

- sions and normal appearing white matter of multiple sclerosis. *Brain* 2001;124:1743–1753.
27. Creange A, Chazaud B, Plonquet A, et al. IFN-beta decreases adhesion and transmigration capacities of lymphocytes in Guillain-Barré syndrome. *Neurology* 2001;57:1704–1706.
28. Özenci V, Kouwenhoven M, Teleshova N, Pashenkov M, Frederickson S, Link H. Multiple sclerosis: pro- and anti-inflammatory cytokines and metalloproteinases are affected differentially by treatment with INF- β . *J Neuroimmunol* 2000;108:236–243.
29. Galbois Y, Shapiro S, Lahat N, Rawashdeh H, Miller A. Matrix metalloproteinases and their tissue inhibitors as markers of disease subtype and response to interferon-beta therapy in relapsing and secondary-progressive multiple sclerosis patients. *Ann Neurol* 2001;50:443–451.
30. Kouwenhoven M, Ozenci V, Gomes A, et al. Multiple sclerosis: elevated expression of matrix metalloproteinases in blood monocytes. *J Autoimmun* 2001;16:463–470.
31. Johnston J, Zhang K, Silva C, et al. HIV-1 tat neurotoxicity is prevented by matrix metalloproteinase inhibitors. *Ann Neurol* 2001;49:230–241.
32. Newman TA, Woolley ST, Hughes PM, Sibson NR, Anthony DC, Perry VH. T-cell- and macrophage-mediated axon damage in the absence of a CNS-specific immune response: involvement of metalloproteinases. *Brain* 2001;124:2203–2214.
33. Leppert D, Ford J, Stabler G, et al. Matrix metalloproteinase-9 (gelatinase B) is selectively elevated in CSF during relapses and stable phases of multiple sclerosis. *Brain* 1998;121:2327–2334.

Hereditary infantile hemiparesis, retinal arteriolar tortuosity, and leukoencephalopathy

K. Vahedi, MD; P. Massin, MD; J.-P. Guichard, MD; S. Miocque, MD; M. Polivka, MD; F. Goutières, MD; D. Dress, MD; F. Chapon, MD; M.-M. Ruchoux, MD, PhD; F. Riant, MD; A. Joutel, MD, PhD; A. Gaudric, MD; M.-G. Bousser, MD; and E. Tournier-Lasserre, MD

Abstract—Background: The main hereditary vascular conditions involving both retinal and cerebral vessels include cerebroretinal vasculopathy, HERNS (hereditary endotheliopathy with retinopathy, nephropathy, and stroke), and hereditary vascular retinopathy; all are linked to the same locus on chromosome 3p21. Hereditary retinal arteriolar tortuosity is a distinct, autosomal dominant condition characterized by retinal arteriolar tortuosity and recurrent retinal hemorrhages. This condition is known to affect only retinal vessels. **Methods:** Clinical and brain MRI investigations of eight members of a three-generation family and extensive biological and systemic vascular investigations within one affected family member were conducted. **Results:** Six of eight family members were clinically symptomatic; disorders included infantile hemiparesis (2), migraine with aura (3), and retinal hemorrhage (1). Five individuals had retinal arteriolar tortuosities. A diffuse leukoencephalopathy in association with dilated perivascular spaces was observed in six individuals. Two family members had silent, deep cerebral infarcts as demonstrated on MRI. Genetic linkage analysis strongly suggests that this disorder is not linked to the 3p21 hereditary vascular retinopathy/cerebroretinal vasculopathy/HERNS locus. **Conclusions:** The authors describe a novel hereditary autosomal dominant condition affecting both retinal and cerebral vessels and characterized by infantile hemiparesis, migraine with aura, retinal hemorrhage, retinal arterial tortuosity, and leukoencephalopathy with dilatation of perivascular spaces and microbleeds on brain MRI. Investigation of additional families should help to map the gene and to better categorize the spectrum of hereditary cerebroretinal small vessel diseases.

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Some rare hereditary conditions involving both retinal and cerebral vessels have been reported. Cerebroretinal vasculopathy is an autosomal dominant, adult-onset condition characterized by early progressive central visual loss, progressive focal neurologic deficit, cognitive deterioration, seizures, headache,

and contrast-enhancing brain mass lesions.^{1–3} Within the retina, the underlying histopathology consists of bilateral capillary occlusions involving mainly perifoveal vessels leading to multifocal retinal ischemia and neovascularization.¹ Within the brain, there is an obliterative fibrosis of the walls of arteries and

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From the Service de Neurologie (Drs. Vahedi and Bousser), Service d'Ophtalmologie (Drs. Massin and Gaudric), Service de Neuroradiologie (Dr. Guichard), Service d'Anatomie et Cytologie Pathologiques (Dr. Polivka), and Laboratoire de Cytogénétique (Dr. Tournier-Lasserre), Assistance Publique–Hôpitaux de Paris, Hôpital Lariboisière, Paris; Service d'Ophtalmologie (Dr. Miocque) and Service de Neuropathologie (Dr. Chapon), Centre Hospitalier Universitaire de Caen; Unité de Neuropédiatrie (Dr. Goutières), Assistance Publique–Hôpitaux de Paris, Hôpital des Enfants Malades, Paris; Service de Neurologie (Dr. Dress), Centre Hospitalier Mémorial de Saint-Lô; Service de Neuropathologie (Dr. Ruchoux), Centre Hospitalier Universitaire de Lille; and INSERM EMI 99-21 (Drs. Riant, Joutel, Bousser, and Tournier-Lasserre), Faculté de Médecine Lariboisière, Paris, France.

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Address correspondence and reprint requests to Dr. Katayoun Vahedi, Service de Neurologie, Assistance Publique–Hôpitaux de Paris, Hôpital Lariboisière, 2 rue A. Paré, 75010 Paris, France; e-mail: katayoun.vahedi@lrb.ap-hop-paris.fr

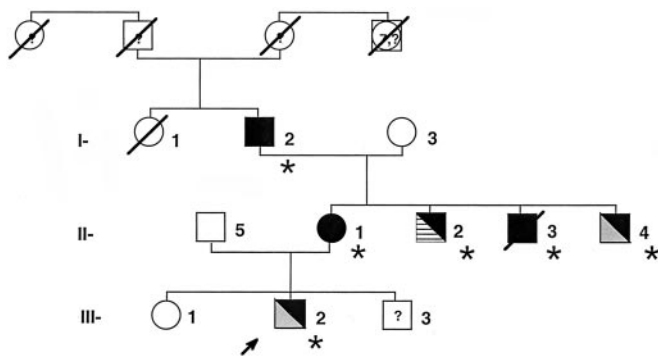


Figure 1. Pedigree of the family. Black = retinal arteriolar tortuosity or retinal hemorrhage; gray shading = infantile hemiparesis; white hatched = possible infantile hemiparesis; asterisk (*) = leukoencephalopathy and dilated perivascular spaces; arrow = proband; ? = unknown.

veins of medium and small caliber within the white matter and basal ganglia that is associated with a variable degree of perivascular inflammation and multiple foci of parenchymal necrosis.¹

HERNS (hereditary endotheliopathy with retinopathy, nephropathy, and stroke) is another autosomal dominant condition reported in a family with clinical and pathologic findings very similar to that of cerebroretinal vasculopathy.⁴ However, renal insufficiency with proteinuria was reported in some affected family members in addition to early progressive visual loss, focal neurologic deficit, dementia, and headache. Electron microscopy studies showed

alterations of vascular walls consisting of multilayered basement membrane of capillary and arteriolar endothelial cells in the brain and other tissues, including the kidney and skin.⁴

Hereditary vascular retinopathy is another autosomal dominant, occlusive microangiopathy of the retina starting in and around the posterior pole.⁵ In addition to the retinopathy, migraine with and without aura, Raynaud's phenomenon, mild cognitive decline, and depression, as well as slight MRI brain white matter abnormalities, have been reported in hereditary vascular retinopathy. However, no brain mass lesions such as those in cerebroretinal vasculopathy or HERNS have been reported in this disorder.^{5,6} Linkage analysis mapped these three conditions to a common locus on chromosome 3p21.⁷

Hereditary retinal arteriolar tortuosity is an autosomal dominant condition characterized by spontaneously regressive retinal hemorrhages and retinal arteriolar tortuosity that may appear or increase throughout life. More than 13 families and some sporadic cases have been reported since 1958.⁸⁻¹⁵ Arteriolar tortuosity predominates in the macula. Capillaries and venules are spared. Arterioles have normal caliber and there has been no report of retinal ischemic changes. The age at onset of retinal hemorrhages is variable, from 8 years old to after the 5th decade. Hemorrhages are often recurrent and usually occur spontaneously, although physical efforts, Valsalva's maneuvers, or trauma have been reported as precipitating factors. The disease has a benign course, as the retinal hemorrhages are usu-

Table Clinical and MRI findings of the family

Subject no.	Age, y	Fundus examination	Neurologic symptoms	Associated diseases	Leukoencephalopathy and dilated perivascular spaces on brain MRI
I-1	75	Not done	Subacute frontal dementia	Invasive glioblastoma	-
I-2	68	Moderate retinal arterial tortuosity in both eyes and diffuse hypopigmentation	Migraine with visual aura	Hypertension Acoustic schwannoma	+
II-1	40	Marked retinal arteriolar tortuosity in both eyes and diffuse hypopigmentation	Migraine with visual aura	None	+
II-2	37	Marked retinal arteriolar tortuosity in both eyes and diffuse hypopigmentation	Migraine with visual and sensory aura Left pyramidal syndrome and shortened left leg	Germinal seminomatous tumor of the mediastinum	+
II-3	32	Not done	None	Retinal hemorrhage Hematuria	+
II-4	28	Moderate retinal arteriolar tortuosity in both eyes and hypopigmentation of the inferior part of the fundus	Infantile hemiparesis with mild mental retardation Febrile convulsions	None	+
III-1	18	Normal	None	None	Unknown
III-2	15	Marked retinal arteriolar tortuosity in both eyes and hypopigmentation of the inferior part of the fundus	Infantile hemiparesis Seizures	None	+

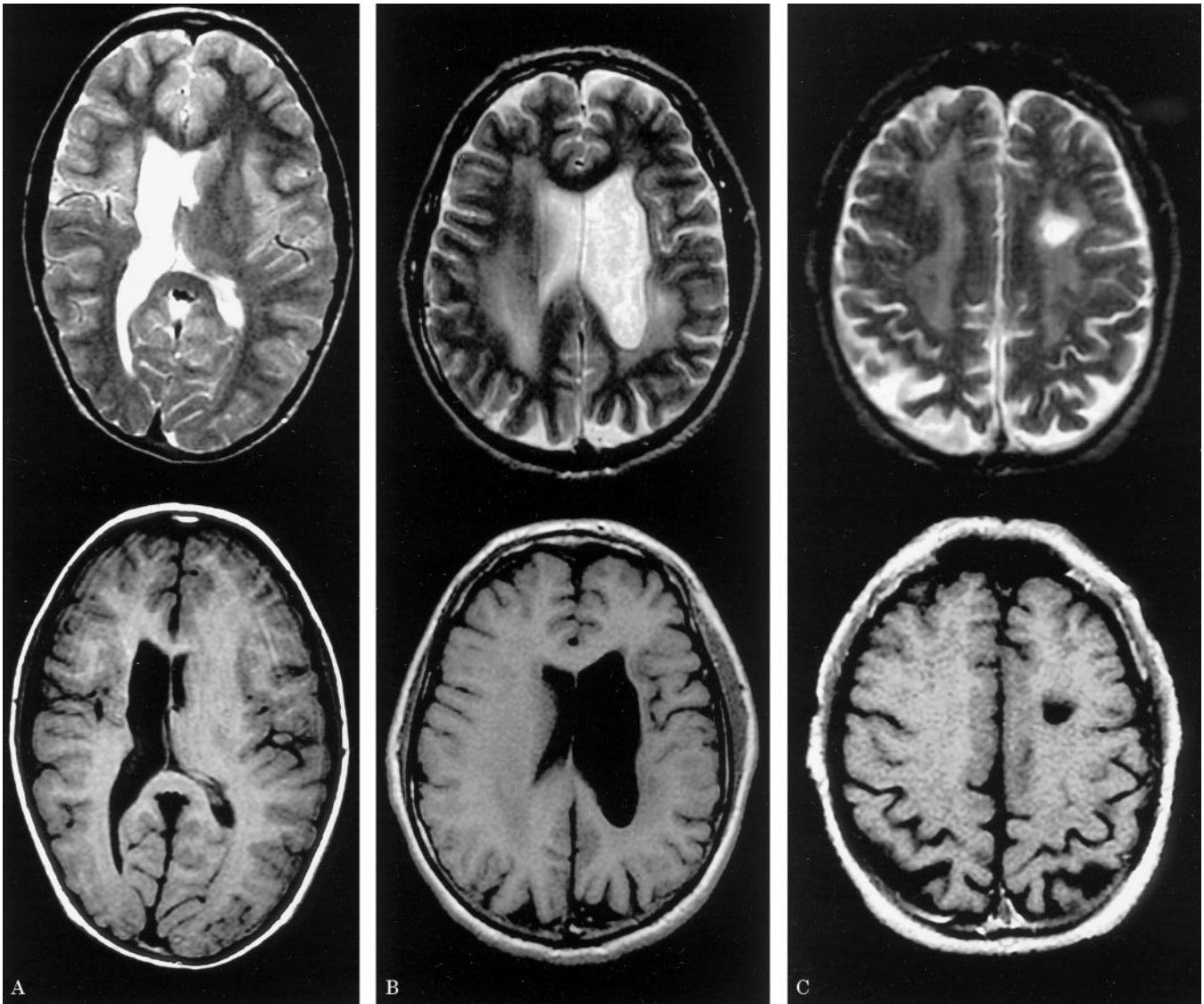


Figure 2. MRI on T2-weighted imaging (top row) and T1-weighted imaging (bottom row) of Case III-2 (A) showing a right-sided ventricular enlargement and a diffuse right cerebral hemisphere atrophy; Case II-4 (B) showing a symmetrical, predominantly posterior leukoencephalopathy, left ventricular enlargement, and left cerebral hemisphere atrophy; and Case I-2 (C) showing a diffuse, symmetrical leukoencephalopathy and a nodular hyperintense signal on T2-weighted imaging and hypointense signal on T1-weighted imaging in the left centrum ovale suggestive of a silent deep infarct.

ally limited, responsible for transient visual loss of a few days' or weeks' duration, and the patient may even be totally asymptomatic. This condition is known to affect only retinal vessels. Its underlying physiopathology remains unknown.

Herein we report a detailed clinical and radiologic description of a three-generation pedigree affected by a novel, autosomal dominant vasculopathy affecting both retinal and cerebral vessels and causing infantile hemiparesis, migraine with aura, retinal hemorrhage, retinal arteriolar tortuosity on fundus examination, and leukoencephalopathy with dilated perivascular spaces and microbleeds on brain MRI.

Subjects and methods. *Subjects.* Eight consenting members over three generations were directly examined. The pedigree is shown in figure 1. In addition, ophthalmologic examination was performed in 6 family members (Cases I-2, II-1, II-2, II-4, III-1,

and III-2) and neuroimaging in 7 family members (Cases I-1, I-2, II-1, II-2, II-3, II-4, and III-2). In addition, extensive systemic vascular investigations were performed in 1 affected member (II-1). These investigations included retinal fluorescein angiography; cerebral MR angiography (MRA); cervical and transcranial ultrasound examination; transthoracic echocardiography; MRA of the aorta and its main branches; complete hematologic, clotting, biochemical, and immunologic laboratory investigation; and a skin biopsy for the study of cutaneous vessels.

MRI investigations. Neuroimaging was performed at 1 to 1.5 T. T1-weighted images (T1WI) were obtained from axial, sagittal, or both planes and T2-weighted images (T2WI) were obtained from axial planes. In addition, Patient II-1 had T2*-weighted gradient echo images in both axial and coronal planes and fluid-attenuated inversion recovery (FLAIR) in axial planes. A neuroradiologist (J.P.G.) blinded to the clinical status of patients reviewed the MRI scans for the presence of any abnormalities.

Genetic studies. Genomic DNA was extracted from peripheral blood cells of all consenting members (I-2, I-3, II-1, II-2, II-3, II-4, II-5, and III-2) using standard procedures. Direct sequencing of exons 3 and 4 of the *notch3* gene was performed as described previ-

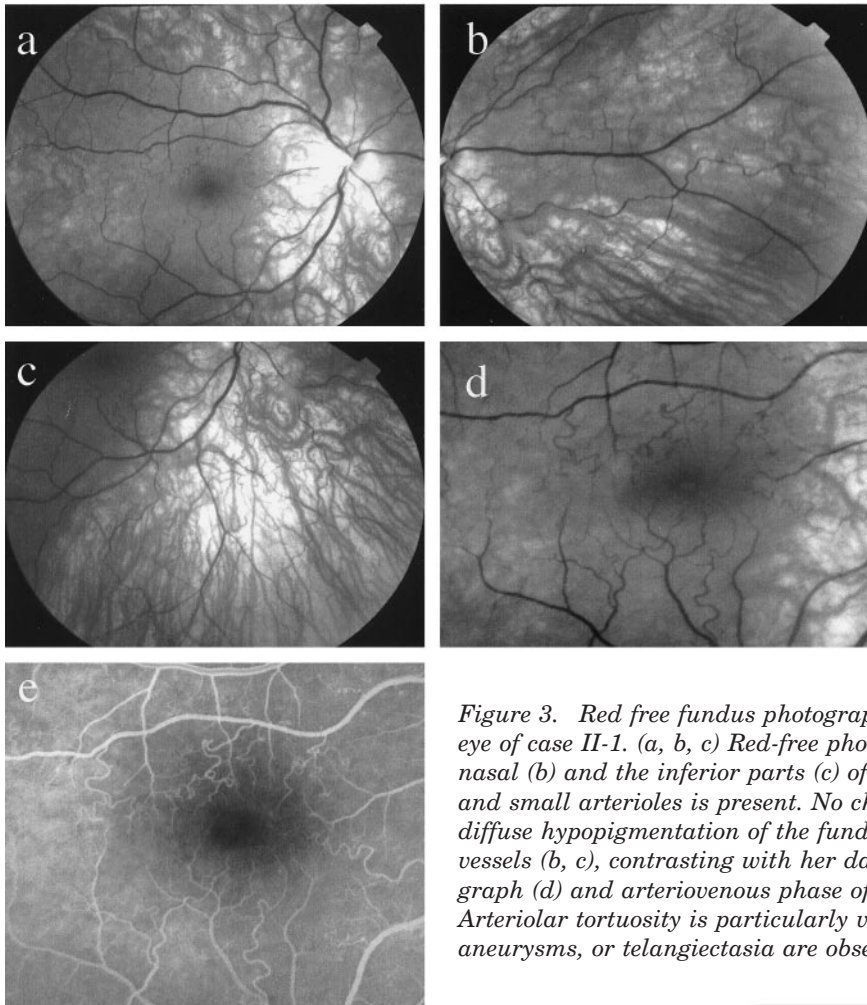


Figure 3. Red free fundus photography and fluorescein angiogram of the right eye of case II-1. (a, b, c) Red-free photographs of the posterior pole (a) and of the nasal (b) and the inferior parts (c) of the fundus. Marked tortuosity of medium and small arterioles is present. No changes are apparent in the veins. Note the diffuse hypopigmentation of the fundus with increased visibility of the choroidal vessels (b, c), contrasting with her dark hair (not shown). (d, e) Red-free photograph (d) and arteriovenous phase of the angiogram (e) in the macular area. Arteriolar tortuosity is particularly visible. No capillary abnormalities, microaneurysms, or telangiectasia are observed.

ously.¹⁶ In addition, we performed genetic linkage analysis with three markers spanning the cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)/*NOTCH3* locus on 19p13, including an intragenic marker (D19S841) and two perigenic markers (D19S226 and D19S199).¹⁷ Genetic linkage to the hereditary vascular retinopathy/cerebroretinal vasculopathy/HERNS locus on chromosome 3p21 was tested using seven microsatellite markers (D3S3685, D3S3564, D3S3582, D3S1581, D3S1578, D3S1289, and D3S3616) spanning this locus and selected from published data.⁷

Results. Case reports. Case III-2. The proband is a 15-year-old boy who has an infantile hemiparesis associated with seizures (table). Detailed pregnancy and birth history obtained from the mother indicated no remarkable event in the neonatal period. The first symptoms were noticed at age 4 months and consisted of a left-sided weakness with pyramidal tract signs. Seizures developed at age 10. It consisted of two episodes of partial seizures with elementary symptomatology (brief scintillating scotomas and head and neck rotation to the left) and secondary generalization. MRI performed at age 10 showed a right-sided ventricular enlargement and right cerebral hemisphere atrophy with midline shift to the right and a large paraventricular area of T1 hypointensity (figure 2). On T2WI there were a few small, well-delineated, and round T2 hyperintensities in the putamen and one in the left centrum ovale, with slight symmetrical white matter pallor in the parietal regions. When examined at age 15, he had left-sided hemiatrophy and pyramidal signs but no mental retardation. He did not report having headaches. Blood pressure was 110/70 mm Hg. There was no history of retinal hemorrhages. Visual acuity was normal in both eyes. Fundus examination disclosed marked retinal arteriolar tortuosity in both eyes, without retinal hemorrhages

and with normal veins. Hypopigmentation of the inferior part of the fundus was noted.

Case II-1. This 40-year-old woman is the mother of the proband (see the table). At age 30, she had a first episode of bilateral scintillating scotomas of abrupt onset accompanied by a diffuse headache of 1 week's duration. Since age 35, she complained once a year of episodes of blurred vision lasting for 30 minutes and accompanied by a right-sided hemicrania with phono- and photophobia. She has no other notable medical history. She did not report other types of headache. She had no history of retinal hemorrhages. Her neurologic examination was normal. Blood pressure was 110/60 mm Hg. Visual acuity was normal in both eyes with a +0.75-diopter (D) correction. Fundus examination showed marked retinal arteriolar tortuosity in both eyes without any retinal hemorrhage or exudate (figure 3). A diffuse hypopigmentation of the fundus was noted. Fluorescein angiography showed no other abnormality; arteriolar caliber was normal and there was no leakage of fluorescein or capillary dropout (see figure 3). The brain MRI showed three types of abnormalities (figure 4). First, there were widespread, symmetrical, predominantly posterior white matter hyperintensities on T2WI and FLAIR. Second, within the putamen and the adjacent white matter, there were multiple, bilateral, well-delineated areas of increased signal of various sizes on T2WI and decreased signal of various sizes on T1WI and FLAIR suggestive of dilated perivascular spaces, with the largest measuring 14 mm. There was also one such area in the deep cerebellum. Third, there were multiple, deep, small, hypointense foci on T2*-weighted gradient echo images suggestive of past microbleeds. They were located in the deep cerebellum, periventricular white matter, and the caudate nucleus. Other investigations including transthoracic echocardiography, aortic and intracranial MRA, cervical and transcranial ultrasound examinations, anticardiolipin antibodies, lupus anticoagulant,

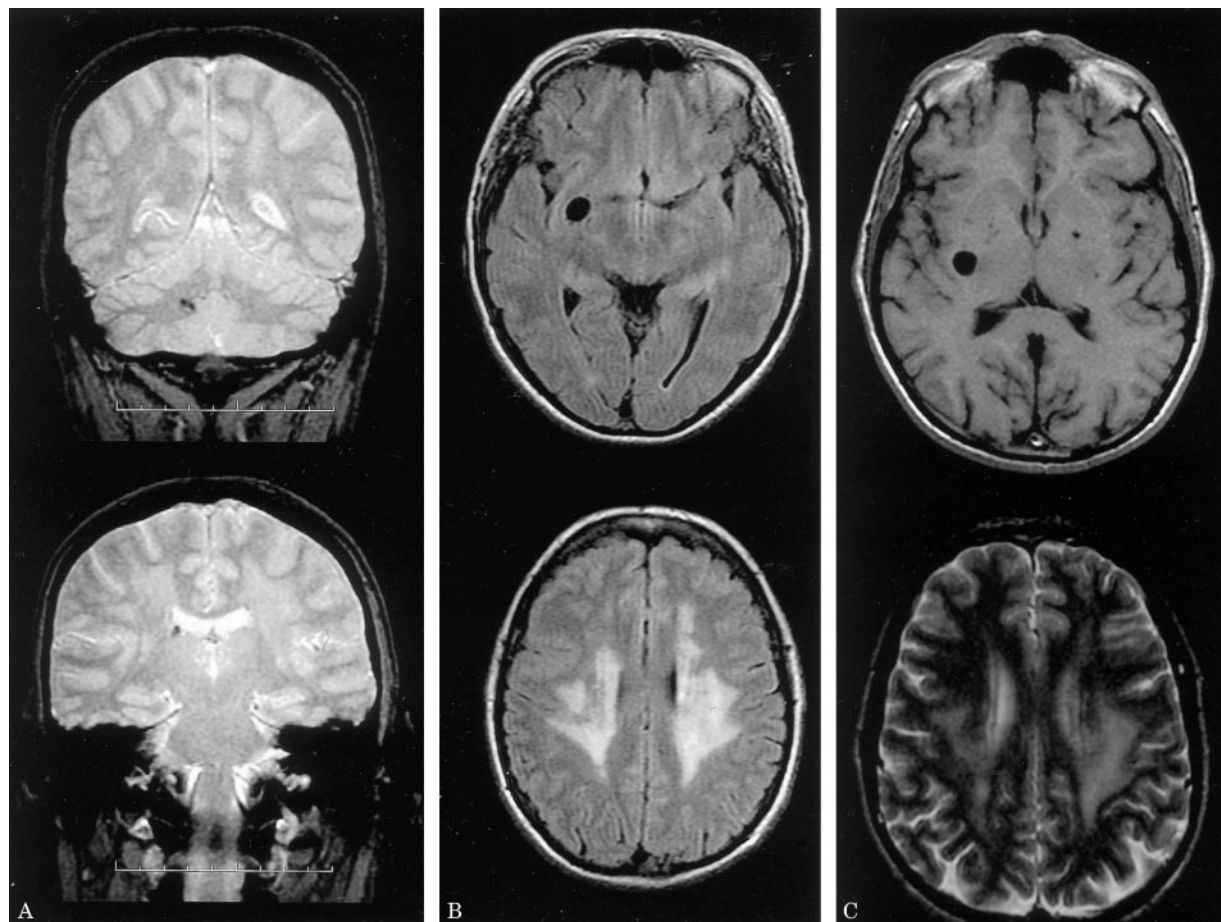


Figure 4. MRI of Patient II-1 (A, B) and Patient II-3 (C). Note the small, deep hypointensities in the cerebellum and the caudate nucleus on T2-weighted imaging suggestive of past microbleeds (A); the large, well-delineated hypointensity in the basal ganglia on fluid-attenuated inversion recovery (FLAIR) and T1-weighted imaging suggestive of dilated perivascular spaces (B, top; and C, top); and the diffuse, symmetrical, predominantly posterior white-matter abnormalities on FLAIR (B, bottom) and T2-weighted imaging (C, bottom).*

antinuclear factor, and creatinine clearance were normal. There was no microalbuminuria. Light microscopic study of a skin biopsy including several arterioles, capillaries, and venules did not disclose vessel-wall lesions; there were no abnormal deposits on PAS and Congo red stains or on antiubiquitin immunohistochemistry. Biopsy for ultrastructural study included only capillaries and some very small venules with no detectable abnormality.

Case II-2. This 37-year-old man is the brother of Case II-1 (see the table). Since age 20, he had episodes of bilateral blurred vision lasting for 5 to 10 minutes. These episodes were followed by paresthesia that, within a few minutes, successively involved his fingers on one side, and then a severe, initially unilateral then diffuse headache with phono- and photophobia and vomiting. Frequency was one attack per week during the first year, then they stopped for a period of 15 years. He recently had a short period of repeated identical attacks. He did not report other types of headache and had no other remarkable medical history except depression at age 33. Neurologic examination disclosed a left pyramidal syndrome with a left Babinski's sign and a 2-cm shortening of the left leg. Blood pressure was 120/80 mm Hg. Fundus examination showed marked bilateral retinal arteriolar tortuosity with diffuse hypopigmentation of the fundus. T2WI of the brain showed a nodular right paraventricular hyperintensity with a slight adjacent ventricular enlargement suggestive of an old deep infarct and symmetrical micronodular areas of increased signal located in the basal ganglia suggestive of dilated perivascular spaces, with the largest measuring 3 mm. On follow-up, the patient had a germinal seminomatous tumor of the mediastinum with carcinomatous lymphangitis.

Case II-3. This 32-year-old farmer is the brother of Cases II-1 and II-2 (see the table). At age 2 he had a severe craniofacial trauma with coma but fully recovered. At age 22 he had an abrupt-onset central scotoma of the right eye reported to be due to a retinal hemorrhage, which completely recovered after 2 months. During investigation of this retinal hemorrhage a microscopic hematuria was found. No medical chart was available. When examined at age 32, his neurologic examination and blood pressure (120/80 mm Hg) were normal. He did not report headache. Brain MRI showed a diffuse, periventricular, predominantly posterior leukoencephalopathy and multiple, bilateral, and well-delineated areas of increased signal on T2- and decreased signal on T1WI in the putamen and the pallidum suggestive of dilated perivascular spaces of various sizes (see figure 4). The largest was in the putamen and measured 10 mm. The patient died 1 year later at age 33, following a major head injury with diffuse pneumoencephalitis, left frontal extradural hematoma, and subarachnoid hemorrhage complicated by multiple, bilateral, large cortical infarctions due to intracranial arterial spasm.

Case II-4. This 28-year-old man is the brother of Cases II-1, II-2, and II-3 (see the table). He has an infantile hemiparesis associated with a mild mental retardation. No fetal distress was reported despite a post-term pregnancy. The first symptoms were noticed at age 7 months and consisted of a right-sided weakness with pyramidal tract signs. He had 1 episode of febrile seizures at age 4. He was taking phenobarbital and then sodium valproate for 8 years with no further seizures. He has no other remarkable medical history and does not report headache. On examination he had a right hemiparesis with spasticity and Babinski's sign and a

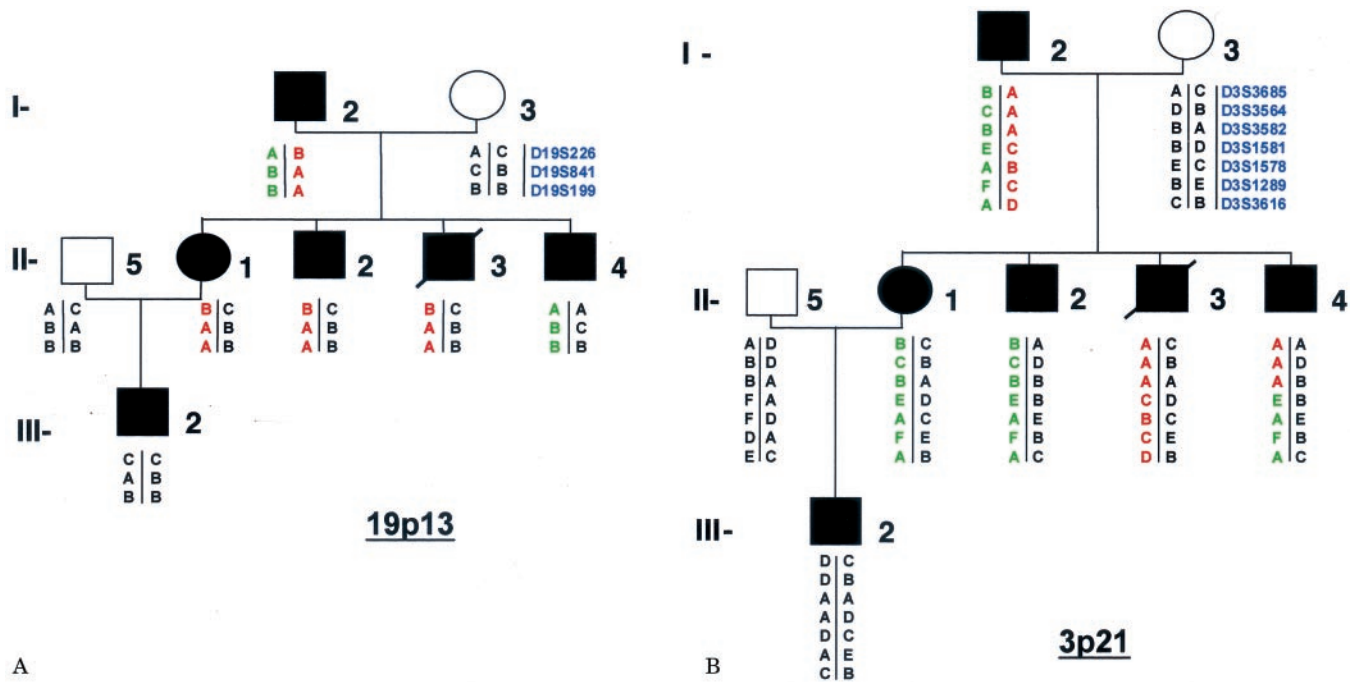


Figure 5. Genetic linkage analysis with chromosome 19 and chromosome 3 markers spanning respectively the CADASIL and the hereditary vascular retinopathy/cerebroretinal vasculopathy/HERNS loci. The various alleles of D19S226, D19S841, and D19S199 for CADASIL (A) and D3S3685, D3S3564, D3S3582, D3S1581, D3S1578, D3S1289, and D3S3616 for hereditary vascular retinopathy/cerebroretinal vasculopathy/HERNS locus (B) carried by each subject are indicated. The haplotype inherited from the affected parent is represented on the left side. For each microsatellite tested, there are at least two affected individuals who do not share any allele with their affected relatives, strongly suggesting that neither of these loci is linked to the disease.

right-sided hemiatrophy with a shortened right leg. Blood pressure was 130/80 mm Hg. Brain MRI at age 28 showed a diffuse left ventricular enlargement extending into the basal ganglia; a left cerebral hemisphere atrophy; a symmetrical, predominantly posterior leukoencephalopathy (see figure 2); and few well-delineated and round areas of increased signal on T2WI and decreased signal on T1WI in the right putamen suggestive of dilated perivascular spaces. Fundus examination disclosed moderate retinal arteriolar tortuosity in both eyes, with hypopigmentation of the inferior part of the fundus.

Case I-2. This 68-year-old man is the father of Cases II-1, II-2, II-3, and II-4. He has a 10-year history of hypertension (see the table). He underwent surgery for a right-sided acoustic schwannoma at age 67. At age 45 he had repeated episodes of bilateral, scintillating scotomas of abrupt onset and of brief duration immediately followed by a severe headache of 30 minutes' duration during a 2-month period. His neurologic examination was normal and his blood pressure was 140/80 mm Hg. Fundus examination showed moderate retinal arteriolar tortuosity in both eyes, with diffuse hypopigmentation of the fundus. Brain MRI showed an old, deep infarct in the left centrum ovale, a symmetrical periventricular leukoencephalopathy on T2WI, a predominantly parieto-occipital atrophy, and a few bilateral, micronodular, round, and well-delineated areas of increased signal on T2WI and decreased signal on T1WI in the putamen suggestive of dilated perivascular spaces.

Case I-1. This 75-year-old woman is the sister of Case I-2 (see the table). She has no remarkable medical history. At age 75, she rapidly developed memory disturbances, psychiatric symptoms with frontal signs, and urinary incontinence. Brain MRI showed a large, gadolinium-enhancing mass involving the corpus callosum and the frontal lobes and extending to the diencephalon. The patient slightly improved with corticosteroids but died after 4 months. Brain autopsy showed an invasive glioblastoma but no brain white matter or vascular wall abnormalities.

Case III-1. This 18-year-old woman is the sister of the proband (see the table). She had no remarkable medical history. Her

neurologic and fundus examinations were normal. Brain MRI was not performed.

Genetic studies. Genomic DNA direct sequencing of exons 3 and 4 of the *notch3* was performed for Case III-2 and did not detect any CADASIL type mutation. Genetic linkage analysis with chromosome 19 markers showed that for each of the 3 markers tested, 2 affected individuals did not share the haplotype transmitted by the affected founder, I-2, to the other affected members, which strongly suggests that this disorder is not linked to the CADASIL locus (figure 5).

Genetic linkage with chromosome 3 markers showed that for each of the 7 markers tested, which were fully informative, there were at least 2 affected individuals who did not inherit the allele transmitted by the affected founder (I-2) to the other affected offspring (see figure 5). These data strongly suggest that this disorder is not linked to the 3p21 hereditary vascular retinopathy/cerebroretinal vasculopathy/HERNS locus.

Discussion. We report a French Caucasian kindred affected over three generations by a retinal and CNS disease consistent with an autosomal dominant pattern of transmission. Six of eight family members were clinically symptomatic: infantile hemiparesis occurred in two patients, migraine with aura in three and retinal hemorrhage in one. Several arguments suggest that this disorder is due to a vasculopathy affecting both retinal and brain vessels. Retinal arteriolar tortuosity was found on fundus examination in five individuals and it was highly suspected in a sixth one who experienced retinal hemorrhage. With regard to cerebral involvement, several clinical and neuroimaging findings suggest a

vascular disease: the occurrence of an infantile hemiparesis in two patients and possibly in a third (Patient II-2); the presence of a silent, old, deep infarct on brain MRI in two other individuals; and the detection of multiple, small foci of decreased signal on T2*-weighted gradient echo images suggestive of microbleeds in Patient II-1, the sole individual in whom this sequence was performed. Interestingly, in addition to these neuroimaging findings, multiple, rounded, and well-delineated areas of hypointense signal on T1WI and hyperintense signal on T2WI located within the basal ganglia and the white matter were also observed in several patients. These images are consistent with dilated perivascular spaces, although it is quite difficult to conclude formally on the nature of the underlying lesions in the absence of neuropathologic data.^{18,19}

Several hereditary conditions have been reported to affect cerebral and retinal vessels, but they can be excluded in the current family based on clinical or genetic linkage analysis. CADASIL, an autosomal dominant small-artery disease of the brain, is characterized by the association of subcortical ischemic strokes, dementia, migraine with aura, and leukoencephalopathy.²⁰ Pathologic analysis showed that CADASIL is underlain by a systemic arteriopathy affecting mainly cerebral vessels but also other small vessels such as retinal vessels.²¹ However, the disorder reported is clearly distinguishable from CADASIL, as infantile hemiparesis, retinal hemorrhage, and arteriolar tortuosity have not been reported in CADASIL.^{20,22} Furthermore, the disease affecting the current family is not linked to CADASIL/*NOTCH3* locus on 19p13.¹⁷

This disorder is also clearly distinguishable from the three cerebroretinal hereditary conditions recently linked to 3p21. Indeed, retinal vascular lesions in those conditions include capillary occlusion, telangiectasia, and microaneurysms, which are absent in our family. In addition, genetic linkage analysis with chromosome 3p21 markers spanning the hereditary vascular retinopathy/cerebroretinal vasculopathy/HERNS locus showed that this disorder is not linked to 3p21.

The retinal vascular lesions observed in our family are identical to those observed in another autosomal dominant condition designated as hereditary retinal arteriolar tortuosity with retinal hemorrhages.⁸⁻¹⁵ The two conditions share marked tortuosity of the medium and small retinal arterioles and the absence of capillary abnormalities, venules tortuosity, retinal ischemic changes, or visual loss. However, hereditary retinal arteriolar tortuosity is known to affect only retinal vessels, except in one case of a migrainous patient with hereditary arteriolar tortuosity and multiple small areas of ischemia in the midbrain on brain MRI.¹⁵ Unfortunately, there was no MRI illustration provided in this report and there are no other neuroimaging data reported in patients with hereditary retinal arteriolar tortuosity.⁸⁻¹⁴

Ophthalmologic investigation of patients with unexplained perinatal ischemic stroke or young individuals with dilated perivascular spaces or brain white matter abnormalities may help to better define the relationship between retinal arteriolar tortuosity and cerebral vessel abnormalities. Gene identification of this novel hereditary cerebral and retinal vasculopathy should help to expand the spectrum of hereditary small vessel diseases of the brain.

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References

- Grand MG, Kaine J, Fulling K, et al. Cerebroretinal vasculopathy: a new hereditary syndrome. *Ophthalmology* 1988;95:649-659.
- Gutmann DH, Fischbeck KH, Sergott RC. Hereditary retinal vasculopathy with cerebral white matter lesions. *Am J Med Genet* 1989;34:217-220.
- Weil S, Reifemberger G, Dudel C, Yousry TA, Schriever S, Noachtar S. Cerebroretinal vasculopathy mimicking a brain tumor: a case of a rare hereditary syndrome. *Neurology* 1999;53:629-631.
- Jen J, Cohen AH, Yue Q, et al. Hereditary endotheliopathy with retinopathy, nephropathy, and stroke (HERNS). *Neurology* 1997;49:1322-1330.
- Storimans CWJM, Van Schooneveld MJ, Oosterhuis JA, Bos PJ. A new autosomal dominant vascular retinopathy syndrome. *Eur J Ophthalmol* 1991;1:73-78.
- Terwindt GM, Haan J, Ophoff RA, et al. Clinical and genetic analysis of a large Dutch family with autosomal dominant vascular retinopathy, migraine and Raynaud's phenomenon. *Brain* 1998;121:303-316.
- Ophoff RA, De Young J, Service SK, et al. Hereditary vascular retinopathy, cerebroretinal vasculopathy, and hereditary endotheliopathy with retinopathy, nephropathy, and stroke map to a single locus on chromosome 3p21.1-p21.3. *Am J Hum Genet* 2001;69:447-453.
- Beyer EM. Familiäre tortuosität der kleinen netzhautarterien mit makulablutung. *Klin Monatsbl Augenheilkd* 1958;132:532-539.
- Goldberg MF, Pollack IP, Green WR. Familial retinal arteriolar tortuosity with retinal hemorrhage. *Am J Ophthalmol* 1972;73:183-191.
- Kalina RE, Kaiser M. Familial retinal hemorrhage. *Am J Ophthalmol* 1972;74:252-255.
- Bartlett WJ, Price J. Familial retinal arteriolar tortuosity with retinal hemorrhage. *Am J Ophthalmol* 1983;95:556-558.
- Kayazawa F, Machida T. Retinal arteriolar tortuosity with macular hemorrhage. *Ann Ophthalmol* 1983;15:42-43.
- Wells CG, Kalina RE. Progressive inherited retinal arteriolar tortuosity with spontaneous retinal hemorrhages. *Ophthalmology* 1985;92:1015-1021.
- Clearkin LG, Rose H, Patterson A, Mody CH. Development of retinal arteriolar tortuosity in previously unaffected family members. *Trans Ophthalmol Soc UK* 1986;105:568-574.
- Sears J, Gilman J, Sternberg P. Inherited retinal arteriolar tortuosity with retinal hemorrhages. *Arch Ophthalmol* 1998;116:1185-1188.
- Joutel A, Vahedi K, Corpechot C, et al. Strong clustering and stereotyped nature of Notch3 mutations in CADASIL patients. *Lancet* 1997;350:1511-1515.
- Tournier-Lasserre E, Joutel A, Melki J, et al. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy maps to chromosome 19q12. *Nat Genet* 1993;3:256-259.
- Poirier J, Derouesne C. Cerebral lacunae. A proposed new classification. *Clin Neuropathol* 1984;3:266.
- Van Swieten JC, Van den Hout JHW, Van Ketel BA, Hijdra A, Wokke JH, van Gijn J. Periventricular lesions in the white matter on magnetic resonance imaging in the elderly. A morphometric correlation with arteriolosclerosis and dilated perivascular spaces. *Brain* 1991;114:761-774.
- Chabriat H, Vahedi K, Iba-Zizen MT, et al. Clinical Spectrum of CADASIL: a study of 7 families. *Lancet* 1995;346:934-939.
- Ruchoux MM, Guerouaou D, Vandenhoute G, Pruvo JP, Vermersch P, Leys D. Systemic vascular smooth muscle cell impairment in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy. *Acta Neuropathol* 1995;89:500-512.
- Robinson W, Galetta SL, McCluskey L, Forman MS, Balcer LJ. Retinal findings in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). *Surv Ophthalmol* 2001;45:445-448.

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K. Vahedi, P. Massin, J.-P. Guichard, et al.

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