Migraine as a Risk Factor for Subclinical Brain Lesions

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Context Clinical series have suggested an increased prevalence of cerebral infarction and white matter lesions (WMLs) in migraine patients. It is not known whether these lesions are prevalent in the general migraine population.

Objectives To compare the prevalence of brain infarcts and WMLs in migraine cases and controls from the general population and to identify migraine characteristics associated with these lesions.

Design Cross-sectional, prevalence study of population-based sample of Dutch adults aged 30 to 60 years.

Participants Randomly selected patients with migraine with aura (n=161), patients with migraine without aura (n=134), and controls (n=140), who were frequency matched to cases for age, sex, and place of residence. Nearly 50% of the cases had not been previously diagnosed by a physician.

Main Outcome Measures Brain magnetic resonance images were evaluated for infarcts, by location and vascular supply territory, and for periventricular WMLs (PVWMLs) and deep WMLs (DWMLs). The odds ratios (ORs) and 95% confidence intervals (CIs) of these brain lesions compared with controls were examined by migraine subtype (with or without aura) and monthly attack frequency (<1 attack, ≥1 attack), controlling for cardiovascular risk factors and use of vasoconstrictor migraine agents. All participants underwent a standard neurological examination.

Results No participants reported a history of stroke or transient ischemic attack or had relevant abnormalities at standard neurological examination. We found no significant difference between patients with migraine and controls in overall infarct prevalence (8.1% vs 5.0%). However, in the cerebellar region of the posterior circulation territory, patients with migraine had a higher prevalence of infarct than controls (5.4% vs 0.7%; *P*=.02; adjusted OR, 7.1; 95% CI, 0.9-55). The adjusted OR for posterior infarct varied by migraine subtype and attack frequency. The adjusted OR was 13.7 (95% CI, 1.7-112) for patients with migraine with aura compared with controls. In patients with migraine with a frequency of attacks of 1 or more per month, the adjusted OR was 9.3 (95% CI, 1.1-76). The highest risk was in patients with migraine with aura with 1 attack or more per month (OR, 15.8; 95% CI, 1.8-140). Among women, the risk for high DWML load (top 20th percentile of the distribution of DWML load vs lower 80th percentile) was increased in patients with migraine compared with controls (OR, 2.1; 95% CI, 1.0-4.1); this risk increased with attack frequency (highest in those with ≥1 attack per month: OR, 2.6; 95% CI, 1.2-5.7) but was similar in patients with migraine with or without aura. In men, controls and patients with migraine did not differ in the prevalence of DWMLs. There was no association between severity of PVWMLs and migraine, irrespective of sex or migraine frequency or subtype.

Conclusions These population-based findings suggest that some patients with migraine with and without aura are at increased risk for subclinical lesions in certain brain areas.

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MIGRAINE IS A COMMON, chronic, multifactorial neurovascular disorder typically characterized by recurrent attacks of disabling headache and autonomic nervous system dysfunction (migraine without aura); up to one third of patients also have neurological aura symptoms (migraine with aura).[1,2] Migraine has been suggested to be an independent risk factor for stroke, but the evidence is conflicting and seems to be restricted to certain subpopulations (eg, women with migraine with aura who are younger than 45 years, particularly ones who smoke or use oral contraceptives [OCs]).[3-9] Case reports on patients with so-called migrainous infarction suggest that the posterior circulation territory (PCT) is most commonly affected.[8,9] However, data are lacking on prevalence of subclinical infarcts in a wide spectrum of migraine patients in the general population.

Patients with migraine may also be at increased risk of more diffuse subclinical lesions in the deep white matter or periventricular areas that are only detected on neuroimaging.[10-12] Several clinic-based magnetic resonance imaging (MRI) studies have reported this,

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but cardiovascular risk factors[13,14] and use of vasoconstrictor (migraine) agents, which may also be associated with these lesions, were not always accounted for. As with brain infarction, there are no data on the prevalence of these lesions in patients with migraine from the general population.

In view of the high prevalence of migraine, it is important to establish whether migraine is an independent risk factor for subclinical infarcts and white matter lesions (WMLs). Both types of brain lesions have been shown to increase the risk of adverse sequelae, including clinical stroke events, physical limitations, and cognitive impairment, including dementia.[14-16]

Herein, we report the results of a large, population-based MRI study designed to investigate (1) whether unselected migraine cases from the general population are at increased risk of brain infarcts and WMLs, (2) whether this risk varies by migraine subtype and attack frequency, (3) whether certain areas of the brain are particularly vulnerable, and (4) whether traditional cardiovascular risk factors may modify the risk of brain lesions.

METHODS

Study Population

Cases and controls were randomly selected from the Genetic Epidemiology of Migraine (GEM) study, a population-based survey of Dutch adults aged 20 to 60 years living in 2 representative Dutch municipalities (Maastricht and Doetinchem). The 3-step case-finding procedure for migraine cases has been detailed elsewhere.[17] Briefly, everyone in the cohort answered 5 screening questions regarding significant headache and aura in a self-administered questionnaire. Screen-positive participants were administered a detailed questionnaire on headache and aura characteristics, including all signs and symptoms of migraine as listed by the International Headache Society (IHS).[1] A further random 83% sample of screen-positive participants and a 5% sample of screen-negative participants were followed up with a semi-structured interview administered by a trained interviewer. A final diagnosis, based on IHS criteria,[1] was made in conference with 2 physicians experienced in migraine (M.D.F. and G.M.T.). This procedure identified 863 cases of migraine; 54% of the cases had not been previously diagnosed by a physician.

For the Cerebral Abnormalities in Migraine, an Epidemiological Risk Analysis (CAMERA) study, 2 diagnostic groups (patients with migraine with and without aura) were randomly selected from the GEM cases aged 30 to 60 years; the control group was randomly selected from the cohort to frequency match the cases by sex, municipality, and 5-year age strata. Controls were people who indicated that they had no severe headaches that interfered with their daily activities and rated whatever headaches they had as 0 on the pain scale. Effectively, this excluded people with chronic daily headache and cluster headache, but people with minor migraine attacks or an occasional tension headache might have been included. We invited 631 individuals (205 patients with migraine with aura, 197 patients with migraine without aura, and 229 controls); 481 participated (81% of patients with migraine and 68% of controls), 114 actively declined participation, and 36 could not participate for various logistical reasons. All participants gave written informed consent and participated without any financial reimbursement. The study protocol was approved by the Leiden University Medical Center ethics committee.

The CAMERA protocol included a structured telephone interview and a clinic visit for a brain MRI, blood draw, and a standard physical and neurological examination. The clinical visit took place within 10 days of the telephone interview; migraine case patients underwent examinations in a headache-free period (≥3 days after a migraine attack). A complete magnetic resonance examination was performed in 435 participants (134 patients with migraine without aura, 161 patients with migraine with aura, and 140 controls) (TABLE 1). The 46 individuals who did not undergo MRI did not differ from those who underwent MRI in terms of age, sex, body mass index (BMI), smoking, cholesterol level, blood pressure (BP), diabetes, and OC use. There were also no differences in these demographics and cardiovascular risk factors between responders and nonresponders or between nonresponding cases and controls; responders had slightly more years of formal schooling than nonresponders ($P = .07$).

Assessment of Migraine

To check the stability of the diagnosis given in the GEM study (made on average 3.5±0.5 years before), we administered the same GEM screening and diagnostic questions to everyone. Of the 435 participants, 14 were reclassified from the GEM diagnosis: 5 control subjects were now classified as having migraine, 2 migraine cases were reclassified as controls, and 7 migraine without aura cases were reclassified as migraine with aura because their first aura symptoms started after the GEM interview. Attack frequency may vary during the migraine period. To help the participants estimate headache and aura attack frequency, we structured the interview so they could recount their history of migraine using their own benchmarks for when a different pattern started and stopped. These benchmarks were used to define periods. In addition to reported age at first and last migraine and aura attack, these data were used to calculate a weighted average of the number of attacks per month. If applicable, participants gave estimates about frequency (never, sometimes, about half the number of attacks, most attacks) and amounts of specific antimigraine medication (ergotamines, triptans) they used in the years they had migraine attacks.

Magnetic Resonance Imaging

Brain MRIs were acquired on a 1.5-T unit in Maastricht (ACS-NT; Philips Medical Systems, Best, the Netherlands) and a 1.0-T unit in Doetinchem (Magnetom Harmony; Siemens AG, Erlangen, Germany). Protocols in the 2

centers were comparable. Whole brain images were acquired with 48 contiguous, 3-mm axial slices (field of view, 22 cm; matrix, 190-205×256). Pulse sequences included a combined proton density and T2-weighted fast spin-echo (repetition time/echo time/excitations/echo-train length, 3000/27-120/1/10 for the ACS-NT and 3000/14-85/2/5for the Magnetom Harmony) and fluid-attenuated inversion-recovery (FLAIR; repetition time/echo time/inversion time/excitations/echo-train length, 8000/100/2000/2/19 for ACS-NT and 8000/105/2000/2/7 for Magnetom Harmony).

One neuroradiologist (M.A.v.B.), who was blinded to the migraine diagnosis and clinical data, rated infarcts and WMLs on hard copies. Infarcts were defined as 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 and proton density images.[18,19] Number, location, and size of infarcts were recorded. Virchow-Robin spaces were excluded as infarcts based on location, shape, size, and absence of a hyperintense border.[19] To determine whether there was preferential damage in any one vascular system,[8,9] we scored infarct by location and vascular supply. Topographical maps[20,21] were used to define 4 categories that reflected the 2 major territories of blood supply to the brain (anterior/carotid circulation and PCT) and 2 areas with a heterogeneous blood supply (basal ganglia and corona radiata/centrum semiovale).

White matter lesions had to be hyperintense on all sequences. The reading protocol was based on semiquantitative scales with known interrater and intrarater reliability.[22,23] Periventricular WMLs (PVWMLs) were assessed in 3 regions (frontal and posterior horns and bands) and rated as 0 (no PVWML), 1 (pencil-thin lining), 2 (smooth halo or thick lining), or 3 (large confluent lesions). The 3 regional scores were added for the final score (range, 0-9). Deep WMLs (DWMLs) were rated by lobe location, number, and size, as measured with a caliper on the FLAIR image. The count of WMLs was combined to get a quantitative measure of load by multiplying each lesion by a size-dependent constant (0.0042 mL for small [≤3 mm] lesions, 0.114 mL for medium [4-10 mm], and 0.90 mL for large [>10 mm] lesions).

Measurement of Confounders and Covariates

Sociodemographic and medical characteristics were assessed by interview. Education was categorized into low (primary school or lower vocational education) and high. Smoking history was defined as never, former, and current and, for ever smokers, pack-years of exposure. The average alcohol intake in the past year was based on responses to questions on frequency and quantity of drinks per occasion and categorized into none, moderate (1-3 drinks per day), and high (≥3 drinks per day). Women reported the number of years they used OCs. Self-reported weight and height were used to calculate BMI (weight in kilograms divided by the square of height in meters). Blood pressure was the mean of 3 measurements obtained at 1-minute intervals in the upper arm with an electronic oscillometric BP monitor (OMRON 711, Omron Healthcare Europe, Hoofddorp, the Netherlands). Hypertension was de-

Table 1. Characteristics of Study Participants*

Characteristic	Controls (n = 140)	Patients With Migraine Without Aura (n = 134)	Patients With Migraine With Aura (n = 161)
Age, mean (SE), y	48.0 (0.7)	48.8 (0.7)	48.2 (0.6)
Female, No. (%)	100 (71)	101 (75)	116 (72)
Maastricht research center, No. (%)	75 (54)	58 (43)	80 (50)
Low education, No. (%)†	72 (51)	68 (51)	87 (54)
Body mass index, mean (SE)	24.4 (0.3)	25.0 (0.3)	25.6 (0.4)‡
Blood pressure, mean (SE), mm Hg			
Systolic	134.8 (1.5)	133.7 (1.5)	134.6 (1.4)
Diastolic	90.8 (0.8)	91.0 (0.9)	91.8 (0.8)
Hypertension, No. (%)§	45 (32)	54 (40)	68 (42)
Cholesterol, mean (SE), mmol/L	5.2 (0.1)	5.3 (0.1)	5.4 (0.1)
Diabetes, No. (%)	5 (4)	3 (2)	1 (1)
Smoking			
Never, No. (%)	48 (34)	53 (40)	57 (35)
Pack-years, mean (SE)	11 (1.2)	9 (1.0)	10 (1.1)
Alcohol use, No. (%)			
None	21 (15)	40 (30)‖	27 (17)
≥3 units/d	22 (16)	7 (5)¶	15 (9)
≥15 Years of oral contraceptive use (women only), No. (%)	24 (24)	19 (19)	34 (29)
Previous physician diagnosis of migraine, No. (%)	. . .	61 (46)	95 (59)#
Migraine attack frequency, attacks per year			
Median	. . .	11.9	10.2
25th-75th percentile	. . .	7-23	6-18
Ever use of specific antimigraine medication**			
Triptans	. . .	8 (6.0)	14 (8.7)
Ergotamines	. . .	9 (6.7)	9 (5.6)

SI conversion factors: To convert cholesterol to mg/dL, divide by 0.0259.
*P values are based on the χ^2 test for the comparison of proportions or the t test for the comparison of means. Unless indicated otherwise, differences were not statistically significant ($P>.05$).
†Low education indicates primary school or lower vocational education.
‡Compared with controls: $P = .01$.
§Hypertension was defined as a systolic blood pressure of 160 mm Hg and higher or a diastolic blood pressure of 95 mm Hg and higher or current use of antihypertensive drugs.
‖Compared with controls: $P = .003$; compared with patients with migraine with aura: $P = .008$.
¶Compared with controls: $P = .005$.
#Compared with patients with migraine without aura: $P = .03$.
**No participants reported (ever) use of both types of specific antimigraine medication.

fined as a systolic BP of 160 mm Hg and higher or a diastolic BP of 95 mm Hg and higher or current use of antihypertensive drugs. A measure of total cholesterol was available from the baseline GEM examination.[24]

Statistical Analysis

We used χ^2 tests, unpaired *t* tests, and 1-way analyses of variance to test for any differences in the distributions and means of measured characteristics among the study groups. Using logistic regression models, we examined the risk (odds ratios [ORs], 95% confidence intervals [CIs]) for the MRI outcomes by migraine status (yes/no), subtype of migraine (migraine with and without aura vs controls), mean attack frequency (<1 and ≥1 attack per month vs controls), and a combination of migraine type by attack frequency. For evaluating WML load, we assumed a baseline prevalence of 20%. For a 2-tailed test and an α of .05, we had 91% power to detect a significantly increased risk of 2.1 and greater. For the infarct analysis, we assumed a baseline prevalence of 5%. With an α of .05, we had 100% power to detect a significantly increased risk of 5.0 and greater.

The association between PVWMLs and migraine was assessed by comparing the distributions and mean grades of severity of PVWMLs among the diagnostic groups. Additionally, we compared the diagnostic groups by clustering severity grades of PVWMLs: no PVWML (grade=0), no more than a pencil-thin lining in 1 or 2 regions (grade=1 or 2), and more than a pencil-thin lining in 1 or 2 regions (grade >2). Other types of clustering were assessed, but this did not reveal any differences.

Using logistic regression, we estimated the association of migraine to the risk of DWMLs by comparing each quintile of DWML load to the group with no lesions. Risk estimates were similar up to the fourth quintile, so we collapsed them and show the results for the upper quintile (high DWML load) vs the rest. Three models were estimated; model 1 included sex, municipality, age, and migraine; model 2 also included education, BMI, hypertension, cholesterol level, alcohol use categories, smoking, and, among women, long-term OC use (<15 vs ≥15 years). In model 3, we included antimigraine medication (ever use of ergotamines and ever use of triptans separately). Potentially confounding effects of diabetes, heart failure, and known coagulation disorder were investigated but did not alter the results presented herein. Analyses were stratified by sex because of the difference in prevalence and reported risk of stroke.[3-6] Furthermore, we estimated the risk of infarct and DWMLs associated with attack frequency (at the median split: <1 or ≥1 attack per month) and evaluated the consistency of the association by estimating the significance of a trend variable over quintiles of attack frequency. Finally, based on previous reports that the risk of stroke among young women was particularly high in those with hypertension, users of OC,

Table 2. Prevalence of Infarcts and White Matter Lesions*

MRI Outcome Variable	Controls (n = 140)	Patients With Migraine (n = 295)	Migraine Subgroup	
			Without Aura (n = 134)	With Aura (n = 161)
Participants with ≥1 brain infarct				
Any location in the brain	7 (5.0)	24 (8.1)	9 (6.7)	15 (9.3)
No. of infarcts	9	51	19	32
By category of vascular supply				
Anterior/carotid circulation	. . .	6 (2.0)†	4 (3.0)	2 (1.2)
No. of infarcts	0	8	4	4
Posterior circulation	1 (0.7)	16 (5.4)‡	3 (2.2)	13 (8.1)§
No. of infarcts	1	33	8	25
Basal ganglia	5 (3.6)	4 (1.4)	2 (1.5)	2 (1.2)
No. of infarcts	7	5	3	2
Corona radiata/centrum semiovale	1 (0.7)	3 (1.0)	2 (1.5)	1 (0.6)
No. of infarcts	1	5	4	1
DWMLs				
≥1 medium DWML lesion	54 (39)	110 (37)	54 (40)	56 (35)
High DWML load‖	22 (16)	65 (22)	31 (23)	34 (21)
PVWML score¶				
0	30 (21)	57 (19)	22 (16)	35 (22)
1-2	99 (71)	209 (71)	95 (71)	114 (71)
3-6	11 (7.9)	29 (9.8)	17 (13)	12 (7.5)

Abbreviations: DWMLs, deep white matter lesions; MRI, magnetic resonance imaging; PVWML, periventricular white matter lesion.
*Data are number of individuals (percentage of diagnostic group). Unless otherwise indicated, *P*≥.10.
†Compared with controls: *P* = .10.
‡Compared with controls: *P* = .02.
§Compared with patients with migraine without aura: *P* = .03.
‖High DWML load reflects the upper 20th percentile of the total DWML volume distribution.
¶Scores range from 0 to 9, with 0 indicating no periventricular lesion and 9 most severe extension of periventricular lesions; effectively, no score was more than 6.

and smokers,[3,5] we tested for statistical interaction between migraine and separately for each of these risk factors. This was done by adding a cross-product term to model 2 (ie, migraine by hypertension). Because of small numbers, this was done only for the DWML outcome; in addition, we could not estimate the risk of DWMLs for those with more than 1 risk factor. Analyses and appropriate regression diagnostics were conducted with SPSS statistical software (version 10.0.5; SPSS Inc, Chicago, Ill).

RESULTS

The demographic characteristics and risk factors of the participants according to their migraine diagnosis are shown in Table 1. No participant reported a history of stroke or transient ischemic attack or showed relevant abnormalities at standard neurological examination.

Infarcts

In total, 60 brain infarcts were detected in 31 individuals (TABLE 2). Infarct size ranged from 2 to 21 mm. Compared with controls, proportionately more migraine patients had at least 1 infarct (8% vs 5%; $P=.23$ [unadjusted]). Of the 60 infarcts, 34 (57%) were located within the PCT of 17 participants: 16 cases (5.4%) and 1 control (0.7%; $P=.02$). The 13 patients with migraine with aura and the 3 patients with migraine without aura together had 1 PCT infarct located in the pons and the remaining 32 infarcts in the cerebellum. The 1 affected control had 1 PCT infarct in the cerebellum. Combining migraine subtypes, the risk of PCT infarcts was 7.1 times higher in the patients with migraine compared with controls (95% CI, 0.9-55; TABLE 3). The risk increased with increasing attack frequency (P for trend $<.005$) and was, compared with controls, 9.3 times higher in those with 1 attack or more per month. Prevalence of PCT infarcts differed between patients with migraine without aura (2.2%) and those with migraine with aura (8.1%, $P=.03$). Migraine with aura but not migraine without aura was associated with a significantly increased risk for PCT infarcts. The group with migraine with aura and 1 or more attack per month had the highest risk of PCT infarct (OR, 15.8; 95% CI, 1.8-140). There was no significant difference between patients with migraine and controls in the location of the other infarcts. Because the total number of infarcts was relatively low, we could not determine whether these associations differed between men and women. The OR was slightly lowered after we added to the model the variable indicating ever use of ergotamines (OR, 12.1; 95% CI, 1.3-113) for patients with migraine with aura with 1 or more attack per month. There was no change in the ORs after adding the variable ever use of triptans.

Table 3. Risk of PCT Infarcts by Migraine Diagnosis, Subtype, Attack Frequency, and Combination*

Migraine Characteristic	Total No. of Participants	No. of Participants With PCT Infarct	OR (95% CI)	
			Model 1	Model 2
Migraine history				
No (controls)†	140	1	1.0	1.0
Yes	295	16	7.6 (1.0-58)	7.1 (0.9-55)
Diagnostic groups†				
Migraine without aura	134	3	2.6 (0.3-26)	2.3 (0.2-23)
Migraine with aura	161	13	12.9 (1.6-101)	13.7 (1.7-112)
Migraine attacks†				
<1 attack per month	159	6	5.6 (0.7-47)	5.1 (0.6-44)
≥1 attacks per month	136	10	9.9 (1.2-79)	9.3 (1.1-76)
Migraine attacks and subtype†				
Migraine without aura				
<1 attack per month	67	0	. . .	. . .
≥1 attacks per month	67	3	5.0 (0.5-50)	4.4 (0.4-45)
Migraine with aura				
<1 attack per month	92	6	10.5 (1.2-91)	11.3 (1.3-102)
≥1 attacks per month	69	7	15.8 (1.9-134)	15.8 (1.8-140)

Abbreviations: CI, confidence interval; PCT, posterior circulation territory; OR, odds ratio.
*The ORs have been calculated by logistic regression analysis, controlling for age, sex, municipality (model 1) and low education, body mass index, hypertension, cholesterol level, and alcohol use categories (model 2). Ellipses indicate that the ORs for the patients with migraine without aura with fewer than 1 attack per month could not be calculated (no cases had PCT infarcts).
†Controls are the reference group in all subanalyses.

White Matter Lesions

There were no differences in the distributions and the mean values of grades of severity of PVWMLs between patients with migraine (mean [SD] grade, 0.92 [0.58]) and controls (mean [SD], 0.89 [0.61]; $P=.60$). Furthermore, no differences were found between the diagnostic groups comparing clusters of severity (Table 2). These results did not vary by sex, migraine subtype, and/or migraine attack frequency.

Surprisingly, a high proportion (38%) of these relatively young individuals in both the migraine and control groups had at least 1 medium-size DWML (Table 2). There was no association of high DWML load to migraine in men (OR, 0.7; 95% CI, 0.3-1.8; model 1). This did not vary by subtype or attack frequency (patients with migraine without aura: OR, 0.7; 95% CI, 0.2-2.4; patients with migraine with aura: OR, 0.6; 95% CI, 0.2-2.0; <1 attack per month: OR, 0.5; 95% CI, 0.1-1.6; ≥1 attack per month: OR, 0.9; 95% CI, 0.3-2.7).

There was, however, an increased risk for DWMLs among women. Among women, compared with controls, migraine patients had a significantly increased risk of high DWML load (OR, 2.1; 95% CI, 1.0-4.1; model 1) that was similar for patients with migraine without aura (OR, 2.1; 95% CI, 1.0-4.7) and patients with migraine with aura (OR, 2.0; 95% CI, 1.0-4.3). This risk increased with increasing attack frequency (P for trend=.008); compared with controls, female migraine patients with fewer than 1 attack per month had

Table 4. Risk of High DWML Load in Women in Relation to Migraine Status and Coexistent Risk Factors*

	Controls (n = 100)		Patients With Migraine (n = 217)	
Risk Factor	No. of Women†	OR (95% CI)	No. of Women†	OR (95% CI)
Hypertension				
No	8/68	1.0	25/134	2.0 (0.8-5.0)
Yes‡	5/32	1.6 (0.5-5.8)	26/83	3.3 (1.3-8.6)
Smoking				
No	9/86	1.0	43/192	2.3 (1.0-5.1)
Yes‡	4/14	3.2 (0.7-14.5)	8/25	4.2 (1.3-13.7)
Long-term OC use (≥15 years)				
No	12/76	1.0	36/164	1.4 (0.7-3.1)
Yes‡	1/24	0.3 (0.05-3.5)	15/53	4.0 (1.5-10.9)

Abbreviations: CI, confidence interval; DWML, deep white matter lesion; OC, oral contraceptive; OR, odds ratio.
*High DWML load reflects the upper 20th percentile of the total DWML volume distribution. The ORs have been calculated by logistic regression, controlling for age, sex, municipality, low education, body mass index, hypertension, cholesterol, alcohol use categories, smoking, and, among women, long-term OC use (model 2).
†Number of women with high DWML load/total number of women in this subgroup.
‡Variable not included in the model.

an OR of 1.6 (95% CI, 0.8-3.5) and those with 1 or more attack per month had an OR of 2.6 (95% CI, 1.2-5.7). These risks were not attenuated with the addition of the cardiovascular risk factors (model 2, for all female migraine patients: OR, 2.0; 95% CI, 1.0-4.2). Hypertension and smoking each slightly increased the risk of high DWML load in female migraine patients, but the risk in smoking or hypertensive migraine patients was not higher than expected if the risks worked additively (TABLE 4; *P* for interaction between migraine and hypertension and smoking >.10). Although the interaction between migraine and long-term OC use was significant (*P*=.002), there was only 1 subject in the long-OC-using control group with high DWML load.

We evaluated, among the women, whether ever use of specific antimigraine medication (model 3) was associated with DWMLs. The addition of ever use of triptans did not change the results. The addition of ever use of ergotamines, however, modified the results slightly. For patients with migraine with aura, the OR was 1.9 (95% CI, 0.9-4.1); for patients with migraine without aura, the OR was 1.9 (95% CI, 0.9-4.2); for those with fewer than 1 attack per month the OR was 1.6 (95% CI, 0.7-3.4); and for those with 1 or more attack per month the OR was 2.4 (95% CI, 1.1-5.3).

COMMENT

These results suggest that patients with migraine from the general population are at increased risk of subclinical cerebellar PCT infarcts and that the risk increases with increasing attack frequency. Patients with migraine with aura and a high attack frequency are at greatest risk. In addition, women, but not men, with migraine with and without aura are at increased risk of high DWML load, and this risk also increases with increasing attack frequency. There was no association between PVWMLs and migraine. Traditional cardiovascular risk factors known to be associated with ischemic stroke or WMLs did not modify these risk estimates.

The major strengths of this study include its population-based design, a standardized diagnosis of migraine following IHS criteria,[1] and the full description of the cohort that allowed us to control for possibly confounding factors due to other cardiovascular diseases or the use of vasoconstrictor migraine agents. A sensitive imaging protocol[25] with thin slices (3 mm) read by an experienced neuroradiologist blinded to migraine diagnosis minimized the possibility that lesions were misclassified. A subsequent interview of the sample after 3 to 4 years showed the diagnosis to be highly reliable and consistent; recent changes in migraine characteristics were incorporated. Furthermore, responders and nonresponders were similar on various cardiovascular and sociodemographic characteristics. Although our measure of attack frequency was retrospective and potentially subject to recall bias, we are confident that by using relative wide frequency classes it produced a valid ranking of individuals with high or low attack frequency. Similar effects were reported based on recent additional analyses of a previously published clinic-based study.[26]

Previous studies[8,9] suggested an overrepresentation of clinical stroke in the occipital lobe and/or the posterior cerebral artery territory in migraine patients. Our study confirms the vulnerability of the PCT, especially for the cerebellum in migraine patients with aura. The particular vulnerability of the cerebellum in migraine is also found in a type of migraine with aura, familial hemiplegic migraine. In familial hemiplegic migraine, decreased cerebellar blood flow, cerebellar degeneration, and cerebellar dysfunction all have been reported.[27] Familial hemiplegic migraine is often caused by missense mutations in the *CACNA1A* calcium channel subunit gene, which are associated with cerebellar apoptosis.[27,28]

The origin of the infarcts found in these subjects is not known. A standard textbook on PCT strokes notes the clinical presentation of stroke attributed to migraine is different from that due to atherosclerosis.[29] The PCT infarcts in younger patients have been explained by intra-arterial occlusion resulting from nonatherosclerotic vasculopathy or embolism.[30] For instance, thrombi in the posterior cerebral arteries have been described in migraine patients with occipital infarcts,[31] and narrowed or occluded basilar arteries have been described in some migraine patients with brainstem and cerebellar infarcts.[32]

Several hemodynamic features of migraine may contribute to the pathogenesis of both WMLs and infarcts in migraine. Repeated or prolonged reduced perfusion pressure, reduced blood flow, and oligemia in large and/or small ar-

teries,[33,34] combined with activation of the clotting system[35,36] or vasoconstriction, possibly mediated or induced by endothelium perturbation (endothelin 1),[37,38] could lead to arterial or venous (micro)embolism, thrombosis, or ischemia. Dehydration during migraine attacks might contribute to formation of local thromboses. It is also possible that local changes during migraine attacks, such as excessive neuronal activation, neurogenic inflammation, neuropeptide and cytokine release,[39] or excitotoxity,[40] directly lead to tissue damage. Cardiac abnormalities, such as patent foramen ovale or mitral valve prolapse, might also increase the risk of ischemic brain changes in patients with migraine.[41-43]

Although the results suggested that the risk for both cerebellar infarcts and high DWML load was slightly mediated by the use of ergotamines, numbers were too small to separate the effects of the medication per se and attack frequency. Therefore, we cannot exclude that using ergotamines is a marker of severity of disease. Although ergotamines are known to cause vasoconstriction in the extracranial circulation, it is not known what effect they have in the brain.

Damage to the white matter is hypothesized to be the result of ischemic complications of various microvascular processes,[44] such as (even brief) ischemia, hypoglycemia, energy deprivation, oxidative stress,[45,46] or platelet hyperaggregability.[47] Why only women and not men should be at increased risk for WMLs is not known, but this finding is consistent with women being at increased risk for stroke. Based on a suggested difference in pathogenesis, in most neuroimaging studies that assess WMLs, a subclassification of PVWML and DWML is applied. The fact that we found differences between female migraine patients and controls in severity of DWMLs, but not in severity of PVWMLs, might also be explained by different mechanisms that affect the deep and periventricular white matter.

Based on the current evidence, further study into the possible etiologic mechanisms of brain lesions in migraine patients is required. This will not only provide important clues about the pathophysiology of migraine but also contribute to management guidelines for migraine. Based on the finding of higher risks in those with higher migraine attack frequency, it is necessary to assess whether prevention or (early) abortion of migraine attacks will also decrease the risk for brain lesions and whether there is a subgroup most likely to benefit.

Author Contributions: As principal investigator, Dr Kruit had full access to all the data in the study and takes responsibility for the integrity of the data.
Study concept and design: Kruit, van Buchem, Ferrari, Launer.
Acquisition of data: Kruit, Hofman, Bakkers, Terwindt.
Analysis and interpretation of data: Kruit, van Buchem, Hofman, Ferrari, Launer.
Drafting of the manuscript: Kruit, van Buchem, Ferrari, Launer.
Critical revision of the manuscript for important intellectual content: van Buchem, Hofman, Bakkers, Terwindt, Ferrari, Launer.
Statistical expertise: Kruit, Ferrari, Launer.
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What is all knowledge too but recorded experience, and a product of history; of which, therefore, reasoning and belief, no less than action and passion, are essential materials.
—Thomas Carlyle (1795-1881)