New phenotype of the cerebral autosomal dominant arteriopathy mapped to chromosome 19: migraine as the prominent clinical feature

M Vérin, Y Rolland, F Landgraf, H Chabriat, B Bompais, A Michel, K Vahedi, J P Martinet, E Tournier-Lasserve, M H Lemaitre, G Edan

Abstract
A survey was carried out on a large family presenting the symptoms of familial arteriopathy (CADASIL) recently mapped to chromosome 19. This is characterised clinically by recurrent subcortical infarcts developing into pseudobulbar palsy and subcortical dementia, and radiologically by early MRI abnormalities.

To characterise this familial condition, 43 members older than 20 years and spreading over four generations were studied clinically (31 living, 12 deceased), genetically, and radiologically by MRI (n = 31).

Twenty out of 43 were found to be clinically symptomatic and of these 13 out of 31 had MRI abnormalities. Genetic studies mapped this condition to the locus of CADASIL (lod score > 3). The natural history suggests a chronological clinical-radiological staging of this phenotype of CADASIL: stage I between 20 and 40 years with frequent migraine-like episodes and well delineated lesions of the white matter; stage II between 40 and 60 years with stroke-like episodes, bipolar or monopolar-like psychotic disorders, coalescent lesions of the white matter, and well delineated lesions of the basal ganglia; and stage III over 60 years with subcortical dementia, pseudobulbar palsy, diffuse leukoencephalopathy, and multiple well delineated lesions of the basal ganglia.

This phenotype differs from the other two previously described by high frequency of migraine, frequency of psychotic disorders, and early neurological manifestations.

The new acronym “cerebral autosomal dominant arteriopathy with subcortical infarcts, leukoencephalopathy, and migraine” (CADASILM) is proposed to better describe this particular subvariety of CADASIL.

(Keywords: hereditary cerebrovascular disease; CADASIL; migraine; psychosis)

Introduction
We describe, in a large pedigree originating from Brittany, a new phenotype of the cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) recently described and mapped to chromosome 19.1 Although the radiological symptoms (MRI) were similar in our patients and in those of the two CADASIL pedigrees already described,2 the clinical presentation distinguished this pedigree from the other two: early neurological manifestations, frequency of migraine, and psychotic mood disorders are the particular features of this phenotype.

These clinical characteristics also distinguish this phenotype from the other familial arteriopathies reported, consistent with an autosomal dominant pattern of inheritance but not yet linked to the CADASIL locus.4-9

Subjects and methods
SUBJECTS
Forty three members (31 living, 12 deceased) of a French family (fig 1) originating from eastern Brittany (Morbihan, Ille-et-Vilaine) were studied clinically either directly (for
Table 1  Summary of the clinicoradiological presentation of the 20 patients with CADASIL

<table>
<thead>
<tr>
<th>Family member</th>
<th>Age of onset (y)</th>
<th>Age of death (y)</th>
<th>Age of examination (y)</th>
<th>Neuroimaging</th>
<th>Clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td>I-1</td>
<td>Teens</td>
<td>64</td>
<td></td>
<td></td>
<td>Since teens: multiple episodes of blurred vision or paraesthesia in the head, upper and lower limbs, followed by headache for several hours</td>
</tr>
<tr>
<td>I-4</td>
<td>Teens</td>
<td>60</td>
<td>70</td>
<td>—</td>
<td>Died from liver cancer</td>
</tr>
<tr>
<td>I-5</td>
<td>Teens</td>
<td>55</td>
<td></td>
<td></td>
<td>Progressive dementia</td>
</tr>
<tr>
<td>II-1</td>
<td>Teens</td>
<td>—</td>
<td>0</td>
<td>67</td>
<td>Since teens: multiple episodes of headache (12 h) frequently preceded by blurred vision 40 y: transient hemiplegic episode (48 h) 51 to 55 y: melancholic relapses alternated with hypompanic episodes</td>
</tr>
<tr>
<td>II-3</td>
<td>Teens</td>
<td>—</td>
<td>0</td>
<td>58</td>
<td>Since teens: frequent episodes of isolated headache resembling migraine 57 y: sudden episode of hemianopsia lasting several days From 65 y: troubles of memory (recall) At 67 y: subcortical dementia with adynamia, apragmatism, grasping reflexes, behavioural perseverations, tetrapyramlidal syndrome, mild parkinsonism with akinesia and rigidity</td>
</tr>
<tr>
<td>II-6</td>
<td>Teens</td>
<td>46</td>
<td>—</td>
<td>71</td>
<td>46 y: sudden episode of expressive dysphasia 57 y: rapidly progressive right hemiparesia followed by severe headache for 12 h without complete recovery</td>
</tr>
<tr>
<td>II-7</td>
<td>Teens</td>
<td>38</td>
<td>—</td>
<td>—</td>
<td>From 57 y: progressive pseudobulbar palsy, severe motor disability, and apragmatism</td>
</tr>
<tr>
<td>II-8</td>
<td>Teens</td>
<td>—</td>
<td>0</td>
<td>69</td>
<td>Since teens: frequent episodes of headache resembling migraine</td>
</tr>
<tr>
<td>II-12</td>
<td>Teens</td>
<td>41</td>
<td>—</td>
<td>—</td>
<td>In adulthood: multiple relapsing depression 35 y: left hemiplegia with partial remission 41 y: sudden right hemiplegia leading to death with pseudobulbar palsy, tetrapyramidal syndrome, and subcortical dementia</td>
</tr>
<tr>
<td>II-13</td>
<td>Teens</td>
<td>55</td>
<td>—</td>
<td>—</td>
<td>Since teens: frequent episodes of headache resembling migraine</td>
</tr>
<tr>
<td>II-14</td>
<td>Teens</td>
<td>20</td>
<td>—</td>
<td>58</td>
<td>20 y: transient episodes of paraplegia followed by headache</td>
</tr>
<tr>
<td>III-1</td>
<td>Teens</td>
<td>—</td>
<td>0</td>
<td>30</td>
<td>Since teens: frequent episodes of isolated headache resembling migraine 50 y: sudden episode of blurred vision for several days, with spontaneous recovery From 52 y: progressive clinical deterioration with sudden aggravation (paresis and aphasia)</td>
</tr>
<tr>
<td>III-9</td>
<td>Teens</td>
<td>36</td>
<td>—</td>
<td>46</td>
<td>71 y: death with pseudobulbar palsy, severe motor disability, subcortical dementia, and tendency to mutism</td>
</tr>
<tr>
<td>III-11</td>
<td>—</td>
<td>—</td>
<td>Hypertension</td>
<td>44</td>
<td>Hypertension, bilateral Hoffmann’s sign, and ankle clonus</td>
</tr>
</tbody>
</table>

Note: The table provides a summary of the clinicoradiological presentation of the 20 patients with CADASIL, including their age of onset, age of death, age of examination, neuroimaging findings, and clinical features. Details are provided for each case, with specific emphasis on neurological symptoms and their progression.
**Table 1 (continued)**

<table>
<thead>
<tr>
<th>Family member</th>
<th>Age of onset (y)</th>
<th>Age of death (y)</th>
<th>Vascular risk factors</th>
<th>Age of examination (y)</th>
<th>Neuroimaging</th>
<th>Clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td>III-15</td>
<td>44</td>
<td>-</td>
<td>0</td>
<td>45</td>
<td>Well delineated lesions of the basal ganglia</td>
<td>44 y: sudden episode of scintillating spots in the right eye (1 min) followed by hypesthesia of the right then the left hemiface (several minutes), at last hypesthesia of the left upper limb (several hours) followed by mild headache</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Coalescent lesions of the white matter</td>
<td>Sudden hypesthesia of the right hemiface (several hours)</td>
</tr>
<tr>
<td>III-16</td>
<td>20</td>
<td>-</td>
<td>0</td>
<td>46</td>
<td>Well delineated lesion of the basal ganglia</td>
<td>See the case reports section</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Coalescent lesions of the white matter</td>
<td>Since teens: frequent episodes of bifrontal headache resembling migraine</td>
</tr>
<tr>
<td>III-22 Teens</td>
<td>-</td>
<td>0</td>
<td>32</td>
<td></td>
<td>Well delineated lesions of the white matter</td>
<td>32 y: troubles of memory (difficulties to recall), hyperreflexia, and bilateral Hoffmann’s sign</td>
</tr>
<tr>
<td>III-24</td>
<td>-</td>
<td>0</td>
<td>39</td>
<td></td>
<td>Well delineated lesions of the white matter</td>
<td>Isolated hyperreflexia with ankle colonas</td>
</tr>
<tr>
<td>IV-1 Teens</td>
<td>-</td>
<td>0</td>
<td>20</td>
<td></td>
<td>Well delineated lesions of the white matter</td>
<td>See the case reports section</td>
</tr>
</tbody>
</table>

![Figure 2](http://jnnp.bmj.com/)

**Figure 2** Patient II-8. (A) T1 weighted MRI shows multiple well delineated lesions of the basal ganglia. (B) T2 weighted MRI shows diffuse leukoencephalopathy.

The 31 living members) or from medical files or history given by the family (for the 12 deceased members). The 31 living subjects were genetically and radiologically studied after giving their informed consent. For ethical reasons, all the subjects were more than 20 years old.

The status of the living non-consenting members (n = 10) was considered as unknown. All the consenting living spouses of the family members (n = 12) were clinically examined.

**NEUROIMAGING**

Magnetic resonance imaging of the brain was performed in 31 subjects (0.5 Tesla, MR Max, GE-CGR). In all cases, sagittal and axial gradient echo T1 and axial and coronal spin echo T2 weighted images were obtained. The neuroradiologists (YR and BB) were blinded to all clinical and genetic information when they evaluated the MRIs. Patient II-8 had four vessel angiography.

**GENETIC STUDY**

Blood was drawn from potentially informative subjects who gave their informed consent. DNA was extracted from peripheral blood leucocytes. Three informative chromosome 19 markers spanning the interval containing the CADASIL gene were selected—namely, D19S221, D19S226, and D19S199. Genetic linkage analysis was conducted as described previously. Briefly, the status for linkage analysis was based on MRI data. All clinically symptomatic subjects having an abnormal MRI were considered as affected as well as asymptomatic subjects born from an affected subject and having an abnormal MRI. Asymptomatic subjects with normal cerebral MRI were considered as having an unknown status when they were under 35. Linkage analysis was conducted using allele frequencies found for the selected markers in the CEPH families as previously described.

**OTHER INVESTIGATIONS**

All the living symptomatic members had standard investigations including complete blood counts, protein electrophoresis, acti-
vated partial thromboplastin time, and prothrombin time tests, serum electrolytes, creatine kinase enzymes, renal and liver function tests, glycaemia, total and high density lipid cholesterol, triglycerides, and ECG. In one clinically affected patient (II-8) more extensive investigations were performed—namely, detailed lipid metabolism, extensive platelet, coagulation, and fibrinolysis studies, nerve conduction velocities, hexoaminidases A and B, arylsulphatases A and B, α galactosidases, homocystinaemia, free and total serum carnitine concentrations, blood lactates and pyruvates at rest and after exercise, extensive immunological investigations, and visual evoked potentials. Examination of CSF, including protein electrophoresis, was also performed.

Case reports

Table 1 summarises the clinical presentation of the 20 clinically symptomatic patients. Three demonstrative cases will be fully reported (family members II-8, III-16, and IV-1).

PATIENT II-8

This 69 year old woman had presented acute recurrent episodes of severe headache (like migraine according to the International Headache Society criteria) since her teens, lasting about 12 hours. These episodes were sometimes isolated but were more often preceded by transient episodes of blurred vision (many times) or expressive dysphasia (three times), each of these deficits lasting about 30 minutes and followed by complete recovery. At the age of 62, psychomotor slowing and psychiatric disturbances with depressive symptoms appeared, but she recovered completely. At the age of 65, an extrapyramidal syndrome with akinesia, rigidity, and bilateral moderate resting tremor appeared. She experienced an episode of transient expressive dysphasia for 24 hours followed by bilateral headache. From the age of 66 years onwards, there appeared a progressive subcortical dementia with moderate spatiotemporal disorientation, distractibility, loss of initiative, perseveration, apragmatism, and bilateral grasping reflexes. At the age of 69, she experienced an episode of mutism with severe anxiety, but without any other neurological signs. Intravenous imipramine treatment rapidly improved her condition. General examination was normal. Blood pressure was 130/80 mm Hg. Brain MRI investigations (fig 2, A and B) showed a diffuse leukoencephalopathy, with multiple well delineated lesions of the basal ganglia, brainstem, cerebellar white matter, and corpus callosum.

PATIENT III-16

Since the age of 20, this 46 year old man presented several episodes of blurred vision or diplopia followed by bifrontal headache lasting 12 hours and resembling migraine. Several episodes of paraesthesia of the tongue appeared, followed by bifrontal headache lasting 12 hours. He had fewer such episodes between the ages of 35 and 45. At 45, he experienced a sudden left hemiparaesthesia including the hemiface, with partial recovery. At 46, he presented a sudden dysarthria and paresis of the right upper limb for 30 minutes, followed by migraine-like headache for 12 hours. We recently saw an episode of melancholic depression with self accusation, self deprecation, suicidal ideation, sexual inhibition, and severe anxiety, partially responsive to oral anti-depressive treatment. The first clinical examination showed only persistent left hemiparaesthesia and hyperreflexia. Blood pressure was 125/80 mm Hg. Neuropsychological examination showed bradyphrenia, bilateral grasping reflexes, oral and gestural perseverations, imitation behaviour, and a recall memory deficit. Verbal fluency was diminished. The patient found only two categories on the
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Wisconsin card sorting test, suggesting prefrontal dysfunction. We saw neither apraxia, agnosia, nor aphasia. Global intellectual efficiency was roughly preserved (Folstein’s mini mental status = 27/30). At this time, MRI investigations showed well delineated lesions of the basal ganglia, most predominant in the right lentiform nucleus, and coalescent lesions of the white matter (fig 3, A and B). Six months later, we found a progressive extrapyramidal syndrome (akinesia and rigidity) in the absence of any neuroleptic treatment and a subcortical dementia (adynamia, apragma-
Figure 5 Frequency of the main clinical symptoms of the phenotype in three age groups (20 to 40 years, 40 to 60 years, > 60 years).

Discussion

Initially we noted three patients (II-8, III-15, and III-16) with clinical presentations resembling the two families described previously which permitted one of us (ET-L) to find the CADASIL locus on chromosome 19. The MRI study of the family shows that five males and eight females presented abnormalities. The disease is transmitted either paternally or maternally and affects about 50% of offspring. The offspring of unaffected parents are also unaffected. This pattern is consistent with an autosomal dominant pattern of inheritance. The linkage analysis proved that this familial condition was mapped to chromosome 19 in the same locus as CADASIL.

The clinical presentation in this pedigree suggested a particular phenotype of CADASIL. Indeed, when compared with the other two pedigrees previously described13 and genetically proved as presenting CADASIL (table 3), this phenotype differed by the frequency of migraine and psychotic disorders. Because of the absence of clinically asymptomatic and radiologically symptomatic patients, this phenotype can also be distinguished from the other two by its early neurological manifestations. The absence of psychotic disorders and the low frequency of migraine (two patients out of 18) in the healthy family (II-18) (results of MRI investigations) provide confirmatory evidence that these two kinds of symptoms are part of this phenotype and not only coincidences, as suggested recently by Bowler and Hachinski.14

The recent mapping of a familial hemiplegic migraine15 and an autosomal dominant migraine with MRI white matter abnormalities16 to the same locus as CADASIL should be other arguments in favour of a relation between migraine and CADASIL. The frequency of strokes and subcortical dementia is, however, a common characteristic of the three phenotypes and other familial cerebral arteriopathies already described but not yet mapped to chromosome 19.4

Because of its high frequency of migraine, this particular subvariety of CADASIL, different from the basic phenotype2,3 but also from the other hereditary cerebral arteriopathies,4 might be better described by the new acronym CADASILM for "cerebral autosomal domi-
nant arteriopathy with subcortical infarcts, leukoencephalopathy, and migraine."

Psychotic disorders were found in seven patients out of 20 (35%), as either bipolar depressive psychosis in two (29%) or monopolar depressive psychosis in five (71%). The relatively frequent occurrence of psychiatric disorders in this phenotype of CADASIL raises two important and interrelated questions. Firstly, are these psychotic symptoms part of this genetic disease—that is to say, related directly to the genomic abnormality in chromosome 19? In this hypothesis, the gene of CADASIL would be a candidate gene for the study of familial forms of bipolar psychotic disorders. Another hypothesis could be that the CADASIL gene and the gene of a bipolar psychotic affection are localised in the same part of chromosome 19. Secondly, what is the role of the subcortical lesions, in particular those affecting the basal ganglia, in the emergence of psychiatric symptoms? Several neuroimaging studies have shown subcortical lesions in poststroke mood disorders, characterised by either depression or mania. A further prospective study which is underway, especially in young patients with few subcortical lesions, and a comparison of both the psychiatric and neuroradiological symptoms will soon help answer these questions.

The correlations that we found between the age of the patients, the appearance of the clinical symptoms, and the type of cerebral lesions shown by MRI, allow us to propose a chronological clinicaloradiological staging that summarises the natural history of this phenotype. Stage I evolves from 20 to 40 years with migraine (with or without aura), and MRI investigations show well delineated lesions of the white matter (for example, patient IV-1). Stage II evolves between 40 and 60 years with strokes and/or transient ischaemic attacks and psychotic disorders, and MRI investigations show coalescent lesions of the white matter and well delineated lesions of the basal ganglia (for example, patient III-16). Finally, stage III evolves after 60 years with subcortical dementia, and MRI investigations show diffuse leukoencephalopathy and multiple well delineated lesions of the basal ganglia (for example, patient III-8).

Our pedigree, with the other two already described and genetically proved, as well as several others currently collected in Europe and North America, will soon permit an identification of the CADASIL gene. This major step will provide an important advance in our knowledge of the genetics of not only cerebrovascular disease, but also familial migraine and inherited bipolar or monopolar depressive psychosis. Finally, the description of this particular phenotype of CADASIL will permit neurologists to recognise this condition in their patients, together with the description of other phenotypes. This description will permit the real frequency of CADASIL to be determined more accurately.

We are grateful for the support of Professor MG Bousser, Professor M Cartin, and Professor P Chauvel.

Addendum

Since the original submission of this manuscript, a fourth pedigree of CADASIL has been published (Sabbadini G, Francia A, Celandriello L, Di Biasi C, Triasimiani G, Gualdi GF, et al. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL): clinical, neuroimaging, pathological and genetic study of a large Italian family. Brain 1995;118:207–15), the clinical spectrum of which is not different from that of the pedigrees described by Tournier-Lasserre et al and Mas et al, in particular without occurrence of migraine.

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