Migraine With Aura and Brain Magnetic Resonance Imaging Abnormalities in Patients With CADASIL

Katayoun Vahedi, MD; Hugues Chabriat, MD, PhD; Claude Levy, MD; Anne Joutel, MD, PhD; Elisabeth Tournier-Lasserve, MD; Marie-Germaine Bousser, MD

Background: Migraine with aura (MA) is one of the clinical hallmarks of CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy), a small vessel disease of the brain caused by mutations in the NOTCH3 gene, but its exact mechanisms are unknown.

Objectives: To describe the patterns of MA in CADASIL and to compare brain magnetic resonance signal abnormalities between CADASIL patients with and without MA.

Design: Comparison of brain magnetic resonance signal abnormalities between cases and controls.

Setting: Patients with CADASIL seen at Lariboisière Hospital.

Patients: Forty-one CADASIL patients with MA and 31 age-matched CADASIL controls without MA.

Results: The mean age at onset of MA was significantly younger in women compared with men and occurred a mean of 15 years prior to stroke onset. A majority of patients (56%) reported at least 1 migraine attack with atypical aura. All CADASIL patients either with or without MA had white matter signal abnormalities on T2-weighted imaging. There was no difference in the frequency and distribution of brain signal abnormalities between CADASIL patients with and without MA.

Conclusions: In CADASIL, MA is characterized by an unusually high frequency of attacks of migraine with atypical aura. The distribution and extent of magnetic resonance signal abnormalities did not differ according to migraine phenotype.

Arch Neurol. 2004;61:1237-1240

ADASIL (CEREBRAL AUTOSOMAL DOMINANT ARTERIOPATHY WITH SUBCORTICAL INFARCTS AND LEUKOENCEPHALOPATHY) is an autosomal dominant arteriopathy leading to subcortical strokes and dementia due to severe alterations of vascular smooth muscle cells. The underlying genetic defect consists of highly stereotyped mutations of the NOTCH3 gene that affect only the extracellular domain of the protein, a transmembrane receptor. NOTCH3 expression is restricted to vascular smooth muscle cells in normal human adult tissues, but its exact function remains unknown. The clinical hallmarks of CADASIL are ischemic manifestations, which usually begin after the fourth decade, and a progressive subcortical dementia with pseudobulbar palsy leading to death after the sixth decade. Years before the onset of the first clinical manifestations, brain magnetic resonance (MR) imaging discloses diffuse white matter (WM) signal abnormalities.

Among other neurological symptoms, migraine with aura (MA) is reported in 20% to 40% of CADASIL patients, but it has not been studied in detail; its underlying mechanisms of action are still unknown. The objectives of this article were to study the patterns of MA associated with NOTCH3 mutations in a large group of patients and to compare brain MR image signal abnormalities in CADASIL patients with and without migraine. Previous case-control studies have reported a higher frequency of MR image WM abnormalities in patients with MA than in controls. Our hypothesis was that in CADASIL, a higher frequency or a specific distribution of WM signal abnormalities could be expected according to the migraine phenotype.

METHODS

PATIENTS AND CONTROLS

We studied the clinical spectrum of migraine in 41 nondemented CADASIL patients with MA belonging to 17 unrelated families. In addition, we compared the frequency and severity of brain MR image signal abnormalities in those who underwent MR imaging at the time of examination (n=31) with a group of age-matched controls who had CADASIL.
but no dementia and no migraine history (either with or without aura) at the time of MR imaging examination. All patients were shown either to carry a NOTCH3 mutation or to share the affected haplotype cosegregating with the disease phenotype at the NOTCH3 locus within their affected relatives (data not shown). All patients were prospectively and personally interviewed by a neurologist with experience in migraine (K.V., H.C., or M.-G.B.) using a structured interview. Diagnostic criteria of the International Headache Society (IHS) were used to define the migraine phenotype. A local ethics committee approved the study.

Neuroimaging was performed at 1 to 1.5 T as previously described. Briefly, T1-weighted images (WI) (echo time [TE]=5-20 milliseconds, repetition time [TR]=400-600 milliseconds) and T2-WI (TE=120 milliseconds, TR=2000-7300 milliseconds) were obtained with continuous slices (3-, 7-, or 9-mm thickness) from axial planes using the neurocruellar planes for reference. Magnetic resonance image signal abnormalities were assessed by a neuroradiologist (C.L.) who was blind to the clinical status of patients. Briefly, on T1-WI, the presence of hypointensities (identical to those found in cerebrospinal fluid signal) was systematically assessed on both sides for the cortex, WM, caudate nucleus, putamen, pallidum, thalamus, cerebellum, mesencephalon, and medulla. On T2-WI, the presence of hyperintensities was systematically assessed on both sides for the cortex, periventricular WM, and deep WM, including internal capsule, subcortical WM, external capsule, caudate nucleus, putamen, pallidum, thalamus, cerebellum, mesencephalon, and medulla. The severity of WM lesions was graded using the semiquantitative rating scale from Scheltens et al and a global rating scale derived from Bots et al.

STATISTICAL ANALYSIS

The clinical and MR imaging characteristics were compared between the groups of patients using the $\chi^2$ test or the paired t test. In addition, analysis of variance was used to compare the hyperintensity scores between the 2 groups. The statistical analysis was computed using StatView 4.5 software (StatView Software, Cary, NC).

RESULTS

Among the 41 CADASIL patients with MA, 25 were women and 16 were men (mean ± SD age, 45±10.2 years; range, 21-64 years). Various patterns of migraine according to the IHS classification were observed. Eighteen patients (44%) always had attacks of migraine with typical aura, whereas 11 (27%) had attacks with both typical and atypical aura, including MA without headache, hemiplegic migraine, basilar migraine, and acute-onset aura (IHS (Figure)). The remaining 12 patients (29%) only had attacks of migraine with atypical aura (Figure). The patterns of MA did not differ according to sex. Overall, 9 patients (22%) (8 women and 1 man) reported attacks of migraine with and without aura.

The overall mean age at onset of MA was 29.9±11.4 years (range, 6-48 years). Age was significantly younger in women (26.2±11.3 years; range, 6-43 years) than in men (35.8±9.2 years; range, 14-48 years; $P=.01$ (t test)). The mean age at onset of migraine without aura was 17.0±7.5 years (range, 7-24 years).

The most frequent aura symptoms were visual (38/41; 93%), sensory (28/41; 68%), aphasic (19/41; 46%), and motor (9/41; 22%). Most patients (27/41; 66%) reported a combination of aura symptoms during the migraine attacks, but 14 reported only one aura symptom per attack (visual in 12 and sensory in 2). Thus, motor and aphasic aura never occurred in isolation. Each aura symptom developed gradually over a few minutes in all patients but 5 who had acute-onset aura (visual in 4 and sensory in 1). Headache was absent in 4 of them (acute-onset aura without headache). Among the 29 patients who reported attacks of migraine with typical aura, the headache followed the aura in 24 (83%), began simultaneously with the aura in 4 (14%), and began after the aura in the remaining patient (3%). Seven patients (17%) reported at least one attack of migraine with prolonged aura, with at least one aura symptom lasting more than 1 hour.

Different varieties of visual aura symptoms were reported. Scintillating scotomas or photopsia were the most commonly reported (n=20/38), followed by blurred vision (n=12) and lateral homonymous hemianopia (n=8). Other visual aura symptoms included kaleidoscopic vision (n=2), diplopia (n=2), optic ataxia (n=2), and prosopagnosia (n=1). Various types of visual symptoms could occur in combination. The location of the sensory aura involved predominantly the face and arm, whereas motor aura involved predominantly the arm. Speech disturbances consisted mainly of an expressive aphasia with reduced fluency and paraphasia. Other symptoms reported during migraine attacks were fatigue (4/41), confusion (4/41), and gait ataxia or vertigo (3/41).

The frequency of migraine attacks was variable from 2 per week to 1 every 3 to 4 years or less. Triggering factors were occasionally reported by 17 patients and consisted of stress (7), flashing lights (4), fatigue (2), vacation (2), physical exercise (2), head trauma (2), strong
Table 1. Comparison of Brain MR Imaging Signal Abnormalities Frequency Between CADASIL Patients With and Without Migraine

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Controls (31 Patients Without Migraine)</th>
<th>Cases (31 Patients With Migraine)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean ± SD (range)</td>
<td>45.1 ± 11.9 (20-65)</td>
<td>45.2 ± 11.6 (20-64)</td>
<td>.98</td>
</tr>
<tr>
<td>Sex, M/F</td>
<td>17/14</td>
<td>15/16</td>
<td>.79</td>
</tr>
<tr>
<td>Hyperintensity on T2-weighted images, No./total No. (%)</td>
<td>31/31 (100)</td>
<td>31/31 (100)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>White matter</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Periventricular</td>
<td>27/31 (87)</td>
<td>31/31 (100)</td>
<td>.12</td>
</tr>
<tr>
<td>Deep white matter</td>
<td>28/31 (90)</td>
<td>27/31 (87)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Superficial white matter</td>
<td>24/31 (77)</td>
<td>25/31 (80)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Cortex</td>
<td>2/31 (6)</td>
<td>0/31</td>
<td>.47</td>
</tr>
<tr>
<td>Basal ganglia</td>
<td>18/31 (58)</td>
<td>18/31 (58)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Brainstem</td>
<td>12/31 (39)</td>
<td>8/31 (26)</td>
<td>.42</td>
</tr>
<tr>
<td>Hypointensity on T1-weighted images, No./total No. (%)</td>
<td>24/31 (77)</td>
<td>24/31 (77)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>White matter</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Periventricular</td>
<td>12/31 (39)</td>
<td>6/31 (19)</td>
<td>.16</td>
</tr>
<tr>
<td>Deep white matter</td>
<td>4/31 (13)</td>
<td>8/31 (26)</td>
<td>.33</td>
</tr>
<tr>
<td>Superficial white matter</td>
<td>5/31 (16)</td>
<td>4/31 (13)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Cortex</td>
<td>1/31 (3)</td>
<td>0/31</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Basal ganglia</td>
<td>7/31 (23)</td>
<td>5/31 (16)</td>
<td>.87</td>
</tr>
<tr>
<td>Pons</td>
<td>6/31 (19)</td>
<td>2/31 (6)</td>
<td>.27</td>
</tr>
<tr>
<td>Mesencephalon</td>
<td>2/31 (2)</td>
<td>0/31</td>
<td>.47</td>
</tr>
</tbody>
</table>

Abbreviations: CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; MR, magnetic resonance.

smells (1), angiography (1), post partum (1), insomnia (1), missing meals (1), and cold temperature (1).

A positive history of stroke was found in 8 patients, ischemic stroke in 7, and thalamic hemorrhage in 1, with onset at a mean age of 46.5±11.6 years (range, 28-62 years). Three of these 8 patients had experienced stroke before developing migraine.

**MR IMAGE STUDY**

All CADASIL patients, both cases and controls, had WM signal abnormalities on T2-WI with no significant differences in distribution (either periventricular or deep or subcortical WM) between cases and controls (Table 1). Signal abnormalities were also found in the basal ganglia (18/31 cases and 18/31 controls, P> .99) and the brainstem (8/31 cases and 12/31 controls, P = .42). The cortex was affected in only 2 of 31 controls and no cases (P = .47).

For the global rating scale, we did not find a significant difference in hyperintensity scores between cases and controls, but the grade for severity of T2-WI hyperintensities dramatically increased with age in both groups (P<.001), as previously reported.6

Using the semiquantitative rating scale described by Scheltens et al,13 we found no significant difference in regional scores between cases and controls except for the occipital subcortical WM hyperintensity score, which was significantly lower in CADASIL patients with vs those without migraine (P = .02) (Table 2).

The frequency (24/31 in each group) and distribution of MR imaging signal abnormalities on T1-WI did not differ between cases and controls. Hypointensities on T1-WI (suggesting infarcts) were detected in the cortex in 1 control and in no cases (Table 1). The frequency of hypointensities was not statistically different between cases and controls in the basal ganglia, the pons, or the mesencephalon.

In this series of 41 CADASIL patients with MA, 18 (44%) reported attacks with typical aura. The frequency of attacks and the triggering factors, when reported, were similar to those of migraine in the general population. However, some differences with usual migraine were observed such as late age at onset (the third decade), the low frequency of migraine without aura present in less than one fourth of the patients, and the high number of patients experiencing atypical aura (56%), as previously reported.14 In particular, 4 patients had acute-onset aura without headache, which is not individualized as a subtype of MA in the IHS classification but has been reported among patients with migraine in the general popu-
lation, raising great diagnostic difficulties with transient ischemic attack.\textsuperscript{15}

There are thus many similarities in the clinical features of MA in the general population and in patients with CADASIL. As a first consequence, in clinical practice, almost half of CADASIL patients with symptoms of MA are diagnosed as having typical MA and will not undergo appropriate investigations for the diagnosis of CADASIL until they develop stroke or dementia. What should help clinicians make this diagnosis is, first, the particularly high frequency of attacks of migraine with atypical aura such as hemiplegic migraine, basilar migraine, migraine with prolonged aura, and migraine aura without headache, and second, any family history of ischemic stroke or dementia. However, until a therapeutic approach is proven to prevent the progression of the disease, screening of young CADASIL patients with MA is not justified until they request it and after informed consent and consideration of all ethical aspects. Experiences from other inherited late-onset diseases should be used to define a genetic counseling protocol in patients with CADASIL.\textsuperscript{16}

Besides these clinical arguments, a crucial tool pointing to the diagnosis of CADASIL is MR imaging results. The symptoms of MA in CADASIL meet IHS criteria for migraine except for the presence of MR image WM abnormalities seen as areas of increased signal on T2-WI. These abnormalities are one of the hallmarks of the disease. In the present study, all CADASIL patients with MA and their age-matched CADASIL controls had WM signal abnormalities on T2-WI. Abnormalities appear predominately in the periventricular and deep WM areas. The severity dramatically increases with age as previously shown,\textsuperscript{20} but the distribution and extent do not differ between patients with and without MA. However, less extensive hyperintensities in the subcortical occipital WM on T2-weighted MR images of patients with MA suggest that the extent of subcortical WM lesions may influence the occurrence of MA in CADASIL. However, we cannot exclude that this difference may be due to chance given the number of comparisons.

The underlying mechanisms of migraine in CADASIL remain unknown. First, should MA be considered as directly due to an ischemic event?\textsuperscript{27} This seems unlikely because the infarcts in CADASIL are subcortical with a typical presentation of lacunar syndromes,\textsuperscript{4,5} whereas the migraine disturbances are cortical as suggested by the very high frequency of visual aura symptoms such as progressive scintillating scotoma and/or photopsia observed in the present series. Furthermore, the first attacks of migraine precede the onset of ischemic strokes by many years—16 years in this study, 10 to 15 years according to the literature.\textsuperscript{4,5} Second, is MA related to a cortical spreading depression independent of parenchymal lesions? Ultrastructural vascular smooth muscle cell modifications are present very early in the course of CADASIL and can affect meningeal and cortical vessels.\textsuperscript{2}

In the present study, the mean age at onset of MA was significantly younger in women than in men, which is not so in CADASIL in general. There were also more women with migraine without aura and more men with MA without headache. Although the number of patients studied is small, this suggests that the expression of migraine in CADASIL is also influenced by factors other than NOTCH3 gene mutations. Additional studies on genotype and phenotype correlations and on the role of other genetic and environmental factors should help to better understand the variability of migraine phenotype in CADASIL and thus give insight into migraine in general and into the relationship among migraine, small artery disorders, and cerebral infarcts.

Accepted for publication: February 13, 2004.

Correspondence: Katayoun Vahedi, MD, Service de Neurologie, Hôpital Lariboisière, 2 rue A. Paré, 75010 Paris, France (katayoun.vahedi@lrh.ap-hop-paris.fr).

Author Contributions: Study concept and design: Vahedi, Chabriat, and Bousser. Acquisition of data: Vahedi, Levy, Joutel, and Tournier-Lasserve. Analysis and interpretation of data: Vahedi and Chabriat. Drafting of the manuscript: Vahedi. Critical revision of the manuscript for important intellectual content: Chabriat, Levy, Joutel, Tournier-Lasserve, and Bousser. Statistical expertise: Chabriat. Administrative, technical, and material support: Vahedi. Study supervision: Vahedi, Chabriat, Levy, Joutel, Tournier-Lasserve, and Bousser.

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