neurol Neurosurg Psychiatry 1994; 57(10): 1208–1211.
7. Le Pira PF, Zappala G, Giuffrida S, Lo Bartolo ML, Reggio E, Morana R, et al. Memory disturbances in migraine with and without aura: a strategy problem? Cephalalgia 2000; 20(5): 475–478.
8. Bell BD, Primeau M, Sweet JJ and Lofland KR. Neuropsychological functioning in migraine headache, nonheadache chronic pain, and mild traumatic brain injury patients. Arch Clin Neuropsychol 1999; 14(4): 389–399.
9. Gaist D, Pedersen L, Madsen C, Tsiropoulos I, Bak S, Sindrup S, et al. Long-term effects of migraine on cognitive function: a population-based study of Danish twins. Neurology 2005; 64(4): 600–607.
10. Pearson AJ, Chronicle EP, Maylor EA and Bruce LA. Cognitive function is not impaired in people with a long history of migraine: a blinded study. Cephalalgia 2006; 26(1): 74–80.
11. Sakai F and Meyer JS. Regional cerebral hemodynamics during migraine and cluster headaches measured by the 133Xe inhalation method. Headache 1978; 18(3): 122–132.
12. Schoenen J. Clinical neurophysiology studies in headache: a review of data and pathophysiological hints. Funct Neurol 1992; 7(3): 191–204.
13. The International Classification of Headache Disorders. 2nd edition. Cephalalgia 2004; 24(Suppl 1): 9–160.
14. Navon D. How many trees does it take to make a forest? Perception 1983; 12(3): 239–254.
15. Fan J, McCandliss BD, Sommer T, Raz A and Posner MI. Testing the efficiency and independence of attentional networks. J Cogn Neurosci 2002; 14(3): 340–347.
16. Eriksen BA and Eriksen CW. Effects of noise letters on the identification of a target letter in a nonsearch task. Perception Psychophysics 1974; 16: 143–149.
17. Posner MI. Orienting of attention. Q J Exp Psychol 1980; 32(1): 3–25.
18. Niemi P and Naatanen R. Foreperiod and simple reaction time. Psychological Bulletin 1981; 89: 133–162.
19. Kane MJ, Conway AR, Miura TK and Colflesh GJ. Working memory, attention control, and the N-back task: a question of construct validity. J Exp Psychol Learn Mem Cogn 2007; 33(3): 615–622.
20. Ditchfield JA, McKendrick AM and Badcock DR. Processing of global form and motion in migraineurs. Vision Res 2006; 46(1–2): 141–148.
21. McKendrick AM, Badcock DR and Gurgone M. Vernier acuity is normal in migraine, whereas global form and global motion perception are not. Invest Ophthalmol Vis Sci 2006; 47(7): 3213–3219.
22. Ketter TA, Post RM and Theodore WH. Positive and negative psychiatric effects of antiepileptic drugs in patients with seizure disorders. Neurology 1999; 53(5 Suppl 2): S53–S67.
23. Badcock JC, Whitworth FA, Badcock DR and Lovegrove WJ. Low frequency filtering and the processing of local-global stimuli. Perception 1990; 19(5): 617–629.
24. McKendrick AM, Vingrys AJ, Badcock DR and Heywood JT. Visual field losses in subjects with migraine headaches. Invest Ophthalmol Vis Sci 2000; 41(15): 1239–1247.

Chapter 9

Summary and general discussion

This thesis describes the results of studies on subjects with migraine and controls without migraine within the population based "Cerebral abnormalities in migraine an epidemiological risk analysis II (CAMERA II) study". These studies include longitudinal brain imaging (part I), right-to-left shunt (RLS) investigation (part II), and cognitive and cerebellar function evaluation (part III). Two clinical based studies are also included; 1) to evaluate the transient effects of the acute migraine attack on cognitive function and 2) to investigate an association between non-shunting cardiac abnormalities and migraine aura.

I Migraine and brain imaging

In our population-based cohort that was followed up after 9 years, women with migraine had a higher volume of deep white matter hyperintensities and also more new lesions. This was not related to the presence of aura symptoms. Measures of migraine severity (eg attack frequency or life time attack load) were not related to progression of brain lesions. In men no difference between migraineurs and controls in deep white matter volume nor progression was found. **(Chapter II)** The prevalence of infratentorial hyperintensities was also higher in female migraineurs (both with and without aura) than in controls. Also progression of infratentorial hyperintensities during follow up was more frequent in migraineurs (trend). Again this was not found in men. (**Chapter II**)

White matter hyperintensities are common with age and increase over time. They are likely ischemic in origin, probably caused by chronic hypo-perfusion at borderzones of vessels and arteriolosclerosis. [1;2] Recently, it was shown that, like in the acute state of ischemia, a border zone with decreased cerebral blood flow, the so called penumbra, surrounds white matter hyperintensities in general, also suggesting an ischemic origin.[3] In our study, female migraineurs were found to have more progression of supratentorial deep white matter lesions and infra-tentorial hyperintensities, not specific for a migraine subtype. These findings somewhat differ from those in a meta-analysis of six population-based and 13 clinical-based studies, in which an increased risk was only present in migraine with aura, and not as in our study in both migraine with and without aura.[4] However studies included in this meta-analysis were heterogeneous, and often did not distinguish between deep and peri-ventricular white matter lesions which is important as their origin is hypothesized to be quite

different. Only one other population based study also reported longitudinal data like our study. The Atherosclerosis Risk in Communities cohort (ARIC) study cross-sectionally found an association between migraine and white matter hyperintensities which was in line with our finding, but they did not find differences in progression over time.[5] Furthermore they did not find a gender effect in this association. Possibly these differences can be explained by the fact that the ARIC study, like most studies in the previous mentioned meta-analysis, did not distinguish between deep and peri-ventricular white matter lesions. Also the headache assessment was only done at baseline, so some controls might have become migraine patients during follow-up and were not analyzed as such. Recently a cross-sectional study with only female twins with and without migraine also did not find an association between deep white matter hyperintensities and migraine. Subjects with cardiovascular history were excluded in this study, and specificly migraineurs with aura were excluded on this history. Also responder rates in migraine were higher than in controls. Both might have biased findings in this study.[6]

Our study was unique as we had a long follow up of both MRI as well as of clinical and migraine specific variables. In this way we were able to show that progression of white matter hyperintensities was not dependent on persistence migraine activity, but also occurred in migraineurs who stopped having attacks. Likewise, progression of lesions was not dependent on attack frequency or total amount of attacks during life time

We have shown that a migraine attack related mechanism does not explain the association between migraine and deep white matter lesions. Thus which attack unrelated mechanism can explain this association? An underlying factor influencing, and causing, both migraine and lesions may be possible, such as a shared genetic factor. An example of this is the co-occurrence of migraine with aura in one third of patients with CADASIL who develop also white matter lesions and stroke and is caused by mutations in the Notch3 gene. Other possible explanations may be non-genetic factors that are associated with migraine as well as white matter lesions, such as endothelial dysfunction. Furthermore, a reduced resting cerebral flow in the brain in the white matter, as reported to be lower in female migraineurs compared to controls, could also explain the higher prevalence of white matter lesions. [7]

For patients and treating doctors is seems reassuring that the migraine attacks itself does not seem to be causative for the lesions. Therefore, preventative migraine medication is not advocated to prevent white matter hyperintensities in women with migraine.

During the follow up of our cohort, new posterior circulation silent infarcts were found in migraineurs, irrespective of gender or migraine type, in 5% compared to 0% of controls. This again was not associated with persistent migraine activity, nor with migraine frequency or life time migraine attack load. (**Chapter II**)

One of the questions that remained after CAMERA-I was: "What is the actual pathological substrate of the so called infarct like lesions, which are found more in the cerebellum of migraine patients"? [8] A recent human combined ex vivo MRI and histopathological study on 40 cerebellar specimens demonstrated that deep cavities in the cerebellum with "infarct-like" appearance on MRI, similar as those identified in our migraine study MRI scans, were indeed true infarcts. The observation of migrainous stroke occurring during a migraine attack would also support the hypothesis of ischemia.[9] Silent infarcts in the cerebellum by definition have not caused any noticeable clinical symptoms, however these silent infarcts were associated with an increased risk of clinical stroke in a non-migraine study.[10] A recent meta-analysis[4] of 19 studies showed that silent infarcts were not more common in migraine wit aura than controls (p=0.52). After this meta-analysis the population based Northern Manhattan Study (NOMAS) was published, which was partly inline with our findings, that migraine was associated with silent brain infarction, however location was not predominantly in the cerebellum which was not consistent with our study.[11] The underlying mechanism of the relation we found between silent cerebellar infarcts and migraine (both with and without aura) remains unclear.

Hypotheses raised are essentially the same as for the relation between white matter lesions and migraine. We found that migraineurs with silent cerebellar infarcts had a less favorable cardiovascular risk profile compared to the migraineurs without these infarcts, but the numbers behind this observation are small, thus results must be interpreted carefully. Both hypertension and hypercholesterolemia were overrepresented in the silent infarct group. An underlying (genetic) factor influencing, and causing, both migraine and infarcts may be possible. It also has been shown that migraineurs have endothelial dysfunction[12] and increased aortic stiffness. [13] Recently it was also shown that high sensitivity C-reactive Protein (hs-CRP) and fibrinogen (both biomarkers of hypercoagulability and inflammation) were elevated in persons with migraine compared to controls.(personal communication) These are all systemic findings increasing the cardiovascular risk.

Right-to-left shunts (RLS) which we found to be more prevalent in migraineurs with aura, can only (partially) explain the risk as these are only over-represented in migraineurs with aura. However we did find a trend towards more cerebellar silent infarcts in subjects with RLS (see also part II, the heart and migraine).

II Migraine and the heart

We showed that the prevalence of RLS in migraine with aura was increased compared to controls without migraine and migraineurs without aura. (**Chapter III**) However, the relative risk was not as high as in clinic based studies, probably because in our study the occurrence of RLS was also relative common in the control group. In our study all investigators were blinded for migraine diagnosis, in contrast to the earlier clinic based studies, making our finding more likely to be reliable. A broad range of embolic structures is able to cause migraine attacks, although the occurrence of actual attacks in these specific embolic rich circumstances seems quite low. (**Chapter IV**)

Both the finding of the association between RLS and migraine with aura in the general population, as well as the finding that persistence of migraine activity was associated with the presence of spontaneous RLS, add to the evidence of an association between RLS and migraine, especially in migraine with aura. Several hypotheses have been raised to explain the higher prevalence of RLS in this subtype of migraine. A widely accepted theory is that small emboli from the venous circulation bypassing the pulmonary filter by crossing a right-to-left shunt may induce migraine aura as these emboli reach the cerebral circulation. In this model the RLS enables emboli reaching the brain. **Chapter V** summarizes numerous case-reports of patients developing migraine aura after pathological induced emboli. From animal studies there is accumulating evidence that emboli can indeed induce cortical spreading depression, the underlying pathophysiological substrate of the aura phase. In patients with ischemic stroke these cortical spreading depressions have been recorded with subdural electrocorticography.[15] Another theory is that RLS enables metabolites like serotonin or carbon dioxide from the venous circulation to enter the systemic circulation. Recently, it was shown that migraineurs with RLS have a reduced capacity of effective cerebral vasodilatation, which suggests that mentioned substances from the venous circulation may affect this auto-regulation.[16] The evidence for a link between RLS and migraine aura is quite strong, although the actual role of RLS is probably limited.

Our study (**Chapter III**) was the first to include both migraineurs with persistent migraine activity as well as migraineurs who had ceased having attacks. We showed that persistence of activity was related to the presence of spontaneous RLS.

This is in line with the theory in which RLS enables passage of emboli. However it is evident that the presence of RLS not fully explains the occurrence migraine aura, as not all migraineurs with aura have a RLS, and migraineurs without aura also (but in a lower percentage) have RLS and never experience an aura. Well designed randomized, sham-controlled, RLS closure studies are needed to prove if this association is causal.

RLS was not associated with subclinical cerebellar infarcts, although there was a trend for this association in the posterior circulation. (**Chapter III**)

Several studies provided evidence that RLS (specific patent foramen ovale) is associated with clinical (crypotogenic) stroke. Well known risk factors for ischemic (silent) stroke are hypertension, smoking, diabetes and atrial fibrillation.[17] The additional risk of an RLS probably is relatively small. Due to limited number of cerebellar infarcts, adjustments for all major riskfactors on methodological grounds unfortunately in our study was not possible. Except for some studies [18;19] showing that cardiac emboli favor the posterior cerebral circulation, there are no good explanations why RLS subjects in our study showed a trend for more cerebellar silent infarcts. In a migraine patient who suffers a (silent) stroke in the posterior circulation and who does not have additional cardio-vascular risk factors, screening for RLS seems a reasonable advice.

We also showed that aortic root replacement in a heterogeneous group of cardiac patients was associated specific with migraine with aura. (**Chapter V**)

We were the first to show that the increased migraine (in particular with aura) prevalence among Marfan patients was specifically found in the group who underwent aortic root replacement. Several other large vessel diseases have been associated with migraine. For example being a migraineur doubled the risk of carotid artery dissection [20] and subjects with angiographically confirmed carotid artery dissection have been described with attacks of transient symptoms exactly resembling migraine wit aura. Recently a genetic study on carotid dissection and a study on migraine both identified the same variant on chromosome 6 (PHACTR1 gene), reducing the risk of carotid dissection as well as the risk of migraine with aura.[21-22] Interestingly wide aortic root diameter also is a risk factor of carotid dissection,[23-24]

and widening of the aortic root in Marfan patients was the main reason to perform aortic root replacement. An underlying large artery arteriopathy is evident in Marfan and believed in carotid dissection. Also in reversible vasoconstriction syndrome (RCVS), migraine is considered a risk factor. And some patients both have RCVS and carotid dissection, and 60% of these subjects were migraineurs.[25] All these findings point towards a role of abnormal large vessel dilatation (or altered cerebrovascular tone) in migraine, although the mechanisms and possible causative link remain to be proved.

The Delphi approach was used to define recommendations from cardiologists specialized in rhythm disorders for safe use and EKG monitoring of high dose of verapamil. These experts agreed on performing a pretreatment EKG in patients using verapamil for the first time. Pretreatment EKG was deemed not necessary in subjects who did not have cardiac adverse events during a previous period of verapamil use. No consensus was reached on EKG monitoring during verapamil treatment and dose adjustments. Consensus about absolute and relative contra-indications for continuing high dose verapamil largely followed FDA recommendations.No consensus-based recommendations on EKG monitoring during verapamil treatment and around dose increases can be given although, based on the literature EKG prior and after every dose increase would be our recommendation. Individual patient characteristics always have to be taken into account.
(**Chapter VI**)

III Migraine and brain function

We did not find any impaired interictal (in between attacks) cognitive function in migraine using a large battery of neuropsychological tests covering function of supratentorial brain structures. (**Chapter II**). We did show that a high white matter lesion load was probably (trend) associated with impairment of memory. This again did not differ between migraineurs and controls. (**Chapter II, etable 3**) In our study evaluating cognitive function shortly after a migraine attack, we found interictal differences unrelated to the previous attack. Migraineurs showed impairment in the processing of global visual features compared with controls. (**Chapter VIII**)
Some studies reported inter-ictal cognitive deficits in migraineurs, while other reported no differences between migraine and controls.[26-30] The previously found

differences represented different domains like psychomotor speed, executive function, language, attention, memory and visual processing. In our CAMERA-II study no difference were found between groups on memory, concentration, attention, executive function, psychomotor, processing speed, organization, fluid intelligence and visuospatial skills. Our study had the strength that it was large and investigators were blinded. The absence of impairment among migraineurs (and even a better global cognition) was recently shown in a large population study, results which were (partly) in line with our study.[31]

We were able to show (trend) that deep white matter lesions were associated with impaired memory function. This is in line with previous studies[32] and underlines the sensitivity of used cognitive battery, as the amount of white matter lesions compared to non-migraine studies was limited.

If the impaired cognitive functions among migraineurs in these clinical based studies were the result of repeated migraine attacks, we hypothesized that impairment is more pronounced shortly after an attack. Therefore we studied cognitive function shortly after a migraine attack. (**Chapter VIII**). However no evidence for temporary changes in cognitive function could be found in the post-ictal state.

Our study design was unique as migraineurs were studied after the migraine attack, they had to be pain free. This allowed us to rule out any negative effect on cognitive function caused by pain itself. This however on the other hand led to an average of 17 hours following the end of the attack before testing. The use of controls was a strength of our study, in that way we were able to eliminate the effect of a learning effect.
We did however find that migraineurs did not show the global precedence effect (perceiving the global letter, which was built from a number of so called local letters first and faster) which was present in controls. In other words migraineurs were impaired in seeing the wood for the trees. This may point towards dysfunction of higher visual cortical areas or connectivity between areas involved in visual processing. Our finding is in line with a study that migraineurs have higher thresholds for the recognition of global shapes.[33]

Contrary to smaller studies, we could not demonstrate an impaired inter-ictal function of the cerebellum in (non-hemiplegic) migraine subjects, using several measurements sensitive for dysfunction of several cerebellar anatomic regions. Migraineurs did not differ from non-migraine controls for fine motor speed

and coordination, perceptual intelligence and motor function, cerebellar motor coordination and learning of limb movements, associative cerebellar motor learning and vestibular motor coordination.(**Chapter VII**).

Our study was the first to assess a broad range of cerebellar functions in a population based study and with investigators blinded for migraine/ control status. We failed to find any evidence of impaired cerebellar function using an array of tests covering the functions of the main parts of the cerebellum. Previous studies which suggested subclinical cerebellar dysfunction were all small clinical based and unblinded.[34-38] Our test battery consisted of highly sensitive clinical tests, which was shown by the fact that they did show deficits in a relatively small group of FHM patients which were tested with the same test protocol. Thus, in contrast to previous findings, our findings argue against the hypothesis that cerebellar function is subclinically impaired in migraine patients. Also in general these cerebellar infarcts did not cause any functional impairment.

Future perspectives

We showed that both subclinical cerebellar infarcts as well as deep white matter hyperintensities in migraine patients occur irrespective of current migraine activity or past and present attack load. Most likely an underlying factor, for instance endothelial dysfunction or a shared genetic factor may be the causal link in this association. The role of comorbid RLS on ischemic lesions seems small, if any. Future studies should focus on identifying the underlying mechanism between migraine and white matter lesions in women.

The association between RLS and migraine with aura, which we now demonstrated in the general population, adds to the evidence that emboli can be able to induce cortical spreading depression which is the underlying mechanism for the migraine aura. However, as evidence for a prophylactic effect of RLS closure is currently still lacking, we advice against screening for RLS in migraine with aura patients.

Although migraine is associated with subclinical structural brain changes, this seems unrelated to attack load and these lesions do not cause functional impairment. Also does migraine (by any other mechanism) not lead to impairment of brainfunction. Future studies should focus on identifying the underlying mechanism between migraine and white matter lesions specific in women.

Reference List

1 Erten-Lyons D, Woltjer R, Kaye J et al. Neuropathologic basis of white matter hyperintensity accumulation with advanced age. *Neurology* 2013;81:977-983.

2 Kim KW, MacFall JR, Payne ME. Classification of white matter lesions on magnetic resonance imaging in elderly persons. *Biol Psychiatry* 2008;64:273-280.

3 Promjunyakul N, Lahna D, Kaye JA et al. Characterizing the white matter hyperintensity penumbra with cerebral blood flow measures. *Neuroimage Clin* 2015;8:224-229.

4 Bashir A, Lipton RB, Ashina S, Ashina M. Migraine and structural changes in the brain: a systematic review and meta-analysis. *Neurology* 2013;81:1260-1268.

5 Hamedani AG, Rose KM, Peterlin BL et al. Migraine and white matter hyperintensities: the ARIC MRI study. *Neurology* 2013;81:1308-1313.

6 Gaist D, Garde E, Blaabjerg M et al. Migraine with aura and risk of silent brain infarcts and white matter hyperintensities: an MRI study. *Brain* 2016;139:2015-2023.

7 Zhang Q, Datta R, Detre JA, Cucchiara B. White matter lesion burden in migraine with aura may be associated with reduced cerebral blood flow. *Cephalalgia* 2016.

8 Kruit MC, Launer LJ, Ferrari MD, van Buchem MA. Infarcts in the posterior circulation territory in migraine. The population-based MRI CAMERA study. *Brain* 2005;128:2068-2077.

9 Wolf ME, Szabo K, Griebe M et al. Clinical and MRI characteristics of acute migrainous infarction. *Neurology* 2011;76:1911-1917.

10 Sorensen PS, Marquardsen J, Pedersen H, Heltberg A, Munck O. Long-term prognosis and quality of life after reversible cerebral ischemic attacks. *Acta Neurol Scand* 1989;79:204-213.

11 Monteith T, Gardener H, Rundek T et al. Migraine, white matter hyperintensities, and subclinical brain infarction in a diverse community: the northern Manhattan study. *Stroke* 2014;45:1830-1832.

12 Gonzalez-Quintanilla V, Toriello M, Palacio E et al. Systemic and cerebral endothelial dysfunction in chronic migraine. A case-control study with an active comparator. *Cephalalgia* 2016;36:552-560.

13 Schillaci G, Sarchielli P, Corbelli I et al. Aortic stiffness and pulse wave reflection in young subjects with migraine: A case-control study. *Neurology* 2010;75:960-966.

14 Kruit MC, Launer LJ, Overbosch J, van Buchem MA, Ferrari MD. Iron accumulation in deep brain nuclei in migraine: a population-based magnetic resonance imaging study. *Cephalalgia* 2009;29:351-359.

15 Dohmen C, Sakowitz OW, Fabricius M et al. Spreading depolarizations occur in human ischemic stroke with high incidence. *Ann Neurol* 2008;63:720-728.

16 Guo ZN, Liu J, Xing Y et al. Dynamic cerebral autoregulation is heterogeneous in different subtypes of acute ischemic stroke. *PLoS One* 2014;9:e93213.

17 Sacco RL, Benjamin EJ, Broderick JP et al. American Heart Association Prevention Conference. IV. Prevention and Rehabilitation of Stroke. Risk factors. *Stroke* 1997;28:1507-1517.

18 Pallesen LP, Ragaller M, Kepplinger J et al. Diagnostic Impact of Transesophageal Echocardiography in Patients with Acute Cerebral Ischemia. *Echocardiography* 2016;33:555-561.

19 Ryoo S, Chung JW, Lee MJ et al. An Approach to Working Up Cases of Embolic Stroke of Undetermined Source. *J Am Heart Assoc* 2016;5:e002975.

20 Rist PM, Diener HC, Kurth T, Schurks M. Migraine, migraine aura, and cervical artery dissection: a systematic review and meta-analysis. *Cephalalgia* 2011;31:886-896.

21 Debette S, Kamatani Y, Metso TM et al. Common variation in PHACTR1 is associated with susceptibility to cervical artery dissection. *Nat Genet* 2015;47:78-83.

22 Freilinger T, Anttila V, de VB et al. Genome-wide association analysis identifies susceptibility loci for migraine without aura. *Nat Genet* 2012;44:777-782.

23 Rubinstein SM, Peerdeman SM, van Tulder MW, Riphagen I, Haldeman S. A systematic review of the risk factors for cervical artery dissection. *Stroke* 2005;36:1575-1580.

24 Metso TM, Tatlisumak T, Debette S et al. Migraine in cervical artery dissection and ischemic stroke patients. *Neurology* 2012;78:1221-1228.

25 Mawet J, Boukobza M, Franc J et al. Reversible cerebral vasoconstriction syndrome and cervical artery dissection in 20 patients. *Neurology* 2013;81:821-824.

26 Hooker WD, Raskin NH. Neuropsychologic alterations in classic and common migraine. *Arch Neurol* 1986;43:709-712.

27 Waldie KE, Hausmann M, Milne BJ, Poulton R. Migraine and cognitive function: a life-course study. *Neurology* 2002;59:904-908.

28 Coleston DM, Chronicle E, Ruddock KH, Kennard C. Precortical dysfunction of spatial and temporal visual processing in migraine. *J Neurol Neurosurg Psychiatry* 1994;57:1208-1211.

29 Le Pira F, Zappala G, Giuffrida S et al. Memory disturbances in migraine with and without aura: a strategy problem? *Cephalalgia* 2000;20:475-478.

30 Gaist D, Pedersen L, Madsen C et al. Long-term effects of migraine on cognitive function: a population-based study of Danish twins. *Neurology* 2005;64:600-607.

31 Wen K, Nguyen NT, Hofman A, Ikram MA, Franco OH. Migraine is associated with better cognition in the middle-aged and elderly: the Rotterdam Study. *Eur J Neurol* 2016.

32 Boyle PA, Yu L, Fleischman DA, Leurgans S, Yang J, Bennett DA. White matter hyperintensities, incident mild cognitive impairment, and cognitive decline in old age. *Ann Clin Transl Neurol* 2016;10:791-800.

33 Ditchfield JA, McKendrick AM, Badcock DR. Processing of global form and motion in migraineurs. *Vision Res* 2006;46:141-148.

34 Furman JM, Sparto PJ, Soso M, Marcus D. Vestibular function in migraine-related dizziness: a pilot study. *J Vestib Res* 2005;15:327-332.

35 Sandor PS, Mascia A, Seidel L, De P, V, Schoenen J. Subclinical cerebellar impairment in the common types of migraine: a three-dimensional analysis of reaching movements. *Ann Neurol* 2001;49:668-672.

36 Ishizaki K, Mori N, Takeshima T et al. Static stabilometry in patients with migraine and tension-type headache during a headache-free period. *Psychiatry Clin Neurosci* 2002;56:85-90.

37 Harno H, Hirvonen T, Kaunisto MA et al. Subclinical vestibulocerebellar dysfunction in migraine with and without aura. *Neurology* 2003;61:1748-1752.

38 Akdal G, Balci BD, Angin S, Ozturk V, Halmagyi GM. A longitudinal study of balance in migraineurs. *Acta Otolaryngol* 2012;132:27-32.

Chapter 10

Summary in Dutch
Nederlandse samenvatting

In dit proefschrift worden de resultaten besproken van de "Cerebral abnormalities in migraine, an epidemiological risk analysis II (CAMERA II) studie". In dit onderzoek werden deelnemers met migraine uit de algemene populatie (migraineurs) vergeleken met personen zonder migraine (controles). Er werd hiervoor, 9 jaar na de CAMERA-I studie, opnieuw beeldvormend onderzoek van de hersenen verricht (deel I), diagnostiek verricht naar de aanwezigheid van rechts-links shunts (RLS), (deel II) en onderzoeken naar cerebellaire functie als ook longitudinaal onderzoek naar cognitieve functies gedaan (deel III). Tevens worden de resultaten besproken van twee studies die geen deel uitmaakten van de CAMERA-II studie; 1) om de tijdelijke effecten van een acute migraine aanval op de cognitieve functies te onderzoeken en 2) om de relatie tussen migraine met aura en cardiale aandoeningen waarbij er geen RLS aanwezig is te bestuderen.

I Migraine en beeldvormend onderzoek van de hersenen

In ons onderzoek werden deelnemers afkomstig uit de algemene populatie 9 jaar na het initiële CAMERA-I onderzoek vervolgd. Vrouwen met migraine hadden een groter volume diepe witte stof hyperintensiteiten en ook meer nieuwe witte stof lesies. Deze bevindingen werden niet specifiek vaker bij migraine met aura gezien. De ernst van migraine (bv aanvalsfrequentie of het totale aantal aanvallen gedurende het leven) waren niet geassocieerd met de gevonden progressie van witte stof hyperintensiteiten. Bij mannen werd er geen verschil in witte stof hyperintensiteiten gevonden tussen migraineurs en controles. (**Hoofdstuk II**)

De prevalentie van infratentoriële hyperintensiteiten was ook hoger bij vrouwen met migraine (zowel met als zonder aura) vergeleken met controles. Er waren aanwijzingen dat ook de progressie van deze hyperintensiteiten vaker voorkwam bij vrouwelijke migraineurs (trend). Bij mannen werd er geen verschil gevonden. (**Hoofdstuk II**)

Negen jaar na het CAMERA-I onderzoek, werden nieuwe stille herseninfarcten in de achterste circulatie bij 5% van de migraineurs en 0% van de controles gevonden (trend). Migraine variabelen zoals persisterende activiteit van migraine, aanvalsfrequentie of totale aantal aanvallen gedurende het leven hadden, in tegenstelling tot de bevindingen van CAMERA-I, geen invloed op deze uitkomst. (**Hoofdstuk II**)

II Migraine en het hart

De prevalentie van RLS bij migraineurs met aura was verhoogd vergeleken met controles en migraineurs zonder aura. (**Hoofdstuk III**). Het gevonden relatieve risico was echter kleiner dan in eerdere (zogenaamde clinical based) studies. Waarschijnlijk werd dit verklaard doordat in ons onderzoek de prevalentie van RLS bij controles duidelijk hoger was dan in voorgaande studies. In ons CAMERA-II onderzoek waren alle onderzoekers geblindeerd voor migraine diagnose, wat bijdraagt aan de betrouwbaarheid van bevindingen. Indien een RLS aanwezig is, kunnen verschillende soorten veneuze embolieën waarschijnlijk een migraine aanval provoceren. Echter zelfs het optreden van migraine aanvallen in dergelijke bijzondere omstandigheden met talrijke embolieën lijkt echter relatief weinig voor te komen. (**Hoofdstuk IV**)

Door de longitudinale opzet van het onderzoek, waren we als eerste instaat om zowel migraineurs te onderzoeken met persisterende migraine activiteit alsook migraineurs die inmiddels geen aanvallen meer hadden. De aanwezigheid van een spontane RLS bleek geassocieerd met persisterende migraine activiteit. (**Hoofdstuk III**). De aanwezigheid van een RLS toonde een mogelijke associatie (trend) met stille infarcten in de achterste circulatie. **(Hoofdtuk III)**

Migraine met aura werd in een eerder onderzoek met het syndroom van Marfan geassocieerd. Het was echter onduidelijk welk onderliggend pathologisch substraat dit zou kunnen verklaren. In ieder geval was bekend dat bij Marfan patiënten het voorkomen van RLS niet verhoogd is, dus dit leek geen verklaring. We toonden aan dat Marfan patiënten die een aorta wortel vervanging hadden ondergaan specifiek vaker migraine met aura hadden. Kortom ook een cardiale afwijking, waarbij geen RLS aanwezig was, bleek dus geassocieerd met migraine met aura.(**Hoofdstuk V**)

Het gebruik van hoge dosis verapamil is soms nodig bij cluster hoofdpijn of familaire hemiplegische migraine. Hoewel cardiale bijwerkingen en/of ECG afwijkingen vaak voorkomen, ontbreken richtlijnen om deze patienten te screenen en te monitoren tijdens het gebruik van verapamil. Middels de Delphi-methode werden 22 internationale experts op het terrein van hartritmestoornissen geraadpleegd.

Geconcludeerd werd dat het nuttig is om voorafgaand aan het eerste verapamil voorschrift een ECG te maken. Over het hierna te volgen ECG beleid tijdens verder verapamil gebruik kon geen consensus worden bereikt. Desondanks adviseer ik standaard om voor (en ook na) een dosisverhoging verapamil een ECG te maken.

III Migraine en hersenfuncties

Er werden bij het CAMERA-II onderzoek geen verschillen in cognitieve functies gevonden tussen migraineurs en controles in de inter-ictale situatie (buiten een migraine aanval). Hierbij werd gebruik gemaakt van een grote batterij aan neuropsychologische tests die gevoelig zijn voor afwijkingen in de supra-tentoriële hersenstructuren. (**Hoofdstuk II**). De aanwezigheid van veel diepe wittestof schade was mogelijk geassocieerd met stoornissen van het geheugen (trend). Dit was echter niet verschillend voor migraineurs of controles. (**Hoofdstuk II, e-table 3**)
In een ander onderzoek in dit proefschrift werd specifiek de cognitieve functie onderzocht direct na een migraine aanval. Een negatief effect van de migraine aanval zelf kon niet worden gevonden. Wel konden we aantonen dat migraineurs minder goed waren in het verwerken van globale visuele informatie boven lokale informatie, vergeleken met controles. Migraineurs konden, met andere woorden, bij dit onderzoek door de bomen het bos minder goed zien. (**Hoofdstuk VIII**)

Bij de deelnemers aan het CAMERA-II onderzoek werd ook specifiek de functie van het cerebellum onderzocht met behulp van een serie gevoelige tests. Er werd geen verschil gevonden tussen migraineurs en controles op de volgende gebieden: 1) snelheid van fijne motoriek, coördinatie van extremiteiten, stabiliteitstesten en cerebellaire cognitieve testen. Deze tests waren in veel gevallen wel sterk afwijkend bij een extra geteste groep patiënten met familiare hemiplegische migraine, waarbij er klinisch vaak duidelijke cerebellaire klachten bestaan. (**Hoofdstuk VII**)

Conclusie en toekomst

We toonden aan dat zowel diepe witte stof hyperintensiteiten als stille cerebellaire infarcten bij migraineurs, niet geassocieerd zijn met migraine activiteit in heden of verleden. Met andere woorden, de gevonden afwijkingen werden niet veroorzaakt door een optelsom van individuele aanvallen. Dit maakt het onwaarschijnlijk dat de migraine aanval zelf causaal een rol speelt bij de gevonden hersenveranderingen. Waarschijnlijk speelt een onderliggende factor, bijvoorbeeld endotheel dysfunctie of een gedeelde genetische factor een rol. In de toekomst moeten onderzoeken voornamelijk gericht zijn op het onderliggende mechanisme van wittestof lesies bij vrouwen met migraine.

Het verband tussen RLS en migraine met aura hebben we in de algemene populatie aangetoond. Opvallend was dat we vonden dat een spontane RLS geassocieerd was met persisterende migraine aanvallen. Dit draagt bij aan de kennis dat embolieën waarschijnlijk in staat zijn corticale verspreidende depressies (zogenaamde CSDs) uit te lokken en zo aanvallen van migraine met aura zouden kunnen veroorzaken. De bijdrage van een aanwezig RLS aan ischemische hersenlesies bij migraine in het achterste stroomgebied lijkt beperkt. Tot op heden is er geen bewezen effect van profylactisch sluiten van RLS voor beperking van migraine aanvallen en adviseer ik dan ook niet om RLS diagnostiek te doen bij migraine patiënten.

Hoewel migraine geassocieerd was met subklinische hersenveranderingen in dit onderzoek, zorgden deze veranderingen er niet voor dat migraineurs op functietesten minder scoren. Ook leek de impact van een acute aanval geen duidelijk effect te hebben op cognitieve functies, als de pijn verdwenen is.

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Taeke, Kiek en Sien. Dat gezicht achter dat verlichte appeltje was ik. Meestal hadden jullie de ogen al dicht, maar ik beloof; de klep gaat nu ook even dicht.

Curriculum vitae

Hille Koppen was born on July 9th 1975 in Eindhoven, the Netherlands. He attended the Atheneum of the van Maerlant Lyceum in Eindhoven and graduated in 1995. In 1995 he started medical school at the Maastricht University. In 2001 he obtained his medical degree and after working for six months at the neurological department Antonius Hospital in Nieuwegein, he started his residency at the neurological department of the Leyenburg Hospital (now Haga hospital) in The Hague in 2002 (under Dr. T.C.A.M van Woerkom; D.L.J. Tavy, Dr. S.F.T.M. de Bruijn). He spent 6 months of his training at the Parnassia Psycho Medical Center in The Hague (under Prof. Dr. H.W. Hoek) and 6 months at the Leiden University Medical Center (under Prof. Dr. R.A.C. Roos).In 2006 he joined the research group of Prof. Dr. M.D. Ferrari initially on the multi-center Patent Foramen Ovale Closure Study which finally did not take-off and later to conduct the research described in this thesis. He completed his residency in 2009 and is working ever since as a clinical neurologist at the Haga hospital in The Hague, The Netherlands.

List of publications

Volumetric brain changes in migraineurs from the general population.
Palm-Meinders IH, Arkink EB, Koppen H, Amlal S, Terwindt GM, Launer LJ, van Buchem MA, Ferrari MD, Kruit MC.
Neurology. 2017 Oct 11 (epub ahead of print)

Migraine and vascular disease biomarkers: A population-based case-control study.
Tietjen GE, Khubchandani J, Herial N, Palm-Meinders IH, Koppen H, Terwindt GM, van Buchem MA, Launer LJ, Ferrari MD, Kruit MC.
Cephalalgia. 2017 Jan 1 (epub ahead of print)

Iron in deep brain nuclei in migraine? CAMERA follow-up MRI findings.
Palm-Meinders IH, Koppen H, Terwindt GM, Launer LJ, van Buchem MA, Ferrari MD, Kruit MC.
Cephalalgia. 2017 Jul;37(8):795-800.

Spontaneous spinal subdural hematoma. De Beer MH, Eysink Smeets MM, Koppen H.
Neurologist 2017. Jan; 22(1): 34-39

When the laughing stops: subacute combined spinal cord degeneration caused by laughing gas use. Buizert A, Sharma R, Koppen H. Journal of Addiction Medicine, 2017, epub

Fatal hemopericardium after intravenous recombinant transplasminogeen activator (rt-PA) for acute ischemic stroke. Hensen H, Spaander F, Bax M, Koppen H. Am J Emerg Med 2016

Discontinuing oral anti-coagulants in a patient with a cardiac valve prosthesis who suffers traumatic intracranial hemorrhage. Smaal JA, Koppen H. Am J Emerg Med 2016 Aug 34 (8): 1736

Cerebellar function and ischemic brain lesions in migraine patients from the general population. Koppen H, Boele HJ, Palm-Meinders IH, Koutstaal BJ, Horlings CG, Koekkoek BK, van der Geest J, Smit AE, van Buchem MA, Launer LJ, Terwindt GM, Bloem BR, Kruit MC, Ferrari MD, De Zeeuw CI. Cephalalgia. 2016 Apr 7.

Systemic right-to-left shunts, ischemic brain lesions, and persistent migraine activity. Koppen H, Palm-Meinders IH, Mess WH, Keunen RW, Terwindt GM, Launer LJ, van Buchem MA, Kruit MC, Ferrari MD. Neurology. 2016 Mar 11.

Cardiac monitoring of high-dose verapamil in cluster headache: An international Delphi study. Koppen H, Stolwijk J, Wilms EB, van Driel V, Ferrari MD, Haan J. Cephalalgia. 2016 Feb 10

Spontaneous intracranial hypotension as first symptom of aneurysms-osteoarthritis syndrome: a case report. Koppen H, Baars MJ, van Gils A, Vis JC. Headache. 2015 May;55(5):711-2.

Bilateral Heel Numbness due to External Compression during Obstetric Epidural Analgesia. Kamphuis VP, Zegers MP, Koppen H. Case Rep Neurol. 2015 Jan 30;7(1):15-7

Parafalcine empyema, a tricky infectious cause of headache: a case report. van der Stel T, Treuniet FE, Hoffmann C, Koppen H. Am J Emerg Med. 2015 Jul;33(7):992.

Trigeminal Autonomic Headaches caused by a multi-nodular goiter, a case report Headache. Smit RA, Treurniet FE, Koppen H. Headache 2014 Sep;54 (8)

Pro-Con debat: Een MRI-cerebrum bij een poliklinische hoofdpijnpatient is nodig. De Beer M, Koppen H. Tijdschrift voor Neurologie en Neurochirurgie. 2014;1:221-26

Are atraumatic spinal needles as efficient as traumatic needles for lumbar puncture? Pelzer N, Vandersteene J, Bekooij TJ, Schoonman GG, Wirtz PW, Vanopdenbosch LJ, Koppen H. Neurol Sci. 2014 Aug 20

Mimics of subacute subdural hematoma in the ED. de Beer MH, van Gils AP, Koppen H. Am J Emerg Med. 2013 Mar;31(3):634

A missing arch of the atlas vertebra in a patient struck by a tram. Smit RA, Coebergh JA, Treurniet FE, Kuiters RR, Koppen H. Neurol Sci. 2013 Feb 26.

Migraineurs with exercise-triggered migraine have a distinct migraine, Koppen H, van Velthoven P.L.J, J Headache Pain, 2013 Dec 21;14:99

Tijd voor een betere lumbaalnaald. Een pleidooi voor de atraumatische 22G-naald. Pelzer N, Schoonman GG, Koppen H, Wirtz PW, Tijdschrift voor neurologie en neurochirurgie 2012.113:108-14

Reversible cerebellar leukoencephalopathy after MTX, Koppen H, Wessels JA, Ewals JA, Treurniet FE, J Rheumatol. 2012 Sep;39(9):1906-7

Aortic root pathology in Marfan syndrome increases risk for migraine with aura. Koppen H, Vis J, Gooiker D, Knudsen S, Bouma B, Tijssen J, Mol BD, Mulder B, Russell M, Ferrari MD, Cephalagia. 2012 Apr;32 (6):467-72

Structural brain changes in migraine. Koppen H,Palm-Meinders IH, Terwindt GM, Ferrari MD, Kruit MC. JAMA. 2012 Nov 14;308(18):1889-97

Postpartum spontaneous intracranial hypotension A. v Sonderen, Koppen H. Am J Emerg Med. 2013 Feb;31(2):461

Subacute anterior horn disease caused by neuroborreliosis. Hoogers SE, Wirtz PW, Koppen H. Neurol Sci 2013 Jun;34(6):1019-20

Right-to-left shunts and micro-embolization in migraine. Koppen H., Palm-Meinders I.H., Ferrari M.D., Curr Opin Neurol. 2012 Mar 26

Severe unilateral headache caused by skull bone infarction with epidural hematoma in a patient with sickle cell disease. Arends S, Coebergh JA, Kerhoffs JL, van Gils A, Koppen H. Cephalalgia 2011, Sept 31(12) 1325-8

The impact of a migraine attack and its after-effects on perceptual organization, attention, and working memory. Koppen H, Palm-Meinders I, Kruit M, Lim V, Nugroho A, Westhof I, Terwindt G, van Buchem M, Ferrari M, Hommel B. Cephalalgia 2011 Oct 31 (14) 1419-27

Reversible posterior leucoencephalopathy syndrome mimicking low grade glioma, differentiation by post emission tomography. Rath JJ, Koppen H, Treurniet FE, Comans EF, Wirtz PW. Clin Neurol Neurosurg. 2011 Nov;113(9):785-7

Transcranieel Doppler-onderzoek met luchtcontrast, zinvol en bij wie? Editorial. Koppen H, Tijdschrift voor Neurologie en Neurochirurgie 2011, 112 19

A woman with gas behind her eye. Koppen H, de Bruijn SB, Ned Tijdschr Geneesk 2010, 154

Effect of cardiac resynchronization therapy on cerebral blood flow. Van Bommel RJ, Marsan NA, Koppen H, Delgado V, Borleffs CJ, Ypenburg C, Bertini M, Schalij MJ, Bax JJ. Am J Cardiol 2010 Jul 1 106(1)

Neck pain due to tendonitis longus colli muscle, Coebergh, Koppen H, van Gils AP, de Bruijn BF. Ned Tijdschr Geneesk 2010, 154

No indication for PFO closure. Koppen H, Terwindt GM, Haan J, de Bruijn SF, Bax JJ, Ferrari MD., Neth. Heart Journal 2009, vol 9

Space headache; a new secondary headache. Vein AA, Koppen H, Haan J, Terwindt GM, Ferrari MD. Cephalalgia 2009, jun 29(6) 683-6

Percutane sluiting van het foramen ovale persistens bij migraine patienten. De uitkomsten en de implicaties van de laatste studies. Koppen H, Terwindt GM, De Bruijn SF, Ferrari MD (2008;109:70-3) Tijdschrift neurologie neurochirurgie

Efficacy and tolerability of MK0974, a new oral antagonist of calcitonin gene-related peptide receptor. Ho TW, Ferrari MD, Dodick DW, Galet V, Kost J, Fan X, Leibensperger H, Froman S, Assaid C, Lines C, Koppen H, Winner PK. Lancet 2008 Dec (20); 372

Migraine and cardiovascular risk, Terwindt GM, Haan J, Koppen H, Ferrari MD. Ned Tijdschr Geneeskund. 2007 sept 15, 151(37) 2019

Paraneoplastic cerebellar degeneration preceding the diagnosis of Hodgekin's lymphoma Ypma PF, Wijermans PW, Koppen H, Sillevis Smitt PA, Neth J Med. 64(7) 243-7