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Infarcts in the posterior circulation territory in migraine. The population-based MRI CAMERA study

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In a previous study, migraine cases from the general population were found to be at significantly increased risk of silent infarct-like lesions in the posterior circulation (PC) territory of the brain, notably in the cerebellum. In this study we describe the clinical and neuroimaging characteristics of migraine cases with and without aura and controls with PC lesions. In total, 39 PC infarct-like lesions represented the majority (65%) of all 60 identified brain infarct-like lesions in the study sample (*n* = 435 subjects with and without migraine). Most lesions (*n* = 33) were located in the cerebellum, often multiple, and were round or oval-shaped, with a mean size of 7 mm. The majority (88%) of infratentorial infarct-like lesions had a vascular border zone location in the cerebellum. Prevalence of these border zone lesions differed between controls (0.7%), cases with migraine without aura (2.2%) and cases with migraine with aura (7.5%). Besides higher age, cardiovascular risk factors were not more prevalent in cases with migraine with PC lesions. Presence of these lesions was not associated with supratentorial brain changes, such as white matter lesions. The combination of vascular distribution, deep border zone location, shape, size and imaging characteristics on MRI makes it likely that the lesions have an infarct origin. Previous investigators attributed cases of similar 'very small' cerebellar infarcts in non-migraine patients to a number of different infarct mechanisms. The relevance and likelihood of the aetiological options are placed in the context of known migraine pathophysiology. In addition, the specific involvement of the cerebellum in migraine is discussed. The results suggest that a combination of (possibly migraine attack-related) hypoperfusion and embolism is the likeliest mechanism for PC infarction in migraine, and not atherosclerosis or small-vessel disease.

Keywords: migraine; magnetic resonance imaging; brain infarction; posterior circulation; cerebellum

Abbreviations: AICA = anterior inferior cerebellar artery; DWML = deep white matter lesion; MA = migraine with aura; MO = migraine without aura; PC = posterior circulation; PICA = posterior inferior cerebellar artery; PVWML = periventricular white matter lesion; SCA = superior cerebellar artery

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Introduction

Migraine is a prevalent, chronic, multifactorial neurovascular disorder characterized by recurrent attacks of debilitating headache and autonomic nervous system dysfunction (migraine without aura; MO); up to one-third of patients also have neurological aura symptoms (migraine with aura; MA) (Ferrari, 1998; Headache Classification Committee of the International Headache Society, 1988). Migraine is commonly thought to be acutely disabling during attacks, without long-term consequences on the brain. However, we found in our population-based CAMERA study (*n* = 435) that migraine cases had a significantly higher prevalence of white matter hyperintense lesions and cerebellar infarct-like

lesions (Kruit *et al.*, 2004). Traditional cardiovascular risk factors and specific antimigraine medication did not modify the association between the structural brain changes and migraine.

In total, 8.1% of 161 cases with MA compared with 2.2% of 134 cases with MO and 0.7% of 140 controls ($P = 0.05$) had one or more lesions in the cerebellar region of the posterior circulation (PC) territory of the brain (Kruit *et al.*, 2004). The highest risk was in participants with MA with at least 1 attack per month (odds ratio 15.8, 95% confidence interval 1.8–140), compared with controls. These cerebellar lesions appear as infarcts on MRIs, although none of the patients had a clinical history of stroke. Clinical infarcts in patients with migraine were previously suggested (in some clinically-based studies) to be over-represented in the PC territory, notably in the occipital lobes, but not infratentorially (Featherstone, 1986; Broderick and Swanson, 1987; Bogousslavsky *et al.*, 1988; Rothrock *et al.*, 1988; Shuaib and Lee, 1988; Sacquegna *et al.*, 1989; Caplan, 1991; Hoekstra-van Dalen *et al.*, 1996; Milhaud *et al.*, 2001). Reports that detail the location, size and regional distribution patterns of such infarcts in patients with migraine are lacking. Also, little is known about the aetiology of these brain lesions.

Here we describe the clinical and neuroimaging characteristics of cases from the CAMERA study with PC lesions, relate these to what is known of migraine pathophysiology, and provide evidence for an infarct origin of the identified infarct-like lesions.

Methods

Study population

A complete description of the study population and methods has been detailed elsewhere (Kruit *et al.*, 2004). In brief, cases and controls were randomly selected from the Genetic Epidemiology of Migraine (GEM) study, a population-based survey of 6491 Dutch adults aged 20–60 years living in two representative Dutch municipalities (Maastricht and Doetinchem). With this procedure we identified 863 cases of migraine according to International Headache Society criteria; 54% of the cases had not been previously diagnosed by a physician (Launer *et al.*, 1999). For the Cerebral Abnormalities in Migraine, an Epidemiological Risk Analysis (CAMERA) study, two diagnostic groups (cases with migraine with aura and without aura) were randomly selected from the earlier population-based survey cases aged 30–60 years; the control group was randomly selected from the cohort to frequency-match the cases by sex, municipality and 5-year age strata. The study protocol was approved by the ethics committee of the Leiden University Medical Center and included a structured telephone interview and a clinic visit for a brain MRI study, drawing of blood, and a standard physical and neurological examination. A complete protocol was performed in 435 participants (69% overall response): 134 MO, 161 MA and 140 controls. All participants gave written informed consent and participated without any financial reimbursement. The clinic visits took place within 10 days of the telephone interview; patients with migraine underwent examinations in a headache-free period (≥3 days after a migraine attack).

Assessment of confounders, covariates and migraine characteristics

Sociodemographic, medical and migraine 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 had used oral contraceptives. Self-reported weight and height were used to calculate body mass index (weight in kilograms divided by the square of height in meters). Blood pressure was the mean of three measurements obtained at 1-min intervals in the upper arm with an electronic oscillometric blood pressure monitor (Omron 711; Omron Healthcare Europe, Hoofddorp, the Netherlands). Hypertension was defined as a systolic blood pressure of 160 mmHg and higher or a diastolic blood pressure of 95 mmHg and higher or current use of antihypertensive drugs. A measure of total cholesterol was available from the baseline examination (Boer *et al.*, 1998). As previously detailed, migraine cases estimated headache and aura attack frequency, and the frequency and amount of specific antimigraine medication (ergotamines, triptans) they used in the years they had migraine attacks (Kruit *et al.*, 2004).

MRI

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, Erlangen, Germany). Protocols in the two centres 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 sequence [ACS-NT, 3000/27–120/1/10; Magnetom Harmony, 3000/14–85/2/5; relaxation time(ms)echo time(ms)excitations(number)/echo train length (number; inversion time(ms))] and fluid-attenuated inversion-recovery sequence (ACS-NT: 8000/100/2000/2/19; Magnetom Harmony, 8000/105/2000/2/7; relaxation time/echo time/inversion time/excitations/echo train length).

One neuroradiologist (M.A.v.B.), who was blinded to migraine diagnosis and clinical data, rated white matter lesions and infarct-like lesions on hard copies. A complete description of the white matter lesion rating methods has been given previously (Kruit *et al.*, 2004). Infarct-like lesions were defined as non-mass parenchymal defects, with a vascular distribution, isointense to cerebrospinal fluid signal on all sequences, and, when supratentorial, surrounded by a hyperintense rim on fluid-attenuated inversion-recovery and proton density images. In total, 60 brain infarct-like lesions were detected in 31 individuals. The location and size of these lesions were recorded. Supratentorially, Virchow–Robin spaces were discriminated from infarct-like lesions, based on location, shape, size and absence of a hyperintense border on proton density and fluid-attenuated inversion-recovery images (Bokura *et al.*, 1998; Song *et al.*, 2000).

The topography and corresponding dominant arterial territory of the identified infarct-like lesions were determined according to the maps by Tatu and colleagues (Tatu *et al.*, 1996, 1998). The PC territory included all brainstem and cerebellar branches of the vertebral and basilar arteries, and the posterior cerebral arteries and their branches. The infratentorial PC infarct-like lesions were further subclassified as either territorial or junctional (= border zone)

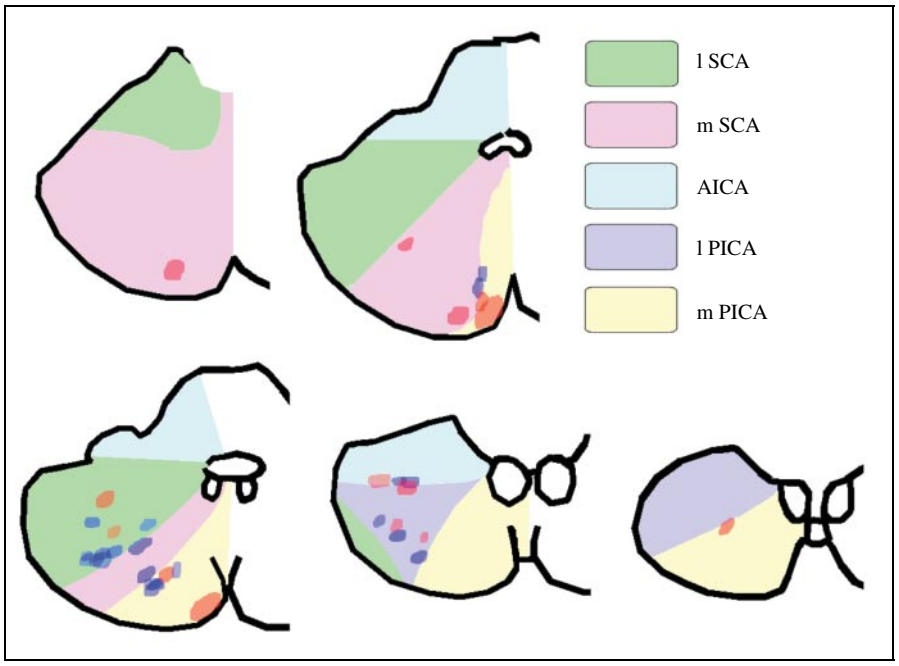

Fig. 1 Infratentorial posterior circulation (PC) infarct-like lesions in the cerebellum (n = 33) superimposed over diagram with arterial territories indicated: the CAMERA study. The size and position of all cerebellar PC infarct-like lesions were copied from hard copy into the vascular territories template. Territories are supplied by the posterior inferior cerebellar artery (PICA), the medial branch of the PICA (m PICA), the lateral branch of the PICA (l PICA), the territory of the superior cerebellar artery (SCA), the medial branch of SCA (m SCA), the lateral branch of SCA (l SCA) or the territory of the anterior inferior cerebellar artery (AICA). Left-sided lesions (coloured red) are mirrored to the right hemisphere for presentation purposes.

according to previously published criteria (Amarenco, 1991; Amarenco *et al.*, 1993; Barth *et al.*, 1993; Canaple and Bogousslavsky, 1999). In the assessment of infratentorial PC territory lesions the following procedure was applied to minimize any form of potential classification bias. First, the indications of the arterial (sub)territories were defined in a diagram of the cerebellum and brainstem (Fig. 1, coloured areas) (Amarenco, 1991; Tatu *et al.*, 1996). Secondly, the position, shape and size of an infratentorial PC lesion was copied from hard copy onto a diagram of the cerebellum and brainstem without the coloured vascular territories (Fig. 1, black lines). This was repeated for each individual lesion in a separate (empty) diagram. Thirdly, all separate drawings were superimposed over the previously defined indications of the arterial (sub)territories (Fig. 1). Thereafter, each infarct-like lesion was classified as either territorial or junctional (= border zone). Territorial lesions occupied the territory of the posterior inferior cerebellar artery (PICA), the medial branch of the PICA (mPICA), the lateral branch of the PICA (lPICA), the territory of the superior cerebellar artery (SCA), the medial branch of the SCA (mSCA), the lateral branch of the SCA (lSCA) or the territory of the anterior inferior cerebellar artery (AICA). Junctional lesions were located at the boundary region (defined as $\leq$5 mm from the indicated border in the template) between two arterial territories.

Statistics

The χ^2 test, the unpaired t-test and analysis of variance controlling for age and sex were used to test for differences in the distributions and means of measured characteristics among the study groups. Analyses were conducted with SPSS statistical software (version 10.0.5; SPSS, Chicago, IL, USA).

Results

Table 1 shows data on the prevalence, characteristics and distribution of the 39 infarct-like lesions identified in the PC territory. These PC infarct-like lesions represent the majority (65%) of all 60 identified infarct-like lesions in the whole brain in the study sample. The percentage of the PC lesions differed between the diagnostic groups: 81% of all infarct-like lesions in MA were in the PC territory, 47% in MO and 44% in controls. In cases with migraine, most PC infarct-like lesions were located infratentorially: 96% of PC lesions in MA and 89% in MO; among the four controls with PC infarct-like lesions, only one subject had an infratentorial lesion. Of the 39 PC infarct-like lesions, 33 were located in the cerebellum (one in a control, eight in three MO, 24 in 13 MA), one in the pons (in an MA) and five in the thalamus (three in three controls, one in an MO and one in an MA). Besides the thalamic infarct-like lesions, no other infarct-like lesions were identified supratentorially in the posterior circulation territory. The mean diameter of the PC infarct-like lesions was 7.1 mm, ranging between 2 and 21 mm, and 69% were located on the right side. The average number of lesions per subject was 1.8. Lesion sizes and number of lesions per subject did not differ between the diagnostic groups.

Infratentorial PC infarct-like lesions were subclassified as either territorial or junctional, as defined previously. Of the 34 infratentorial PC lesions, 30 were classified as junctional. In MA, 92% of the infratentorial lesions were junctional, 75% in MO; the only infratentorial lesion in the one control was

Table 1 Prevalence and characteristics of posterior circulation (PC) infarct-like lesions (ILL): the CAMERA study

	All (n = 435)	Controls (n = 140)	Migraine without aura (n = 134)	Migraine with aura (n = 161)	Significance
PC infarct-like lesions					
Total number of PC ILL (% of all brain ILL)	39 (65%)	4 (44%)	9 (47%)	26 (81%)	*
Subjects with ≥1 PC ILL (% of all participants)	21 (4.8%)	4 (2.9%)	4 (3.0%)	13 (8.1%)	*
Location of PC infarct-like lesions (n = 39)					
Supratentorial (e.g. occipital lobe, thalamus)					
Total number (% of all PC ILL)	5 (13%)	3 (75%)	1 (11%)	1 (4%)	†
Subjects with ≥1 ILL of this type	5 (1.1%)	3 (2.1%)	1 (0.7%)	1 (0.6%)	
Infratentorial					
Total number (% of all PC ILL)	34 (87%)	1 (25%)	8 (89%)	25 (96%)	†
Subjects with ≥1 ILL of this type	17 (3.9%)	1 (0.7%)	3 (2.2%)	13 (8.1%)	†
Location of infratentorial ILL (n = 34)					
Junctional/border zone					
Total number (% of infratent. ILL)	30 (88%)	1 (100%)	6 (75%)	23 (92%)	
Subjects with ≥1 ILL of this type	16 (3.7%)	1 (0.7%)	3 (2.2%)	12 (7.5%)	†
Territorial					
Total number (% of infratent. ILL)	4 (12%)	–	2 (25%)	2 (8%)	
Subjects with ≥1 ILL of this type	3 (0.7%)	–	1 (0.7%)	2 (1.2%)	
Location of junctional ILL(n = 30)					
IPICA-AICA border zone (% of junct. ILL)	4 (13%)	–	1 (17%)	3 (13%)	
IPICA-mPICA border zone (% of junct. ILL)	3 (10%)	–	–	3 (13%)	
IPICA-lSCA border zone (% of junct. ILL)	2 (7%)	–	–	2 (9%)	
mPICA-mSCA border zone (% of junct. ILL)	11 (37%)	1 (100%)	2 (33%)	8 (35%)	
lSCA-mSCA border zone (% of junct. ILL)	10 (33%)	–	3 (50%)	7 (30%)	

Data are number of individuals (%) and number of infarct-like lesions (%). P values are from Pearson's χ^2 test (unadjusted). mPICA = medial branch of the posterior inferior cerebellar artery (PICA); lPICA = lateral branch of the PICA; mSCA = medial branch of the superior cerebellar artery (SCA); lSCA = lateral branch of SCA; AICA = anterior inferior cerebellar artery. Unless stated otherwise, differences were not statistically significant. *$P < 0.05$; †$P < 0.005$.

also junctional. The mPICA–mSCA border zone (37% of all junctional infarct-like lesions; in seven of 16 subjects with junctional infarct-like lesions) and the lSCA–mSCA border zone (33% of all junctional lesions; in eight of 16 subjects with junctional lesions) were mostly involved. These distributions over the separate border zones did not differ between the diagnostic groups. In Fig. 1, all infratentorial PC infarct-like lesions are superimposed over the respective arterial territories of the cerebellar hemispheres. Most lesions were round or oval in shape and more or less clustered in the border zones. Orientation of the junctional infarct-like lesions was mostly along the border between the respective territories. One infarct-like lesion involved a part of the local cerebellar cortex, but all other lesions were located in the deep cerebellar regions. Figure 2 shows four examples of representative cases with infratentorial PC (cerebellar) infarct-like lesions.

Table 2 lists sociodemographic and migraine characteristics and other structural brain damage variables of the subjects with PC infarct-like lesions. Information is provided on the size, side and location of the separate infarct-like lesions, as well as on concurrent infarct-like lesions located outside the PC territory (e.g. anterior/carotid circulation). The presence of a high load of periventricular white matter lesions (high PVWML load) and/or a high load of deep white matter lesions (high DWML load) is indicated for each subject. Eleven subjects had more than one infarct-like lesion ('multiple infarct-like lesions'; 59% of the migraine cases and 25% of the controls). Multiple PC lesions were identified exclusively in cases with migraine; in these seven cases, more than one separate border zone was involved. Although the prevalence of a high DWML load was greater in subjects with PC lesions, this difference was not confirmed in subanalysis for migraine patients separately.

Subjects with infarct-like lesions in the PC territory were significantly older, and had significantly higher cholesterol levels (both in crude data, and after adjusting for age and sex; Table 3). However, differences in cholesterol level did not remain statistically significant in the subanalysis among the cases with migraine. Other cardiovascular risk factors were not more prevalent among those with PC infarct-like lesions. The number of cases with PC lesions was too small to compare the prevalence of cardiovascular risk factors between migraine cases and controls. Cases with migraine with PC lesions tended to have a higher attack frequency, and had previously consulted a physician for their migraine significantly more often (Table 4). Other migraine characteristics did not differ between those with and without PC infarct-like lesions.

Discussion

In a previous population-based study, we found migraine to be a significant risk factor for PC infarct-like lesions, notably in cases with migraine with aura. In the current study, the

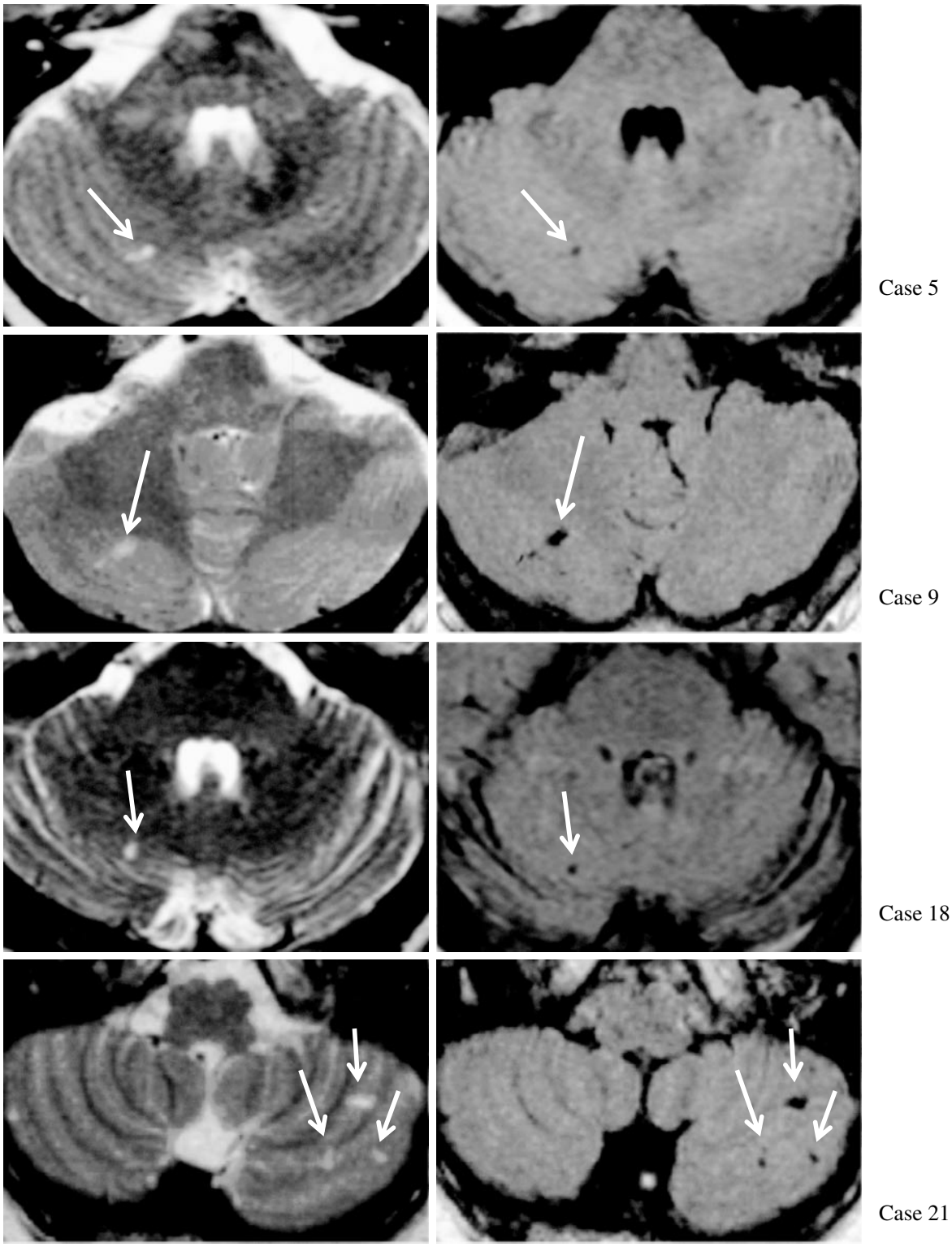

Fig. 2 Cerebellar infarct-like lesions: the CAMERA study. Corresponding T2-weighted (left) and fluid-attenuated inversion-recovery images (right) showing (multiple) cerebellar infarct-like lesions (arrows) in four representative cases (numbers refer to case numbers in Table 2).

topographic details of these parenchymal defects were systematically characterized. All lesions fulfilled MRI criteria for infarcts; therefore, we refer to these lesions in the text as 'infarct-like lesions'. Most pronounced were findings in MA: over 80% of all infarct-like lesions were located in the PC territory areas, and over 90% of these were located in the (deep) arterial border zone areas of the cerebellum. All PC lesions were small, and often multiple PC infarct-like lesions

Table 2 Cases with posterior circulation infarct-like lesions (PC ILL): the CAMERA study

No.	Age/ sex	Migraine characteristics				PC ILL†			Other ILL†	White matter lesions	
		Diag.	Age affected	Attacks/ year	Aura characteristics*	Infratentorial: territorial	Infratentorial: junctional	Supratentorial (any)	Location	PVWML (score)	High DWML load
1	41/F	MA	13–51	51	Visual; 30% MA	–	12 r AICA–IPICA 12 r IPICA–ISCA 5 r mPICA–IPICA	–	–	2	No
2	42/F	MA	32–42	30	Visual	–	5 l mPICA–IPICA	–	–	1	No
3	44/M	MA	2–44	35	Visual; 10% MA from age 14–44	9 l pons	18 r IPICA–AICA 12 r mPICA–mSCA 8 l mPICA–mSCA 21 l mPICA–mSCA‡	8 l thalamus	–	0	No
4	48/F	MA	38–47	2	Visual; always aura w/o headache	–	8 r ISCA–mSCA 5 r mPICA–mSCA 8 l mPICA–mSCA	–	–	1	No
5	52/F	MA	17–35	24	Visual/sensory.	–	8 r mSCA–ISCA 8 l mSCA–mPICA	–	–	2	Yes
6	52/M	MA	21–51	10	Visual; 80% MA from age 35–51	–	6 l mPICA–mSCA	–	–	1	No
7	52/M	MA	36–51	41	Visual	–	10 l AICA–IPICA		9 l frontal lobe 6 r frontal lobe	2	Yes
8	55/F	MA	22–55	6	Visual	3 l ISCA	–	–	–	0	No
9	55/M	MA	18–55	8	Visual/sensory./ aphasia; sometimes aura w/o headache	–	12 r mSCA–mPICA		8 l nc. caud.	1	No
10	56/F	MA	17–53	27	Visual; 70% MA	–	4 r ISCA–mSCA	–	–	2	Yes
11	57/F	MA	40–57	3	Visual	–	5 r IPICA–mPICA	–	–	0	No
12	57/M	MA	35–49	9	Visual	–	6 r mSCA–ISCA	–	–	0	No
13	57/M	MA	22–57	30	Visual; 100% MA from age 30–53	–	5 r ISCA–mSCA 5 r ISCA–mSCA 4 r IPICA–ISCA‡ 4 l ISCA–mSCA‡	–	–	1	Yes
14	58/M	Co	–	–		–	–	5 r thalamus	–	5	Yes
15	59/F	MO	14–59	17	–	–	9 r ISCA–mSCA	–	–	1	No
16	60/M	MO	20–58	24	–	–	10 r ISCA–mSCA 5 r mPICA–mSCA 10 r mPICA–mSCA	–	–	3	Yes
17	61/F	Co	–	–		–	–	2 r thalamus	3 l caps. int. 3 l caps. int.	5	Yes
18	61/F	Co	–	–	–	–	3 r mPICA–mSCA	–	–	1	No
19	61/W	MO	25–50	12	–	–	–	2 l thalamus	3 l caps. int. 2 l cor. rad. 2 l cor. rad.	5	Yes
20	62/M	Co	–	–		–	–	7 r thalamus	–	1	Yes
21	63/F	MO	33–63	51	–	2 r IPICA§ 3 r IPICA§	4 l ISCA–mSCA 6 r AICA–IPICA	–	5 l frontal lobe	2	No

*Unless stated otherwise, MA had in 100% of attacks aura symptoms. †For each individual infarct-like lesion, its size (maximum diameter in mm), side [left (l) or right (r)] and vascular supply territory (for territorial infarct-like lesions) or border zone region between the noted territories (for junctional infarct-like lesions) or anatomical location (for non-PC infarct-like lesions) is indicated. Caps. int. = capsula interna; cor. rad. = corona radiata; nc. caud. = caudate nucleus. ‡Infarct-like lesions located >5 mm but <10 mm from the indicated border zone; treated as junctional. §Infarct-like lesions possibly located in the border zone region between IPICA and ISCA; this could not be determined from the templates. M = male; F = female; MA = migraine with aura; MO = migraine without aura; Co = control. High DWML load = high deep white matter lesion load (those with the highest 20% of total DWML volume); PVWML = score for periventricular white matter lesion load.

Table 3 Age- and sex-adjusted characteristics of subjects with and without posterior circulation infarct-like lesions (PC ILL): the CAMERA study

Characteristic	Total PC ILL		Migraine cases PC ILL		Controls PC ILL	
	No (n = 414)	Yes (n = 21)	No (n = 278)	Yes (n = 17)	No (n = 136)	Yes (n = 4)
Sociodemographic						
Mean age (years)	48.0 (0.4)	54.9 (1.4)†	48.2 (0.5)	53.6 (1.6)†	47.7 (0.7)	60.5 (0.9)†
Female	73%	65%	74%	65%	72%	63%
Low education†	52%	50%	53%	41%	50%	91%
Clinical						
Body mass index (kg/m^2)	25.0 (0.2)	25.4 (0.9)	25.4 (0.3)	25.5 (1.0)	24.3 (0.3)	25.4 (1.9)
Blood pressure						
Systolic (mm Hg)	134.5 (0.8)	130.1 (3.6)	134.3 (1.0)	131.3 (3.9)	135.0 (1.4)	129.5 (8.8)
Diastolic (mm Hg)	91.2 (0.5)	90.6 (2.2)	91.3 (0.6)	91.8 (2.4)	90.9 (0.8)	85.3 (4.9)
Hypertension	38%	39%	41%	45%	33%	15%
Cholesterol (mmol/l)	5.3 (0.04)	5.7 (0.2)*	5.3 (0.1)	5.6 (0.2)	5.2 (0.1)	6.3 (0.4)*
Diabetes	2.0%	2.9%	1.5%	0%	2.9%	28%*
Smoking						
Never	36%	37%	37%	40%	35%	27%
Pack years (among smokers)	10.2 (0.6)	8.4 (2.9)	9.9 (0.8)	5.7 (3.1)	11.0 (1.2)	19.6 (7.0)
Alcohol use						
None	20%	23%	23%	23%	15%	25%
≥3 units/day	11%	0.4%	8%	2%	16%	0%
Oral contraceptive use (women only)						
≥15 years OC use	24%	21%	25%	21%	24%	22%
Other brain damage						
High PVWML load	9%	14%	10%	7%	7%	47%†
High DWML load	19%	35%	22%	32%	15%	51%*

Data are estimated mean (SE) or percentage of subjects, based on univariate analyses of variance, controlling for age and sex. Unless stated otherwise, differences were not statistically significant. P values are based on tests of the between-subjects effect. Low education = primary school or lower vocational education; OC = oral contraceptive; DWML = deep white matter lesion; PVWML = periventricular white matter lesion. *$P < 0.05$; †$P < 0.005$.

were identified in a single subject. No previous studies reported on the prevalence and size of cerebellar infarct-like lesions in migraine, and although a small number of clinicopathological and clinicoradiological studies report on small cerebellar infarcts, in none of these studies was migraine status known or included in the analyses (Amarenco *et al.*, 1990, 1993, 1994; Amarenco, 1991; Barth *et al.*, 1993; Canaple and Bogousslavsky, 1999). However, the 'very small' cerebellar lesions identified in our sample have diameters (2–20 mm), shapes and typical border zone locations similar to those of the small cerebellar infarcts reported in these previous studies.

Border zone infarction is probably best explained by invoking a combination of low flow and embolism: a decrease in cerebral perfusion pressure and associated changes in the cerebral haemodynamics affects the clearance and destination of embolic particles; narrowing of the arterial lumen and intimal and endothelial abnormalities stimulate formation of thrombi; occlusive thrombi further reduce blood flow and brain perfusion (Caplan and Hennerici, 1998). Because the deep cerebellar territories have a pattern of progressively tapering arteries with only few anastomoses present, they are likely to be particularly vulnerable to hypoperfusion-related border zone infarct mechanisms (Duvernoy *et al.*, 1983; Fessatidis *et al.*, 1993). The prevalent involvement of SCA watershed zones might be explained by a longer course of SCA branches compared with PICA and AICA branches (Duvernoy *et al.*, 1983). This hypoperfusion-related concept matches the findings of previous studies in which the small cerebellar border zone infarcts, in particular when multiple, were strongly associated with severe occlusive and/or (artery-to-artery) embolic disease based on vertebrobasilar atherosclerosis, likely to result in hypoperfusion and infarction (Amarenco *et al.*, 1993, 1994; Barth *et al.*, 1993; Canaple and Bogousslavsky, 1999). Non-border zone territorial infarcts were suggested to result from coagulopathy, arteritis and microembolism, due to involvement of small distal arteries (Canaple and Bogousslavsky, 1999). Since we found 'very small territorial infarct-like lesions' (n = 3) only in a minority of cases, this suggests that focal hypoperfusion rather than microembolic occlusion is responsible for the observed cerebellar lesions in migraine.

During and after migraine attacks, sluggish low cerebral flow below an ischaemic threshold has been described (Olesen *et al.*, 1990; Friberg *et al.*, 1994; Woods *et al.*, 1994; Bednarczyk

Table 4 Migraine characteristics of migraine patients with and without posterior circulation infarct-like lesions (PC ILL): the CAMERA study

Migraine characteristic	PC ILL	
	No (n = 278)	Yes (n = 17)
Migraine subtype		
Migraine without aura	130 (47%)	4 (24%)
Migraine with aura	148 (53%)	13 (77%)
Migraine attacks		
Median number of attacks	11.0	24.0
25–75th percentile	6.1–17.4	8.5–32.4
Frequency <1 attack/month	152 (55%)	7 (41%)
Frequency ≥1 attack/month	126 (45%)	10 (59%)
Age (yrs)		
At migraine onset	22.8 (0.7)	22.9 (2.5)
At last migraine attack	46.3 (0.5)	51.9 (1.8)*
Previous physician diagnosis of migraine	143 (52%)	13 (77%)*
Family history of migraine		
≥1 family member (parents, children, siblings)	170 (61%)	9 (53%)
≥1 parent	112 (40%)	5 (29%)
≥1 child	22 (8%)	2 (12%)

Data are number of individuals (%) and mean (SE) values. Unless indicated otherwise, differences were not statistically significant. P values are from Pearson's χ^2 test (unadjusted) and unpaired t-tests. *$P < 0.05$.

et al., 1998; Cutrer *et al.*, 1998; Sanchez del Rio *et al.*, 1999). Reductions of cerebral blood flow vary from a 7% to a 53% decrease (Cutrer *et al.*, 1998; Sanchez del Rio *et al.*, 1999) and persist from 1 h to more than 1 day (Bednarczyk *et al.*, 1998). This is probably the result of the effects of cortical spreading depression, which has been implicated as the generator of migraine aura (Moskowitz *et al.*, 2004), and can also occur in the cerebellum (Ebner and Chen, 2003). Cortical spreading depression (indirectly) alters blood–brain barrier permeability, which might lead to exacerbation of local cellular injury caused by ischaemia. Together with factors predisposing to coagulopathy (Couch and Hassanein, 1977; Silvestrini *et al.*, 1994; Cesar *et al.*, 1995; D'Andrea *et al.*, 1995; Tozzi-Ciancarelli *et al.*, 1997; Tietjen *et al.*, 2001; Salobir *et al.*, 2002) and release of local vasoactive neuropeptides (Edvinsson and Goadsby, 1995; Hargreaves and Shepheard, 1999; Tzourio *et al.*, 2001), this could result in further changes in cerebral haemodynamics, arterial thrombosis and infarction (Milhaud *et al.*, 2001). An impairment in the adaptive cerebral haemodynamic mechanisms in the posterior circulation in migraine patients with aura might be part of the underlying mechanisms between migraine and brain infarcts (Silvestrini *et al.*, 2004).

Although migraine-related clinical strokes are reported to occur most often supratentorially, in the occipital lobes (Featherstone, 1986; Broderick and Swanson, 1987; Bogousslavsky *et al.*, 1988; Rothrock *et al.*, 1988; Shuaib and Lee, 1988; Sacquegna *et al.*, 1989; Caplan, 1991; Hoekstra-van Dalen *et al.*, 1996; Milhaud *et al.*, 2001), we did not find any infarct-like lesions in these areas of the posterior circulation. This difference between clinically manifest supratentorial infarcts and subclinical or silent infratentorial infarcts might be explained by an overall lower prevalence of occipital lobe infarcts compared with cerebellar infarcts in migraine cases, and the assumption that occipital infarcts are far less likely to remain clinically silent. The only supratentorial PC infarct-like lesions we identified were located in the thalamus: in three controls and two patients with migraine (concerning 75% of all PC infarct-like lesions in controls and only 5% in patients with migraine). Data about subclinical thalamic infarcts in migraine are lacking, but clinically manifest thalamic infarcts in migraine have been reported to be significantly more prevalent in younger migraine cases compared with controls (14 versus 6%) (Milhaud *et al.*, 2001).

Results from a number of studies suggest that the cerebellum plays a role in migraine pathophysiology. In common forms of migraine, (subclinical) cerebellar dysfunction has been reported (Sandor *et al.*, 2001; Harno *et al.*, 2003). Although it remains unknown whether structural lesions caused the cerebellar dysfunction in these studies, it raises the question of whether more advanced functional tests could have identified subclinical cerebellar dysfunction in our cases. Cerebellar abnormalities (such as cerebellar atrophy, decreased cerebellar blood flow, and cerebellar dysfunction) have also been described in several cases of familial hemiplegic migraine. Mutations of the P/Q-type Ca^{2+} channel α1 subunit gene (*CACNA1A*) responsible for at least 50% of all cases of this uncommon subtype of migraine (Ducros *et al.*, 2001), but they are involved in the common forms of migraine, notably in MA (Ophoff *et al.*, 1996; Terwindt *et al.*, 2001). In other disorders caused by *CACNA1A* defects, such as episodic and spinocerebellar ataxia, structural cerebellar changes have been described similar as in familial hemiplegic migraine (De Michele *et al.*, 1998; Klockgether *et al.*, 1998; Murata *et al.*, 1998; Melberg *et al.*, 1999; Stevanin *et al.*, 1999; Tournier-Lasserve, 1999). However, the described structural cerebellar changes in these *CACNA1A*-disorders did not comprise infarct-like lesions, but were limited to cerebellar atrophy.

In summary, we described a specific pattern of small cerebellar border zone infarct-like lesions in migraine patients, notably in those with aura. A combination of (possibly migraine-related) hypoperfusion and embolism is the likeliest aetiological mechanism, although other mechanisms could also play a role. Although the sample is small, we did not see an association between PC territory infarct-like lesions and types of supratentorial brain changes, such as deep white matter lesions or periventricular white matter lesions. Furthermore, there were not large differences in cardiovascular risk factors in those with and without PC territory infarct-like lesions. These two factors suggest that the lesions are not atherosclerotic in origin or reflect small-vessel disease. As a limitation of the current study, we could not assess vertebrobasilar vascular status or cardiac abnormalities of the

participants, and neither could we specifically assess prothrombotic conditions other than by asking all participants for a history of thrombosis or (inherited) coagulopathies, which was absent in all cases. Since silent PC infarction might not be negligible and might be related to (subclinical) dysfunctioning, identification of specific risk factors for PC infarction in migraine cases could allow preventive measures in those most at risk.

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References

Amarenco P. The spectrum of cerebellar infarctions. Neurology 1991; 41: 973–9.

Amarenco P, Hauw JJ, Gautier JC. Arterial pathology in cerebellar infarction. Stroke 1990; 21: 1299–305.

Amarenco P, Kase CS, Rosengart A, Pessin MS, Bousser MG, Caplan LR. Very small (border zone) cerebellar infarcts. Distribution, causes, mechanisms and clinical features. Brain 1993; 116: 161–86.

Amarenco P, Levy C, Cohen A, Touboul PJ, Roullet E, Bousser MG. Causes and mechanisms of territorial and nonterritorial cerebellar infarcts in 115 consecutive patients. Stroke 1994; 25: 105–12.

Barth A, Bogousslavsky J, Regli F. The clinical and topographic spectrum of cerebellar infarcts: a clinical-magnetic resonance imaging correlation study. Ann Neurol 1993; 33: 451–6.

Bednarczyk EM, Remler B, Weikart C, Nelson AD, Reed RC. Global cerebral blood flow, blood volume, and oxygen metabolism in patients with migraine headache. Neurology 1998; 50: 1736–40.

Boer JM, Feskens EJ, Schouten EG, Havekes LM, Seidell JC, Kromhout D. Lipid profiles reflecting high and low risk for coronary heart disease: contribution of apolipoprotein E polymorphism and lifestyle. Atherosclerosis 1998; 136: 395–402.

Bogousslavsky J, Regli F, Van Melle G, Payot M, Uske A. Migraine stroke. Neurology 1988; 38: 223–7.

Bokura H, Kobayashi S, Yamaguchi S. Distinguishing silent lacunar infarction from enlarged Virchow-Robin spaces: a magnetic resonance imaging and pathological study. J Neurol 1998; 245: 116–22.

Broderick JP, Swanson JW. Migraine-related strokes. Clinical profile and prognosis in 20 patients. Arch Neurol 1987; 44: 868–71.

Canaple S, Bogousslavsky J. Multiple large and small cerebellar infarcts. J Neurol Neurosurg Psychiatry 1999; 66: 739–45.

Caplan LR. Migraine and vertebrobasilar ischemia. Neurology 1991; 41: 55–61.

Caplan LR, Hennerici M. Impaired clearance of emboli (washout) is an important link between hypoperfusion, embolism, and ischemic stroke. Arch Neurol 1998; 55: 1475–82.

Cesar JM, Garcia-Avello A, Vecino AM, Sastre JL, Alvarez-Cermeno JC. Increased levels of plasma von Willebrand factor in migraine crisis. Acta Neurol Scand 1995; 91: 412–3.

Couch JR, Hassanein RS. Platelet aggregability in migraine. Neurology 1977; 27: 843–8.

Cutrer FM, Sorensen AG, Weisskoff RM, Ostergaard L, Sanchez DR, Lee EJ, et al. Perfusion-weighted imaging defects during spontaneous migrainous aura. Ann Neurol 1998; 43: 25–31.

D'Andrea G, Cananzi AR, Perini F, Hasselmark L. Platelet models and their possible usefulness in the study of migraine pathogenesis. Cephalalgia 1995; 15: 265–71.

De Michele G, Mainenti PP, Soricelli A, Di Salle F, Salvatore E, Longobardi MR, et al. Cerebral blood flow in spinocerebellar degenerations: a single photon emission tomography study in 28 patients. J Neurol 1998; 245: 603–8.

Ducros A, Denier C, Joutel A, Cecillon M, Lescoat C, Vahedi K, 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.

Duvernoy H, Delon S, Vannson JL. The vascularization of the human cerebellar cortex. Brain Res Bull 1983; 11: 419–80.

Ebner TJ, Chen G. Spreading acidification and depression in the cerebellar cortex. Neuroscientist 2003; 9: 37–45.

Edvinsson L, Goadsby PJ. Neuropeptides in the cerebral circulation: relevance to headache. Cephalalgia 1995; 15: 272–6.

Featherstone HJ. Clinical features of stroke in migraine: a review. Headache 1986; 26: 128–33.

Ferrari MD. Migraine. Lancet 1998; 351: 1043–51.

Fessatidis IT, Thomas VL, Shore DF, Hunt RH, Weller RO, Goodland F, et al. Assessment of neurological injury due to circulatory arrest during profound hypothermia. An experimental study in vertebrates. Eur J Cardiothorac Surg 1993; 7: 465–72.

Friberg L, Olesen J, Lassen NA, Olsen TS, Karle A. Cerebral oxygen extraction, oxygen consumption, and regional cerebral blood flow during the aura phase of migraine. Stroke 1994; 25: 974–9.

Hargreaves RJ, Shepheard SL. Pathophysiology of migraine—new insights. Can J Neurol Sci 1999; 26 Suppl 3: S12–9.

Harno H, Hirvonen T, Kaunisto MA, Aalto H, Levo H, Isotalo E, et al. Subclinical vestibulocerebellar dysfunction in migraine with and without aura. Neurology 2003; 61: 1748–52.

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.

Hoekstra-van Dalen RA, Cillessen JP, Kappelle LJ, van Gijn J. Cerebral infarcts associated with migraine: clinical features, risk factors and follow-up. J Neurol 1996; 243: 511–5.

Klockgether T, Skalej M, Wedekind D, Luft AR, Welte D, Schulz JB, et al. Autosomal dominant cerebellar ataxia type I. MRI-based volumetry of posterior fossa structures and basal ganglia in spinocerebellar ataxia types 1, 2 and 3. Brain 1998; 121: 1687–93.

Kruit MC, van Buchem MA, Hofman PA, Bakkers JT, Terwindt GM, Ferrari MD, et al. Migraine as a risk factor for subclinical brain lesions. JAMA 2004; 291: 427–34.

Launer LJ, Terwindt GM, Ferrari MD. The prevalence and characteristics of migraine in a population-based cohort: the GEM study. Neurology 1999; 53: 537–42.

Melberg A, Dahl N, Hetta J, Valind S, Nennesmo I, Lundberg PO, et al. Neuroimaging study in autosomal dominant cerebellar ataxia, deafness, and narcolepsy. Neurology 1999; 53: 2190–2.

Milhaud D, Bogousslavsky J, Van Melle G, Liot P. Ischemic stroke and active migraine. Neurology 2001; 57: 1805–11.

Moskowitz MA, Bolay H, Dalkara T. Deciphering migraine mechanisms: clues from familial hemiplegic migraine genotypes. Ann Neurol 2004; 55: 276–80.

Murata Y, Kawakami H, Yamaguchi S, Nishimura M, Kohriyama T, Ishizaki F, et al. Characteristic magnetic resonance imaging findings in spinocerebellar ataxia 6. Arch Neurol 1998; 55: 1348–52.

Olesen J, Friberg L, Olsen TS, Iversen HK, Lassen NA, Andersen AR, et al. Timing and topography of cerebral blood flow, aura, and headache during migraine attacks. Ann Neurol 1990; 28: 791–8.

Ophoff RA, Terwindt GM, Vergouwe MN, van Eijk R, Oefner PJ, Hoffman, et al. Familial hemiplegic migraine and episodic ataxia type-2 are caused by mutations in the Ca2+ channel gene CACNL1A4. Cell 1996; 87: 543–52.

Rothrock JF, Walicke P, Swenson MR, Lyden PD, Logan WR. Migrainous stroke. Arch Neurol 1988; 45: 63–7.

Sacquegna T, Andreoli A, Baldrati A, Lamieri C, Guttmann S, de Carolis P, et al. Ischemic stroke in young adults: the relevance of migrainous infarction. Cephalalgia 1989; 9: 255–8.

Salobir B, Sabovic M, Peternel P, Stegnar M, Grad A. Classic risk factors, hypercoagulability and migraine in young women with cerebral lacunar infarctions. Acta Neurol Scand 2002; 105: 189–95.

Sanchez del Rio M, Bakker D, Wu O, Agosti R, Mitsikostas DD, Ostergaard L, et al. Perfusion weighted imaging during migraine: spontaneous visual aura and headache. Cephalalgia 1999; 19: 701–7.

Sandor PS, Mascia A, Seidel L, de Pasqua V, Schoenen J. Subclinical cerebellar impairment in the common types of migraine: a three-dimensional analysis of reaching movements. Ann Neurol 2001; 49: 668–72.

Shuaib A, Lee MA. Cerebral infarction in patients with migraine accompaniments. Headache 1988; 28: 599–601.

Silvestrini M, Matteis M, Troisi E, Cupini LM, Zaccari G, Bernardi G. Migrainous stroke and the antiphospholipid antibodies. Eur Neurol 1994; 34: 316–9.

Silvestrini M, Baruffaldi R, Bartolini M, Vernieri F, Lanciotti C, Matteis M, et al. Basilar and middle cerebral artery reactivity in patients with migraine. Headache 2004; 44: 29–34.

Song CJ, Kim JH, Kier EL, Bronen RA. MR imaging and histologic features of subinsular bright spots on T2-weighted MR images: Virchow-Robin spaces of the extreme capsule and insular cortex. Radiology 2000; 214: 671–7.

Stevanin G, Herman A, Brice A, Durr A. Clinical and MRI findings in spinocerebellar ataxia type 5. Neurology 1999; 53: 1355–7.

Tatu L, Moulin T, Bogousslavsky J, Duvernoy H. Arterial territories of human brain: brainstem and cerebellum. Neurology 1996; 47: 1125–35.

Tatu L, Moulin T, Bogousslavsky J, Duvernoy H. Arterial territories of the human brain: cerebral hemispheres. Neurology 1998; 50: 1699–708.

Terwindt GM, Ophoff RA, van Eijk R, Vergouwe MN, Haan J, Frants RR, et al. Involvement of the CACNA1A gene containing region on 19p13 in migraine with and without aura. Neurology 2001; 56: 1028–32.

Tietjen GE, Al Qasmi MM, Athanas K, Dafer RM, Khuder SA. Increased von Willebrand factor in migraine. Neurology 2001; 57: 334–6.

Tournier-Lasserve E. CACNA1A mutations: hemiplegic migraine, episodic ataxia type 2, and the others. Neurology 1999; 53: 3–4.

Tozzi-Ciancarelli MG, De Matteis G, Di Massimo C, Marini C, Ciancarelli I, Carolei A. Oxidative stress and platelet responsiveness in migraine. Cephalalgia 1997; 17: 580–4.

Tzourio C, El Amrani M, Poirier O, Nicaud V, Bousser MG, Alperovitch A. Association between migraine and endothelin type A receptor (ETA −231 A/G) gene polymorphism. Neurology 2001; 56: 1273–7.

Woods RP, Iacoboni M, Mazziotta JC. Brief report: bilateral spreading cerebral hypoperfusion during spontaneous migraine headache. N Engl J Med 1994; 331: 1689–92.