COL4A1 Mutation in a Patient With Sporadic, Recurrent Intracerebral Hemorrhage

Katayoun Vahedi, MD; Nathalie Kubis, MD, PhD; Monique Boukobza, MD; Minh Arnoult, MD, PhD; Pascale Massin, MD; Elisabeth Tournier-Lasserve, MD; Marie-Germaine Bousser, MD

Background and Purpose—Recently COL4A1, a gene encoding the type IV collagen α1 chain, has been found to be involved in families with autosomal-dominant porencephaly and infantile hemiparesis. In addition to neonatal stroke, some family members had experienced, during adulthood, spontaneous intracerebral hemorrhages (ICHs) and leukoencephalopathy, suggestive of underlying small-vessel disease of the brain. We now report a patient with sporadic, recurrent ICHs and a novel COL4A1 mutation.

Methods—We performed a clinical and genetic study of a 25-year-old-patient with an 8-year history of recurrent ICHs.

Results—This young, normotensive patient with a history of infantile hemiparesis had experienced, since the age of 17, recurrent, spontaneous, deep ICHs occurring during sports activities. He became severely disabled. Brain magnetic resonance imaging showed ventricular enlargement, diffuse white-matter abnormalities, and newly appearing, deep, silent microbleeds. Extensive investigations found no cause. There was no family history of stroke or infantile hemiparesis. A novel COL4A1 mutation (G805R) was identified.

Conclusions—The clinical spectrum of COL4A1 mutations includes recurrent ICHs in association with diffuse leukoencephalopathy in young adults, even in the absence of a family history of infantile hemiparesis or ICH. In addition to birth trauma, anticoagulant use, and head trauma previously reported, sports activities may be a precipitating factor of ICHs in persons with COL4A1 mutations. (Stroke. 2007;38:1461-1464.)

Key Words: intracerebral hemorrhage ■ genetics ■ white matter ■ young adults

Infantile hemiparesis (congenital hemiplegia, or hemiparetic cerebral palsy) is considered the consequence of perinatal stroke. The prevalence of perinatal stroke for infants <30 days of age is estimated to be 1 in 4000 live births, with approximately two thirds ischemic and one third hemorrhagic.1 The underlying mechanisms of infantile hemiparesis are heterogeneous. Intrauterine growth restriction, preeclampsia, chorioamnionitis, systemic infection, birth asphyxia, prolonged rupture of membranes, cord abnormalities, and cardiac and coagulation disorders have all been reported as risk factors.1–3 However, infantile hemiparesis can occur after normal pregnancy and normal birth. Families with infantile hemiparesis and autosomal-dominant porencephaly have also been reported.4 Recently, a new mouse mutant that develops fatal perinatal hemorrhage and porencephaly has been identified with a mutation in Col4a1, a gene that encodes the type IV collagen α1 chain.5 Mutant Col4a1 mice have structural alterations of the vascular basement membrane in the brain and other tissues. Recent studies have shown that mutations in COL4A1 on chromosome 13q34 are involved in human families with infantile hemiparesis and porencephaly.5–7 Interestingly, some mutant mice had, depending on their genetic background, a highly tortuous retinal vasculature in addition to perinatal hemorrhage and porencephaly.8 This retinal phenotype has been previously associated with familial infantile hemiparesis in a French family that was shown to have a COL4A1 mutation.8,9 COL4A1 also plays a role in intracranial hemorrhage (ICH) during adulthood in the mouse and in humans.8,10 Herein we describe a novel COL4A1 mutation in a young patient with a history of infantile hemiparesis who experienced, during adulthood, sporadic, recurrent ICHs associated with diffuse white-matter abnormalities.

Subjects and Methods

A 25-year-old male with infantile hemiparesis and recurrent ICHs and his 45-year-old mother were examined. Family history was obtained from the mother. Genomic DNA was extracted from white blood cells of the proband and his mother. Each of the 52 coding exons of the COL4A1 gene was amplified (oligonucleotides and conditions available on request from E.T.-L.). Direct sequencing of
both strands was performed on an ABI3700 automated sequencing apparatus. Informed consent was obtained from the mother. Fifty DNA samples from healthy individuals were available as a control panel.

**Results**

**Clinical Data**

The proband is a 25-year-old man with no remarkable perinatal event except for a postterm forceps delivery. At 3 months of age, the mother first noticed right-sided weakness. Later he developed right-sided hemiatrophy and hand dystonia. Infantile hemiparesis was diagnosed, but he had normal intellectual development. At the age of 17 years, he experienced his first episode of sudden dysarthria during jogging. Brain CT and MRI showed a recent, right lenticular hemorrhage; diffuse, bilateral, white-matter abnormalities; and left lateral ventricle enlargement. Blood pressure was 125/85. Four-vessel cerebral angiography and transesophageal echocardiography disclosed no abnormalities. Extensive biologic investigations, including complete blood count, serum electrolytes, creatinine, liver enzymes, serum and urinary homocysteine, coagulation tests, anticardiolipids, and lupus anticoagulant, were all in the normal range. In addition, albumin urinary concentration was normal with no hematuria. Screening for all coding exons of KRIT1, the sole cerebral cavernous malformation gene known at that time, was negative (oligonucleotides and screening conditions available on request from E.T.-L.). At the age of 18, he had a left eye injury with a posterior retinal hemorrhage and then developed a traumatic cataract. Between the ages of 19 and 21, the patient had 3 recurrent episodes of a sudden worsening of dysarthria and right-sided hemiparesis at each time during sports activities. At each episode, a brain CT and MRI disclosed a new, deep ICH located in the internal capsule or the basal ganglia, multiple new microbleeds within the corpus callosum and midbrain on gradient-echo imaging, and a diffuse leukencephalopathy. At age 22, he had a generalized seizure when swimming, leading to water inhalation and coma. Brain imaging evidenced a large, deep hematoma in the right basal ganglia with a mass effect and intraventricular hemorrhage.

After the last episode of ICH, the patient remained tetraparetic, totally bedridden, and dependent with pronounced generalized spasticity, severe dysphagia, emotional lability, and no verbal communication (modified Rankin scale = 5). His 45-year-old mother was clinically asymptomatic, and her brain MRI examination was normal. She reported no family history of infantile hemiparesis, stroke, or retinal hemorrhage among the proband’s father (of Italian ascent), 18-year-old sister, and grandparents.

**COL4A1** mutation in the proband.

Genomic DNA sequence analysis of COL4A1 revealed a G805R mutation within exon 31 (left panel). This mutation led to the replacement of 1 of the highly conserved glycine residues of the triple-helix domain of COL4A1 and was not present in 50 control DNA samples. Brain CT (right panels) at age 23 shows bilateral ventricular dilatation, diffuse cortical and left skull atrophy, diffuse white-matter abnormalities, and multiple, deep, hypodense lesions surrounded by punctiform calcifications suggesting vascular cavities.

**COL4A1 Gene Screening**

Genomic DNA sequence analysis revealed in this patient a G2413A transition within exon 31 (the Figure). This mutation changed a glycine amino acid to an arginine (G805R) within the triple-helix domain of COL4A1. This mutation was not detected in the control panel and was absent in his healthy mother.

**Discussion**

Herein we report a patient with a novel COL4A1 mutation who had experienced, since age 17, recurrent, sporadic, deep ICHs leading to severe disability and total dependence at age 22. This COL4A1 mutation affects a highly conserved glycine residue involved in repeated Gly-Pro-X motifs within the triple helix, and their mutation has been shown to be pathogenic both in COL4A1 and in various collagen genes.

There are several remarkable particularities in this patient: (1) the early age of onset of ICH; (2) the deep locations of the ICHs and asymptomatic microbleeds; (3) the high frequency of recurrence over a short period of time; (4) the triggering of ICH by sports activities without head trauma; (5) the absence of any cause, including the absence of hypertension; (6) the past history of infantile hemiparesis; and (7) the associated diffuse leukencephalopathy.

Among genetic vascular malformations that eventually cause recurrent ICHs, cerebral cavernous angiomas were ruled out in this patient on the basis of MRI, which did not show the typical patterns of cerebral cavernous angiomas and revealed diffuse, white-matter abnormalities not typically encountered in cerebral cavernous angiomas. In addition, screening of KRIT1 showed no mutation.

The clinical phenotype of deep, recurrent ICHs, leukencephalopathy, and infantile hemiparesis led us to consider COL4A1 as a candidate gene in this young, normotensive patient. All 5 recently reported families with COL4A1 mutations had an autosomal-dominant porencephaly and infantile hemiparesis but with incomplete penetrance, suggesting the possibility of sporadic cases (Table 1). Among the reported families, variations in the phenotypes of COL4A1 mutations were noted, including ICHs during adulthood, diffuse leukencephalopathy on brain imaging, and retinal arteriolar tortuositities, even in the absence of infantile hemiparesis or congenital porencephaly. There is so far no
pathology study of the cerebral vessels in patients with COL4A1 mutations. Endothelial cell basement membrane abnormalities of skin capillaries with focal interruptions or increased thickness have been reported in a patient with COL4A1 mutations and recurrent and disabling ICHs in adulthood. Abnormalities of the basement membrane of cerebral vessels have also been noted in col4a1-mutant mice by electron microscopy. All of these data suggest that COL4A1 mutations cause generalized small-vessel disease with particular involvement of the brain vessels. Herein we report the first sporadic patient with COL4A1 mutation and enlarge the phenotypic spectrum of COL4A1 mutation to early-onset sporadic, recurrent, and disabling deep ICHs.

In our patient, sports activity, in addition to birth trauma, brain trauma, and use of oral anticoagulants previously reported, may have been a precipitating factor of the ICHs associated with the COL4A1 mutation.

Ophthalmologic manifestations of COL4A1 mutations include cataract, spontaneous or traumatic retinal hemorrhage, and retinal arteriolar tortuositities present in 5 of 8 patients previously reported with COL4A1 mutations who underwent fundus examination. It is interesting to note that, depending on their genetic background, some but not all col4a1-mutant mice had retinal vascular tortuositities. Retinal arteriolar tortuositities have also been found in a family without porenephaly but with leukoencephalopathy, hematuria, and renal insufficiency. Whether the COL4A1 gene is also involved in this family is not yet known. Type IV collagen is an essential component of the glomerular basement membrane. Hematuria has been rarely reported in patients with COL4A1 mutations (Table 1) but was not found in our patient.

Because of the lack of pathognomonic neurologic symptoms, specific brain MRI abnormalities, and the possibility of asymptomatic gene carriers and sporadic cases, patients with COL4A1 mutations may be underdiagnosed. Considering our data and the previously reported families with COL4A1 mutations, at least 1 of the following arguments should prompt COL4A1 genetic screening in young patients with deep ICHs of undetermined etiology: (1) a personal or family history of infantile hemiparesis or congenital porenephaly, (2) leukoencephalopathy with silent microbleeds in the absence of hypertension, and (3) the presence of retinal arteriolar tortuositities. Genetic counseling of at-risk young women planning to become pregnant is of major importance, because cesarean delivery should be recommended to try to prevent vascular injury attributable to birth trauma. In at-risk adults, sustained physical activity or sports activities that may cause head trauma should be avoided, and anticoagulant use should be strictly monitored.

COL4A1 mutation features are distinct from those of other known genetic small-vessel diseases of the brain, as congenital hemiplegia and perinatal stroke are not features of cerebral amyloid angiopathy or CADASIL, although silent microbleeds on gradient-echo imaging have been frequently associated with both cerebral amyloid angiopathy and CADASIL (Table 2).

In conclusion, COL4A1 mutations have a wide clinical spectrum, including recurrent and disabling ICHs in young adults, even in the absence of any family history of infantile hemiparesis or stroke. Further studies will be needed to determine the frequency of COL4A1 mutations and the mechanisms by which they lead to hemorrhagic strokes and leukoencephalopathy.

**Acknowledgment**

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**TABLE 1.** Reported Clinical and Imaging Data in 19 Patients With COL4A1 MUTATIONS

<table>
<thead>
<tr>
<th>Neurologic manifestations</th>
<th>Porencephaly and infantile hemiparesis</th>
<th>13/19</th>
<th>3/19 (postterm pregnancy in 2, protracted duration of expulsion in 1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reported perinatal events</td>
<td>Slight to moderate mental retardation</td>
<td>7/19</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Seizures in childhood</td>
<td>4/19</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ICH in adulthood</td>
<td>5/19</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Migraine</td>
<td>5/19</td>
<td>(migraine with aura in 3)</td>
</tr>
<tr>
<td>Neuroradiologic abnormalities</td>
<td>Leukoencephalopathy on brain MRI or CT</td>
<td>16/19</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Porencephaly without infantile hemiparesis</td>
<td>2/19</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Silent microbleeds on gradient-echo MRI</td>
<td>2/4</td>
<td></td>
</tr>
<tr>
<td>Ophthalmologic manifestations</td>
<td>Retinal arteriolar tortuositities</td>
<td>5/8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Retinal hemorrhage</td>
<td>2/7</td>
<td>(traumatic in 1)</td>
</tr>
<tr>
<td>Other clinical manifestations</td>
<td>Cataract</td>
<td>3/19</td>
<td>(traumatic in 1)</td>
</tr>
<tr>
<td></td>
<td>Hematuria</td>
<td>1/19</td>
<td></td>
</tr>
</tbody>
</table>

**TABLE 2.** Main Features of COL4A1 Mutations, CADASIL (NOTCH3 Mutations), and Hereditary Amyloid Angiopathy (CAA)

<table>
<thead>
<tr>
<th></th>
<th>COL4A1</th>
<th>CADASIL (NOTCH3)</th>
<th>CAA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonatal stroke (infantile hemiparesis, porencephaly)</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>ICH</td>
<td>Yes</td>
<td>Rare</td>
<td>Yes</td>
</tr>
<tr>
<td>Cerebral infarcts</td>
<td>Uncertain</td>
<td>Yes</td>
<td>Rare</td>
</tr>
<tr>
<td>Leukoencephalopathy</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Silent microbleeds</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Disclosures
None.

References
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