Structural brain changes in migraine and cluster headache

Arkink, E.B.

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Infratentorial microbleeds: another sign of microangiopathy in migraine

E.B. Arkink
G.M. Terwindt
A.C. de Craen
J. Konishi
J. van der Grond
M.A. van Buchem
M.D. Ferrari
M.C. Kruit
on behalf of the PROSPER Study Group

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Abstract

Background and purpose:

Migraine is a risk factor for clinical stroke and for subclinical white matter hyperintensities and infratentorial infarcts. These subclinical are linked to small-vessel pathology. Cerebral microbleeds (CMBs) are another biomarker of small-vessel disease but have not yet been studied in migraine.

Methods:

Identification of CMBs in 63 migraineurs (25 with aura/35 without aura/3 unknown aura status) and 359 controls (aged, 73-85 years) from the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) magnetic resonance imaging study. We assessed the modifying role of migraine in the co-occurrence of CMBs, infarcts, and white matter hyperintensity-load.

Results:

Infratentorial microbleeds were more prevalent in migraine without aura patients than in controls (14% vs. 4%). Prevalence of other CMBs, infarcts and WMHs did not differ between groups. Migraineurs with CMBs had more often infarcts than controls with CMBs (65% vs. 43%). In comparison with controls with infarcts, migraineurs with infarcts had more commonly CMBs (55% vs. 30%).

Conclusions:

Migraine, notably without aura, is associated with infratentorial CMBs at older age. Furthermore, CMBs and infarcts co-occur more often in migraine than in controls. This supports the hypothesis of small vessel involvement in migraine pathophysiology.

Introduction

Migraine affects ≤33% of women and ≤13% of men during lifetime,[1] and independently increases the risk of ischemic and hemorrhagic stroke.[2] On magnetic resonance imaging (MRI), migraineurs more often have cerebellar infarcts, supratentorial and infratentorial white matter hyperintensities (WMHs),[3] suggesting involvement of small cerebral blood vessels in migraine. Cerebral microbleeds (CMBs) are another hallmark of small vessel disease.[4;5] However, their prevalence has not yet been studied in migraine. Here, we evaluate whether CMBs are more common in lifetime migraineurs, and whether they are more likely to co-occur with other vascular brain lesions in migraine, investigating whether microangiopathy might explain migraine-related cerebrovascular disease.

Methods

Subjects were from the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) MRI study, a placebo-controlled trial assessing effects by pravastatin on cardiovascular disease.[6] In 544 of 554 subjects (aged, 73-85 years), lifetime migraine diagnosis was based on a previously used and validated questionnaire[1] and checked by migraine experts (G.M.T., M.C.K.), addressing all International Headache Society criteria.[7] Validation in twenty migraineurs and six controls resulted in 95% sensitivity and 100% specificity. The institutional review board approved the study. All subjects gave written informed consent.

CBMs were scored[8] (E.B.A. and J.K.) blinded for diagnosis on T2*-weighted images from a 1.5T MRI system. Due to incomplete acquisition and MRI-artifacts, CMB detection was not feasible in 27 of 554 subjects. Because of known increased vulnerability of the posterior fossa in migraine,[3] we a priori differentiated between lobar, basal ganglia and infratentorial CMBs. Interobserver reliability was excellent for the detection of any (κ=0.87), lobar (κ=0.85), basal ganglia (κ=0.95), and infratentorial CMBs (κ=0.94).

Cortical, lacunar, and infratentorial infarcts were scored. WMHs were segmented automatically

using validated software. WMH-volumes above the 80th percentile were classified as high WMH-load.

Inter-rater agreement was assessed using Cohen κ. Demographics were compared with Fisher exact and t-tests (SPSS 20.0.0, Chicago, IL, USA). Subclinical lesion prevalences were compared with logistic regression models adjusting for age, sex, hypertension, diabetes mellitus, smoking status, high-density lipoprotein and low-density lipoprotein cholesterol levels, antithrombotics use (factors previously associated with CMBs[8]) and pravastatin allocation, giving odds ratios (ORs) with 95% confidence intervals.

Results

In 506 subjects with available MRI, lifetime migraine was diagnosed in 63 (12%; men 7% and women 19%); 359 were controls; 67 subjects with severe headache history did not fully meet migraine criteria (probable/possible migraine; Figure 7.1).

Prevalence of sex, hypertension and smoking differed between migraineurs and controls (Table 7.1). Migraineurs with aura had higher total cholesterol and low-density lipoprotein levels compared with controls. Other characteristics did not differ between groups.

Overall CMB prevalence did not differ between migraineurs (29%), migraine with aura (24%), migraine without aura (31%), and controls (24%; Table 7.2). Infratentorial CMBs were more

Figure 7.1 Flow chart of included and excluded subjects.

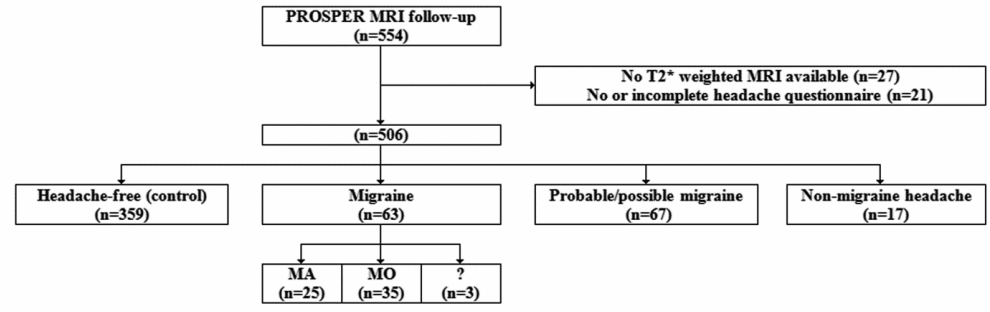

Table 7.1 Demographics

	Controls n=359	Migraine		
		Total n=63	With aura n=25	Without aura n=35
Female sex	130 (36)	43 (68)*#	18 (72)*#	23 (66)*#
Age	77.0±3.2	77.8±3.2	77.9±3.3	77.8±3.3
Blood pressure:				
systolic (mmHg)	157±22	157±21	156±17	159±23
diastolic (mmHg)	85±11	87±13	86±11	90±14
Body mass index (kg/m²)	26.6±3.6	26.5±3.8	26.9±4.0	26.4±3.8
Total cholesterol (mmol/L)	5.7±0.8	5.9±0.9	6.1±0.7*	5.7±0.9
HDL (mmol/L)	1.2±0.3	1.3±0.3	1.3±0.2	1.3±0.3
LDL (mmol/L)	3.9±0.7	4.0±0.7	4.2±0.6*	3.8±0.8
Triglycerides (mmol/L)	1.5±0.7	1.5±0.6	1.6±0.6	1.4±0.7
Current smoking	83 (23)	6 (10)*	3 (12)	2 (6)*
History of:				
hypertension	212 (59)	53 (84)*	19 (76)*	33 (94)*
diabetes	52 (14)	8 (13)	3 (12)	5 (14)
Pravastatin use	164 (46)	37 (59)	16 (64)	20 (57)
Antithrombotics use				
aspirin	110 (31)	21 (33)	13 (37)	7 (28)
anticoagulants	15 (4)	2 (2)	0 (0)	2 (6)

Mean±SD, number (%); HDL indicates high-density lipoprotein; and LDL, low-density lipoprotein; *p<0.05 compared with controls; #the higher proportion of women reflects the normal sex distribution of migraine.

prevalent in migraineurs without aura versus controls (14% versus 4%; p=0.048).When the 67 subjects with probable/possible migraine were included in the migraine group (10% versus 4%; p=0.02) or in the control group (14% versus 5%; p=0.09), similar figures were seen.

Infratentorial CMBs were more prevalent in subjects with migraine and hypertension (11% versus 2%; OR 6.1 [1.5-25]; p=0.01) or migraine and diabetes (25% versus 4%; OR 7.5 [1.4-41]; p=0.02), compared with control subjects without hypertension or diabetes, respectively. However, neither hypertension (5% versus 2%; OR 2.6 [0.7-9.6]; p=0.14) nor diabetes (2% versus 4%; OR 0.4 [0.1-3.5]; p=0.44) increased the odds for infratentorial CMBs in controls significantly.

Overall (31% versus 35%) and infratentorial (14% versus 13%) infarct prevalence and high WMH-load (23% versus 19%) was similar in migraineurs and controls, although there was a

trend for high WHM-load in migraineurs without aura (32% versus 19%, p=0.06). Cerebral infarcts were more prevalent in migraineurs (irrespective of aura status) with CMBs versus controls with CMBs (65% vs. 43%; p=0.05). Migraineurs with infarcts versus controls with infarcts more often had lobar (55% versus 26%; p<0.01), infratentorial (25% versus 5%; p=0.01), and overall CMB prevalence (55% versus 30%; p=0.03). Compared with controls, migraineurs more often had co-occurrence of infarcts and CMBs than only one of these types of brain lesions (42% versus 21%; p=0.02).

Table 7.2 Microbleeds by lifetime migraine status and location

	Controls n=359	Migraine		
		Total n=63	With aura n=25	Without aura n=35
Average CMBs	2.5±3.2	3.5±6.5	1.3±0.5	4.9±8.1
Any CMB				
Prevalence	86 (24%)	18 (29%)	6 (24%)	11 (31%)
Unadjusted OR (95%CI)	1.0 (ref)	1.3 (0.7-2.3)	1.0 (0.4-2.6)	1.5 (0.7-3.1)
Adjusted OR (95%CI)		1.2 (0.6-2.2)	1.0 (0.4-2.8)	1.2 (0.5-2.7)
Lobar CMB				
Prevalence	71 (20%)	16 (25%)	6 (24%)	9 (26%)
Unadjusted OR (95%CI)	1.0 (ref)	1.4 (0.7-2.6)	1.3 (0.5-3.3)	1.4 (0.6-3.1)
Adjusted OR (95%CI)		1.5 (0.8-3.0)	1.6 (0.6-4.2)	1.4 (0.6-3.3)
Basal ganglia CMB				
Prevalence	18 (5%)	4 (6%)	0 (0%)	4 (11%)
Unadjusted OR (95%CI)	1.0 (ref)	1.3 (0.4-3.9)	n.a.	2.4 (0.8-7.7)
Adjusted OR (95%CI)		0.8 (0.2-2.6)	n.a.	1.2 (0.4-4.3)
Infratentorial CMB				
Prevalence	14 (4%)	6 (10%)	1 (4%)	5 (14%)
Unadjusted OR (95%CI)	1.0 (ref)	2.6 (1.0-7.0)	1.0 (0.1-8.0)	4.1 (1.4-12.2)*
Adjusted OR (95%CI)		2.2 (0.7-6.6)	0.9 (0.1-8.3)	3.3 (1.0-11.0)*

Mean±SD, number (%) and OR (odds ratio; 95%CI) *p<0.05; ref=reference; n.a.= not applicable

Discussion

Lifetime migraine, in particular without aura, was an independent risk factor for infratentorial CMBs, a hallmark of small-vessel disease. CMBs and infarcts co-occur more often in migraine than in controls.

CMBs point at a hemorrhage-prone vasculopathy and result from disruption of the endothelial layer of small vessels. Endothelial dysfunction seems a mechanism involved in migraine pathophysiology.[9] Infratentorial CMBs are linked to hypertension,[8] and migraineurs in our study indeed had more frequently unfavorable cardiovascular risk profiles, as reported by others.[10] Notwithstanding, our data suggest that migraine plays an additive and/or independent role in developing infratentorial CMBs, a finding that together with reports on cerebellar infarcts and infratentorial hyperintensities,[3] stresses the vulnerability of the infratentorial microvasculature in migraineurs.

We could not reproduce higher prevalences of infarcts and WMHs as found in younger migraineurs in other studies, likely because of a lack of power, as well as the effect of migraine might have been obscured by prevalent cardiovascular risk factors in current participants. Recall bias in this elderly population and strict migraine criteria possibly explain the lower prevalence of migraine compared with the literature.[1] Applying less strict criteria (including probable/possible migraine) did however not change our results. The relatively small number of cases precluded further post hoc analyses or investigating the effect of attack or aura frequency, activity, duration, chronicity and life course of migraine.

In summary, migraine without aura is associated with higher prevalence of infratentorial CMBs. CMBs and infarcts co-occur more often in migraine than in controls. Small-vessel disease might underlie migraine-associated cerebrovascular damage in at least a subgroup of migraineurs. This should be confirmed in larger populations of elderly migraineurs.

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