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

Received January 31, 2005. Revised April 13, 2005. Accepted April 20, 2005. Advance Access publication July 8, 2005

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 Swanston, 1987; Bogousslavsky et al., 1988; Rothrock et al., 1988; Shuaib and Lee, 1988; Sacquena 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 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, 3000/14–85/2/3; 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)
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 SCA (mSCA), the lateral branch of 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 \( \chi^2 \) 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

<table>
<thead>
<tr>
<th>Location of infratentorial ILL (n = 34)</th>
<th>All (n = 435)</th>
<th>Controls (n = 140)</th>
<th>Migraine without aura (n = 134)</th>
<th>Migraine with aura (n = 161)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Localization (n = 39)</td>
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</tr>
<tr>
<td>Supratentorial (e.g. occipital lobe, thalamus)</td>
<td>Total number (n % of all PC ILL)</td>
<td>5 (13%)</td>
<td>3 (75%)</td>
<td>1 (11%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>subjects with ≥1 ILL of this type</td>
<td>5 (13%)</td>
<td>3 (75%)</td>
<td>1 (11%)</td>
<td>1 (4%)</td>
<td>†</td>
</tr>
<tr>
<td>Infratentorial</td>
<td>Total number (n % of all PC ILL)</td>
<td>34 (87%)</td>
<td>1 (25%)</td>
<td>8 (25%)</td>
<td>25 (96%)</td>
</tr>
<tr>
<td>subjects with ≥1 ILL of this type</td>
<td>17 (39%)</td>
<td>1 (0.7%)</td>
<td>3 (2.2%)</td>
<td>13 (8.1%)</td>
<td>†</td>
</tr>
<tr>
<td>Location of junctional ILL (n = 30)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IPICA-AICA border zone (% of junct. ILL)</td>
<td>Total number (n % of infratent. ILL)</td>
<td>4 (13%)</td>
<td>–</td>
<td>1 (17%)</td>
<td>3 (13%)</td>
</tr>
<tr>
<td>subjects with ≥1 ILL of this type</td>
<td>3 (0.7%)</td>
<td>–</td>
<td>1 (0.7%)</td>
<td>2 (1.2%)</td>
<td></td>
</tr>
<tr>
<td>IPICA-mPICA border zone (% of junct. ILL)</td>
<td>Total number (n % of infratent. ILL)</td>
<td>3 (10%)</td>
<td>–</td>
<td>–</td>
<td>3 (13%)</td>
</tr>
<tr>
<td>IPICA-SCA border zone (% of junct. ILL)</td>
<td>Total number (n % of infratent. ILL)</td>
<td>2 (7%)</td>
<td>–</td>
<td>–</td>
<td>2 (9%)</td>
</tr>
<tr>
<td>mPICA-mSCA border zone (% of junct. ILL)</td>
<td>Total number (n % of infratent. ILL)</td>
<td>11 (37%)</td>
<td>1 (100%)</td>
<td>2 (33%)</td>
<td>8 (35%)</td>
</tr>
<tr>
<td>ISCA-mSCA border zone (% of junct. ILL)</td>
<td>Total number (n % of infratent. ILL)</td>
<td>10 (33%)</td>
<td>–</td>
<td>3 (50%)</td>
<td>7 (30%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Location of infratentorial ILL (n = 34)</th>
<th>All (n = 435)</th>
<th>Controls (n = 140)</th>
<th>Migraine without aura (n = 134)</th>
<th>Migraine with aura (n = 161)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>PC infarct-like lesions</td>
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</tr>
<tr>
<td>Total number of PC ILL (% of all brain ILL)</td>
<td>39 (65%)</td>
<td>4 (44%)</td>
<td>9 (47%)</td>
<td>26 (81%)</td>
<td>*</td>
</tr>
<tr>
<td>Subjects with ≥1 PC ILL (% of all participants)</td>
<td>21 (4.8%)</td>
<td>4 (2.9%)</td>
<td>4 (3.0%)</td>
<td>13 (8.1%)</td>
<td>*</td>
</tr>
<tr>
<td>Location of PC infarct-like lesions (n = 39)</td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Supratentorial (e.g. occipital lobe, thalamus)</td>
<td>Total number (n % of all PC ILL)</td>
<td>5 (13%)</td>
<td>3 (75%)</td>
<td>1 (11%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>subjects with ≥1 ILL of this type</td>
<td>5 (1.1%)</td>
<td>3 (2.1%)</td>
<td>1 (0.7%)</td>
<td>1 (0.6%)</td>
<td>†</td>
</tr>
<tr>
<td>Infratentorial</td>
<td>Total number (n % of all PC ILL)</td>
<td>34 (87%)</td>
<td>1 (25%)</td>
<td>8 (25%)</td>
<td>25 (96%)</td>
</tr>
<tr>
<td>subjects with ≥1 ILL of this type</td>
<td>17 (39%)</td>
<td>1 (0.7%)</td>
<td>3 (2.2%)</td>
<td>13 (8.1%)</td>
<td>†</td>
</tr>
</tbody>
</table>

Data are number of individuals (%) and number of infarct-like lesions (%). P values are from Pearson’s χ² test (unadjusted). mPICA = medial branch of the posterior inferior cerebellar artery (PICA); IPICA = 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.

Discussion

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

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).
<table>
<thead>
<tr>
<th>No.</th>
<th>Age/sex</th>
<th>Migraine characteristics</th>
<th>PC ILL†</th>
<th>Other ILL†</th>
<th>White matter lesions</th>
</tr>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Infra-territorial</td>
<td>Infra-junctional</td>
<td>Supraterritorial (any)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Diag.</td>
<td>Age</td>
<td>Attacks/ year</td>
<td>Aura characteristics</td>
</tr>
<tr>
<td>1</td>
<td>41/F</td>
<td>MA</td>
<td>13–51</td>
<td>51</td>
<td>Visual; 30% MA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5 r IPICA–mSCA</td>
</tr>
<tr>
<td>2</td>
<td>42/F</td>
<td>MA</td>
<td>32–42</td>
<td>30</td>
<td>Visual</td>
</tr>
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<td></td>
<td>8 l IPICA–AICA</td>
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<tr>
<td>3</td>
<td>44/M</td>
<td>MA</td>
<td>2–44</td>
<td>35</td>
<td>Visual; 10% MA</td>
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<td>from age 14–44</td>
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<tr>
<td>4</td>
<td>48/F</td>
<td>MA</td>
<td>38–47</td>
<td>2</td>
<td>Visual; alwaura w/o headache</td>
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<td></td>
<td></td>
<td></td>
<td>8 l mPICA–mSCA</td>
</tr>
<tr>
<td>5</td>
<td>52/F</td>
<td>MA</td>
<td>17–35</td>
<td>24</td>
<td>Visual/sensory.</td>
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<td></td>
<td>6 l mPICA–mSCA</td>
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<tr>
<td>6</td>
<td>52/M</td>
<td>MA</td>
<td>21–51</td>
<td>10</td>
<td>Visual; 80% MA</td>
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<tr>
<td>7</td>
<td>52/M</td>
<td>MA</td>
<td>36–51</td>
<td>41</td>
<td>Visual</td>
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<tr>
<td>8</td>
<td>55/F</td>
<td>MA</td>
<td>22–55</td>
<td>6</td>
<td>Visual</td>
</tr>
<tr>
<td>9</td>
<td>55/M</td>
<td>MA</td>
<td>18–55</td>
<td>8</td>
<td>Visual/sensory/aphasia; sometimes aura w/o headache</td>
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<tr>
<td>10</td>
<td>56/F</td>
<td>MA</td>
<td>17–53</td>
<td>27</td>
<td>Visual; 70% MA</td>
</tr>
<tr>
<td>11</td>
<td>57/F</td>
<td>MA</td>
<td>40–57</td>
<td>3</td>
<td>Visual</td>
</tr>
<tr>
<td>12</td>
<td>57/M</td>
<td>MA</td>
<td>35–49</td>
<td>9</td>
<td>Visual</td>
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<tr>
<td>13</td>
<td>57/M</td>
<td>MA</td>
<td>22–57</td>
<td>30</td>
<td>Visual; 100% MA</td>
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<td>from age 30–53</td>
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<td>58/M</td>
<td>Co</td>
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<tr>
<td>15</td>
<td>59/F</td>
<td>MO</td>
<td>14–59</td>
<td>17</td>
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<tr>
<td>16</td>
<td>60/M</td>
<td>MO</td>
<td>20–58</td>
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<td>19</td>
<td>61/W</td>
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<tr>
<td>21</td>
<td>63/F</td>
<td>MO</td>
<td>33–63</td>
<td>51</td>
<td>—</td>
</tr>
</tbody>
</table>

*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); PWWM = score for periventricular white matter lesion load.
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; Bednarzyk et al., 1994).

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

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total PC ILL</th>
<th>Migraine cases PC ILL</th>
<th>Controls PC ILL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No (n = 414)</td>
<td>Yes (n = 21)</td>
<td>No (n = 136)</td>
</tr>
<tr>
<td><strong>Sociodemographic</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>48.0 (0.4)</td>
<td>54.9 (1.4)†</td>
<td>47.7 (0.7)</td>
</tr>
<tr>
<td>Female</td>
<td>73%</td>
<td>65%</td>
<td>72%</td>
</tr>
<tr>
<td>Low education†</td>
<td>52%</td>
<td>50%</td>
<td>50%</td>
</tr>
<tr>
<td><strong>Clinical</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>25.0 (0.2)</td>
<td>25.4 (0.9)</td>
<td>24.3 (0.3)</td>
</tr>
<tr>
<td>Systolic (mm Hg)</td>
<td>134.5 (0.8)</td>
<td>130.1 (3.6)</td>
<td>135.0 (1.4)</td>
</tr>
<tr>
<td>Diastolic (mm Hg)</td>
<td>91.2 (0.5)</td>
<td>90.6 (2.2)</td>
<td>90.9 (0.8)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>38%</td>
<td>39%</td>
<td>33%</td>
</tr>
<tr>
<td>Cholesterol (mmol/l)</td>
<td>5.3 (0.04)</td>
<td>5.7 (0.2)</td>
<td>5.2 (0.1)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2.0%</td>
<td>2.9%</td>
<td>1.5%</td>
</tr>
<tr>
<td>Smoking</td>
<td>36%</td>
<td>37%</td>
<td>35%</td>
</tr>
<tr>
<td>Pack years (among smokers)</td>
<td>10.2 (0.6)</td>
<td>8.4 (2.9)</td>
<td>11.0 (1.2)</td>
</tr>
<tr>
<td>Alcohol use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>20%</td>
<td>23%</td>
<td>15%</td>
</tr>
<tr>
<td>≥3 units/day</td>
<td>11%</td>
<td>0.4%</td>
<td>8%</td>
</tr>
<tr>
<td>Oral contraceptive use (women only)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥15 years OC use</td>
<td>24%</td>
<td>21%</td>
<td>24%</td>
</tr>
<tr>
<td>Other brain damage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High PVWML load</td>
<td>9%</td>
<td>14%</td>
<td>7%</td>
</tr>
<tr>
<td>High DWML load</td>
<td>19%</td>
<td>35%</td>
<td>22%</td>
</tr>
</tbody>
</table>

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.
Posterior circulation lesions in migraine

<table>
<thead>
<tr>
<th>Table 4 Migraine characteristics of migraine patients with and without posterior circulation infarct-like lesions (PC ILL): the CAMERA study</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Migraine characteristic</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Migraine subtype</strong></td>
</tr>
<tr>
<td>Migraine without aura</td>
</tr>
<tr>
<td>Migraine with aura</td>
</tr>
<tr>
<td><strong>Migraine attacks</strong></td>
</tr>
<tr>
<td>Median number of attacks</td>
</tr>
<tr>
<td>25–75th percentile</td>
</tr>
<tr>
<td>Frequency &lt;1 attack/month</td>
</tr>
<tr>
<td>Frequency ≥1 attack/month</td>
</tr>
<tr>
<td><strong>Age (yrs)</strong></td>
</tr>
<tr>
<td>At migraine onset</td>
</tr>
<tr>
<td>At last migraine attack</td>
</tr>
<tr>
<td><strong>Previous physician diagnosis of migraine</strong></td>
</tr>
<tr>
<td>At least one</td>
</tr>
<tr>
<td>At least two</td>
</tr>
<tr>
<td>At least three</td>
</tr>
<tr>
<td>At least four</td>
</tr>
</tbody>
</table>

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

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 \(\alpha_1\) 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 aetiologial 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.

Acknowledgements
We are indebted to J. T. Wilming P. A. M. Hofman, J. T. N. Bakkers and J. K. Krabbe for their support and help in clinically reviewing the MRI examinations, to the team of MRI technicians in both research centres and to the medical students for their dedication and help. This study was supported by a grant from the Netherlands Heart Foundation (grant 97.108). The Genetic Epidemiology of Migraine study was conducted by the National Institute of Public Health and the Environment, Department of Chronic Disease and Environmental Epidemiology, Bilthoven, The Netherlands.

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