Neonatal Porencephaly and Adult Stroke Related to Mutations in Collagen IV A1

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Objective: **The objective of this study was to describe leukoencephalopathy, lacunar infarcts, microbleeds and macrobleeds in the context of a collagen IV A1 mutation.** ***Methods:*** **We examined a family with autosomal dominant porencephaly, in whom a defect in collagen IV A1 was detected recently. The patients underwent neurological, ophthalmological, and cardiological examinations and magnetic resonance imaging of the brain. Electron microscopy of a skin biopsy was performed. Extensive laboratory screening was performed for thrombophilia and increased bleeding tendency.** ***Results:*** **The porencephaly was symptomatic in the infantile period in two patients, whereas it led to only minor neurological dysfunction in their affected mother. However, she experienced development of recurrent strokes in her 40s. In addition to the porencephaly, all patients had a leukoencephalopathy, which was most severe in the mother. Her magnetic resonance imaging results also showed lacunar infarcts, macrobleeds and a multitude of microbleeds. No other risk factors for recurrent stroke were found. Electron microscopy showed interruptions of the basement membrane of skin capillaries and inhomogeneous thickening of the basement membrane with pools of basement membrane fragments.** ***Interpretation:*** **Leukoencephalopathy, ischemic infarcts, microbleeds, and macrobleeds are indicative of an underlying microangiopathy, of which the best-known causes are hypertension, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, and cerebral amyloid angiopathy. Mutations in collagen IV A1, a major component of the vascular basement membrane, appear to be another risk factor.**

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Porencephaly is a term used to indicate a fluid-filled cavity that is in open communication with the lateral ventricle and is of antenatal or neonatal origin.[1] The most frequent cause is a *hemorrhagic infarction of periventricular tissue related to venous congestion or venous occlusion.*[2] Hemorrhagic venous infarctions occur most often in preterm infants after a germinal matrix hemorrhage and intraventricular hemorrhage, probably causing obstruction of the terminal veins.[2] The disease course is frequently complicated by hydrocephalus, related to the intraventricular blood. Other known risk factors for porencephaly are conditions that cause *thrombophilia,* including heterozygosity for factor V Arg506Gln mutation (factor V Leiden)[3–6] and deficiencies in the protein C anticoagulant pathway,[5] and conditions that cause *increased bleeding tendency* of the newborn, such as perinatal alloimmune thrombocytopenia, von Willebrand's disease, and maternal warfarin use.[4,7,8] Porencephaly can also be related to a *vasculopathy,* as caused by cocaine abuse of the mother or congenital infections.[4,9–11] Finally, porencephaly can be of *traumatic origin,* for instance, related to chorionic villous sampling, amniocentesis, or maternal abdominal trauma.[4,12]

Familial porencephaly with an autosomal dominant mode of inheritance has been reported several times.[13–23] In 2004, linkage to chromosome 13qter was described in a large Italian family.[24] In 2005, the genetic defect in this Italian family and in a Dutch family that Smit and colleagues[15] described earlier was found to reside in a defect in collagen IV A1.[25] The porencephaly related to collagen IV A1 mutations is most likely caused by an antenatal or perinatal intracerebral hemorrhage, although the hemorrhage has never been documented.[13–23] Mice carrying mutations in the *COL4A1* gene experience intracerebral hemorrhage in the perinatal period.[25] Gould and colleagues[25] ascribe the intracerebral hemorrhage to that collagen IV A1 mutations compromise the structural integrity of the vascular basal membrane, rendering vessels susceptible to disruption, especially at times of increased stress such as during parturition.

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Leukoencephalopathy in combination with lacunar infarcts, microbleeds, and macrobleeds is seen in adults and is considered to be an indication of microangiopathy.[26,27] It occurs in the context of several conditions affecting the vessel wall: hypertension,[28,29] cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL),[30–33] and cerebral amyloid angiopathy.[34–36]

In the Dutch family with autosomal dominant porencephaly related to a defect in collagen IV A1, we found, on reexamination of the affected members, a leukoencephalopathy in all three affected patients and lacunar infarcts, microbleeds, and macrobleeds in the oldest patient. It is likely that the collagen IV A1 defect not only led to perinatal hemorrhage and porencephaly, but also to a microangiopathy with later onset leukoencephalopathy and ischemic and hemorrhagic strokes.

Patients and Methods

The Dutch porencephaly family reported previously[15] was reexamined. The family consists of a healthy father, affected mother (Patient 1), affected son (Patient 2), and affected daughter (Patient 3). The second pregnancy of Patient 1 had ended in an unexplained stillbirth at a gestational age of 8 months.

The three patients underwent neurological, ophthalmological, and cardiological examinations. A skin biopsy was obtained for electron microscopy.

Laboratory investigations were performed in all patients to exclude increased bleeding tendency and included platelet count and function (positive irreversible aggregation after addition of adenosine diphosphate, collagen, and ristocetin), von Willebrand antigen and activity, α_2 antiplasmin, factor XIII, and activated partial thromboplastin time (APTT) and prothrombin time, to exclude a deficiency of relevant clotting factors. Thrombophilia screening included assessment of antigen levels of protein C and total and free protein S, activity of protein C and antithrombin, activated protein C resistance, factor V Leiden mutation and prothrombin mutation by polymerase chain reaction analysis, and screening for lupus anticoagulants using the Russel's Vipor Venom time and a lupus anticoagulant-sensitive APTT reagent (PT-LA). Total cholesterol, low- and high-density lipoprotein cholesterol, and triglyceride levels were assessed.

Magnetic resonance imaging (MRI) of the brain was performed. The MRI techniques included sagittal T1-weighted (TR, 570 milliseconds; TE, 15 milliseconds), axial T2-weighted (TR, 3,100 milliseconds; TE, 16 and 98 milliseconds), and axial fluid-attenuated inversion recovery (FLAIR) (TR, 9,000 milliseconds; TE, 105 milliseconds; inversion time, 2,000 milliseconds) images to assess morphological changes. In addition, axial fast low-angle shot (TR, 600 milliseconds; TE, 15 milliseconds; flip angle, 15 degrees) gradient-echo images were acquired to visualize the presence of small amounts of iron, such as that present in hemosiderin residues in old microbleeds. Magnetic resonance angiography was performed to visualize the large arteries at the base of the skull with a three-dimensional time-of-flight technique, using a three-dimensional gradient-echo sequence (TR, 39 milliseconds; TE, 6.5 milliseconds; flip angle, 20 degrees) optimized by magnetization transfer pulses and slab-variable flip angles.

Skin biopsies were fixed in 2% (vol/vol) glutaraldehyde for 30 minutes and 1.5% (wt/vol) osmium tetroxide for 10 minutes, dehydrated with acetone, and embedded in Epon 812 (Sigma, Zwigndrecht, Netherlands). Ultrathin sections were collected on 300-mesh Formavar-coated Nickel grids (Merck, Darmstadt, Germany). The sections were contrasted with uranyl acetate and lead citrate; they were examined using a Jeol 1200 EX electron microscope (Jeol Ltd, Tokyo, Japan).

Results

Patients

Patient 1 is a woman, who was born in 1951. She had an uneventful prenatal history and psychomotor development. At 4 years old, she underwent surgery for a divergent squint. At school she had learning problems and required speech therapy. She underwent a computed tomography (CT) scan of the brain at 24 years old, when her two children were diagnosed with porencephaly in the infantile period. CT scan showed porencephaly in the right frontal area and mild diffuse hypodensity of the cerebral white matter. At 42 years old, she experienced development of an acute left-sided hemiparesis including the face, related to a hemorrhage in the right frontal area. At 46 years old, she had an acute-onset expressive aphasia, related to a hemorrhage in the thalamus on the left. At that time, a mild hypertension of 160/90mm Hg was found, and treatment with nifedipine was instituted, leading to normalization of the blood pressure. The treatment with nifedipine was stopped after a few months, and her blood pressure remained normal. At 47 years old, she experienced development of an acute paresis of gaze to the right and a central facial paresis on the right, related to a hemorrhage in the pontine tegmentum. At 52 years old, she experienced development of an acute increase of the old hemiparesis on the left. CT scan did not show evidence of a fresh hemorrhage. At that time a bilateral cataract was diagnosed, for which she underwent cataract extraction on both sides.

Neurological examination at 54 years old indicated a mild expressive dysphasia. She had a left-sided esotropia. A central facial paresis on the left was present. Otherwise, cranial nerve function was normal. A serious left-sided spastic paresis with hyperreflexia and a Babinski sign was present, affecting the arm more seriously than the leg. She walked with support of a cane or used a wheelchair.

Ophthalmological examination showed status after cataract extraction and mild arteriolar tortuosity of the retinal vessels (Fig 1). Cardiological examination, including electrocardiogram and ultrasound, indicated no abnormalities. Blood pressure was 125/80mm Hg.

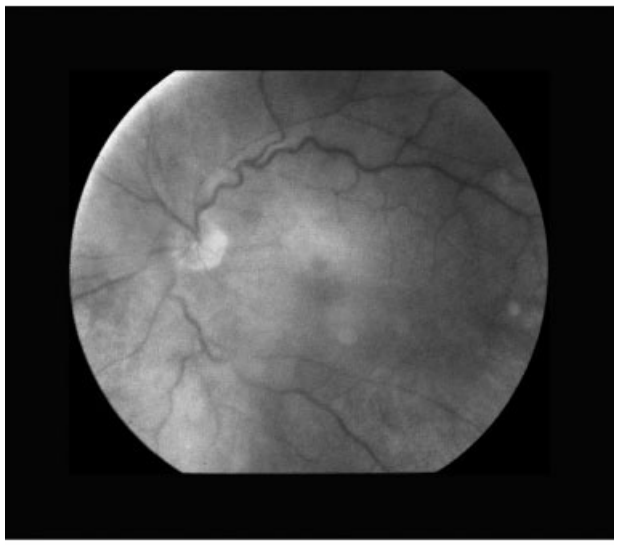

Fig 1. The fundus photo of Patient 1 shows a mild arteriolar tortuosity.

Patient 2, who was born in 1971, is the first child of Patient 1. Delivery took only a few minutes. He presented at the age of 8 months because of developmental delay. A hemiparesis on the right was noted. CT scan showed porencephalic cysts in both frontal areas, larger on the right than on the left. He achieved unsupported walking at the age of 3.5 years. He experienced seizures at 3 years old, which were controlled with antiepileptic medication. He acquired no active speech and had serious cognitive deficits.

Neurological examination at 33 years old showed a mild convergent squint and a mild central facial paresis on the right. There was evidence of pseudobulbar dysfunction with a brisk masseter reflex and continuous drooling. He could not speak and only uttered sounds. A severe spastic hemiparesis affected his right arm more than his right leg. Reflexes were increased on both sides, and bilateral Babinski signs were present. He could walk without support.

Ophthalmological examination showed an incipient polar cataract of both eyes. Retinal vessels were normal. Electrocardiogram and cardiac ultrasound indicated no abnormalities. Blood pressure was 130/60mm Hg.

Patient 3, who was born in 1974, also delivered in only a few minutes, is the third child of Patient 1. Six weeks after birth, she showed signs of a progressive hydrocephalus. Pneumoencephalography showed a marked dilatation of the right lateral ventricle and a midline shift to the left. A ventriculoperitoneal shunt was placed on the right. Follow-up CT scan showed destruction of large parts of the right hemisphere with multifocal calcium deposits in the remaining tissue and overdrainage of the right lateral ventricle. In the course of the first year of life, a left-sided hemiparesis became apparent. Her development was better than that of her brother. She achieved unsupported walking at 1.5 years old. Language development was delayed, but she did learn to speak. She experienced seizures at 5 years old, which were controlled with antiepileptic medication.

Neurological examination at 30 years old showed a mild divergent squint. Masseter reflex was positive. She had a mild central facial paresis on the left and pseudobulbar dysarthria. A serious left-sided hemiparesis was present, affecting the arm much more seriously than the leg. Reflexes were increased bilaterally, but higher on the left, with a Babinski sign on the left. She walked without support.

Ophthalmological examination indicated an incipient nuclear cataract of both eyes. Retinal vessels were normal. Electrocardiogram and cardiac ultrasound results were normal. Blood pressure was 110/70mm Hg.

Genetic Results

A heterozygous c.3706G⟩A mutation in the *COL4A1* gene was found in all three patients, whereas no mutation was detected in the father.[25] This mutation leads to a glycine-to-arginine change at protein level (p.Gly1236Arg). The same mutation was not present in 192 ethnically and geographically matched Dutch control chromosomes.[25]

Vascular Risk Factors

Laboratory investigations in Patients 1and 3 showed no abnormalities. In Patient 2, slightly reduced platelet counts (135×10^9/L) and free protein S levels were found, unlikely to induce clinical relevant bleeding or thrombosis. To exclude a persistent thrombocytopenia or protein S deficiency, we repeated platelet counts and total and free protein S levels, which we found to be normal.

Electron Microscopy of Skin Vessels

In Patient 1, focal interruptions of the basement membrane of capillaries were found, but the basement membrane was of normal thickness. In contrast, about 20% of the capillaries of Patients 2 and 3 displayed striking ultrastructural abnormalities. In these capillaries, the basement membrane of the endothelial cells showed an increase in thickness of up to 2,500nm (normal is approximately 40nm), with focal interruptions and formation of pools of fragmented basement membranes (Fig 2). In addition, the basement membrane of pericytes was increased in thickness, up to 500nm (normal is approximately 40nm) (not shown). Granular osmiophilic material, diagnostic of CADASIL, was not found in any of the patients.

Magnetic Resonance Imaging

MRI in Patient 1 at 47 years old showed a porencephalic enlargement of the right lateral ventricle (Fig 3), which was larger than a CT scan had shown 25 years

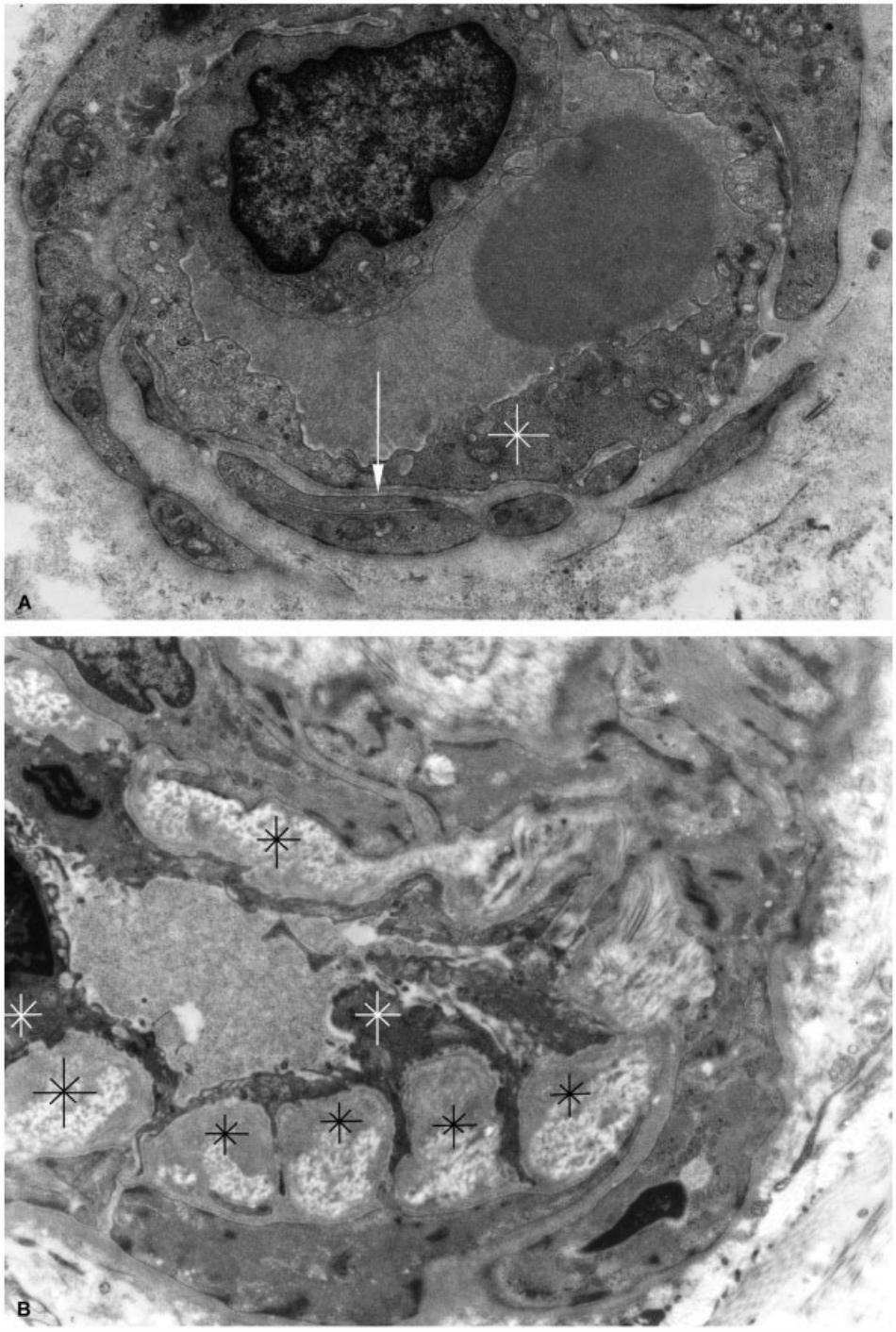

Fig 2. (A) Electron micrograph of a normal skin capillary of Patient 2 (magnification ×12,000). Arrow *indicates a normal basement membrane with a thickness of 40nm.* Asterisk *indicates an endothelial cell. (B) Abnormal skin capillary of Patient 2 (magnification ×15,000). The basement membrane* (black asterisks) *is 2,500nm thick and fragmented, resulting in pools of basement membrane fragments. Endothelial cells are indicated by* white asterisks.

before. In addition, a diffuse signal abnormality of the cerebral white matter was seen sparing the corpus callosum and the U-fibers (see Fig 3). Inhomogeneous, spotlike signal abnormalities were present in the basal ganglia on both sides. Multiple small intraparenchymal cystic lesions were present in the cerebral white matter and basal ganglia. The pyramidal tracts in the brainstem on the right were smaller than on the left, probably related to Wallerian degeneration. The gradient-echo images showed evidence of many small and larger

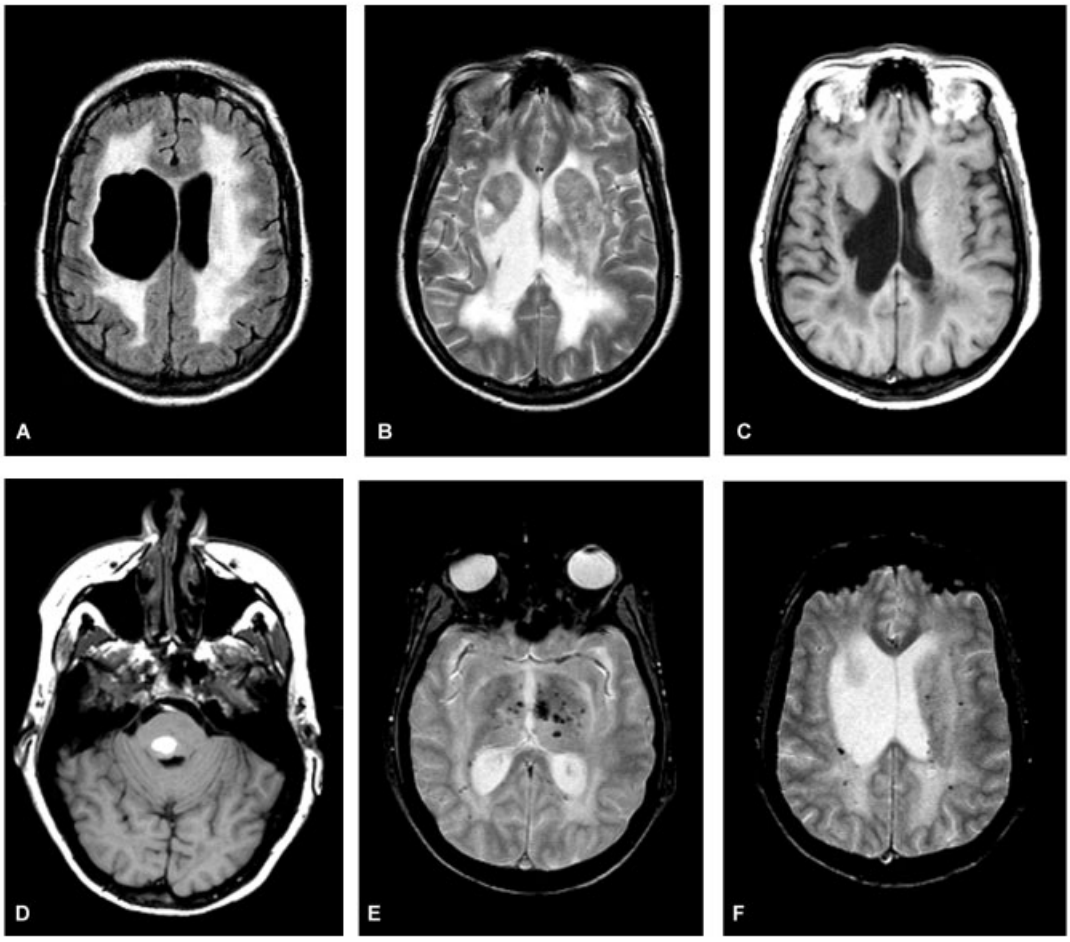

Fig 3. Magnetic resonance imaging of Patient 1 at 47 years old. The axial FLAIR (A) shows a porencephaly on the right and extensive cerebral white abnormalities, relatively sparing the U-fibers. The axial T2-weighted image (B) shows patchy signal abnormalities in the basal ganglia and thalamus. The T1-weighted image at the same level (C) demonstrates multiple small cystic lesions in the basal ganglia and white matter. The T1-weighted image at lower level (D) shows a fresh hemorrhage in the pontine tegmentum. The axial gradient-echo images (E, F) demonstrate many small old hemorrhages spread over the brain, most prominently involving the basal ganglia.

foci of hemosiderin deposition in the cerebral white matter, basal ganglia, thalami, brainstem, and cerebellum (see Fig 3). MR angiography of the large vessels at the base of the skull was normal.

MRI in Patient 2 at 33 years old showed the old porencephalic cysts in the frontal region on both sides (Fig 4), which were unchanged compared with a CT scan obtained 25 years before. The porencephalic cyst on the left was smaller than on the right and located more dorsally, also involving the pyramidal tracts. The pyramidal tracts in the brainstem on the left were smaller than on the right, probably related to Wallerian degeneration. T2-weighted and FLAIR showed increased signal of the periventricular and deep white matter (see Fig 4), of which there had been no evidence on the previous CT scan. The gradient-echo images showed no evidence of microbleeds (see Fig 4). MR angiography of the large vessels at the base of the skull did not show abnormalities.

MRI in Patient 3 at 30 years old showed a collapse of the shunted right lateral ventricle and a major destruction of the right hemisphere, which was comparable with what was seen on a CT scan 20 years before. There was a small subdural effusion on the right. The pyramidal tracts in the brainstem on the right were smaller than on the left, probably related to Wallerian degeneration. T2-weighted and FLAIR showed increased signal of the periventricular and deep white matter of the left hemisphere, of which there had been no evidence on the previous CT scan. Gradient-echo images showed no evidence of microhemorrhages. MR angiography of the large vessels at the base of the skull did not show abnormalities.

Discussion

Microbleeds occur in adults related to particular conditions and risk factors, affecting the wall of small vessels. They are best shown on T2*-weighted gradient-

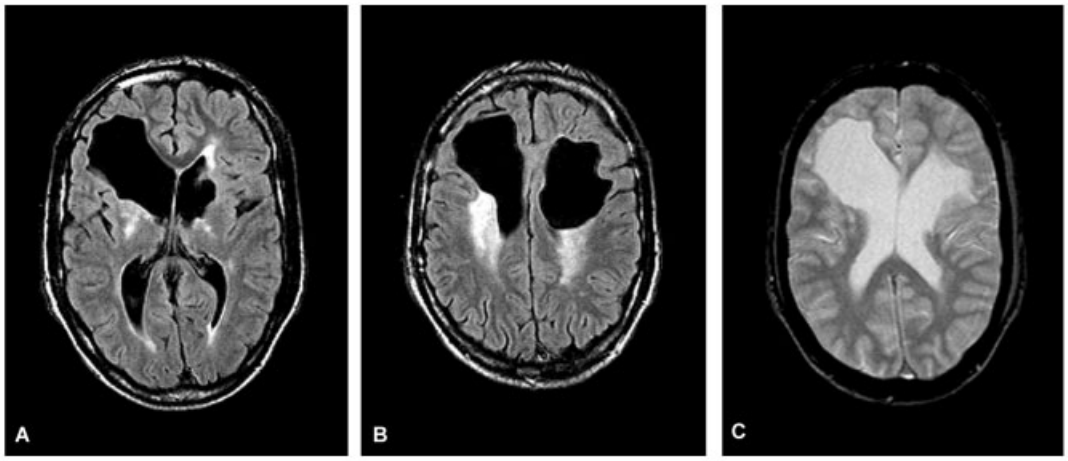

Fig 4. Magnetic resonance imaging of Patient 2 at 33 years old. The axial FLAIR (A, B) show bilateral porencephaly and signal abnormalities in the periventricular (A) and deep (B) cerebral white matter. The gradient-echo images (C) do not show evidence of old small hemorrhages.

echo images, which are sensitive to minor amounts of iron. Correlative MRI histopathology studies have shown that the black spots on T2*-weighted images are related to focal hemosiderin depositions, as evidence for preceding small hemorrhages.[37] Microbleeds do not occur in isolation. There is a linear correlation among microbleeds, cerebral white matter abnormalities, and lacunar infarcts, suggesting a shared pathogenesis: microangiopathy.[28,38] It has been shown that microbleeds are an indicator of the risk for subsequent spontaneous intracerebral hemorrhage, which is related to rupture of small- and medium-sized arteries.[39,40]

The small-vessel disease underlying leukoencephalopathy, lacunar infarcts, microbleeds, and macrobleeds may be of different types. One type is hypertension-induced fibrohyalinosis of small arteries, the most severe form being Binswanger's disease.[40,41] Other types of microangiopathy are CADASIL[30,31–33] and amyloid angiopathy.[34–36]

We describe leukoencephalopathy, lacunar lesions, microhemorrhages, and repeated macrohemorrhages in the context of familial porencephaly and a mutation in collagen IV A1. We suggest that the collagen IV A1 defect may be mainly responsible for the angiopathy. When the porencephaly was detected in her 20s, Patient 1 already had a leukoencephalopathy. She started to have recurrent hemorrhagic and ischemic strokes in her 40s. Her two affected children have a mild leukoencephalopathy in their early 30s, but no evidence of microbleeds. Considering the clinical history of Patient 1, it is probable that the lacunar infarcts, macrobleeds, and microbleeds are of later onset, and that Patients 2 and 3 may still experience them at a later age. Apart from the mutated collagen IV A1, no other significant risk factors were found. Patient 1 had hypertension at the time of the second stroke, but it was transient, mild, and present after the leukoencephalopathy had been documented for years, and she already had had an intracerebral hemorrhage. The hypertension is therefore insufficient to explain the leukoencephalopathy and hemorrhages, although it may have contributed to the microangiopathy.

Type IV collagens are ubiquitous basement membrane proteins, including vascular basement membrane. Collagens IV A1 and A2 are the most abundant type IV collagens and confer strength to basement membranes. Gould and colleagues[25] have shown that mutations in collagen IV A1 lead to focal disruptions of the vascular basement membrane and swelling of vascular endothelial cells with prominent vesicles. We found focal disruptions and a major increase in thickness of the vascular basement membrane of skin capillaries. Whereas focal disruptions of the vascular basement membrane may predispose to hemorrhage, the swelling of vascular endothelial cells and increased thickness of the basement membrane may lead to narrowing of vessels and predispose to ischemic damage.

There are two additional findings in this family. All affected members experienced development of cataract. In Patient 1, mild arteriolar tortuosity was found in the retina. Recently, an autosomal dominant syndrome characterized by infantile onset hemiparesis, retinal arteriolar tortuosity, leukoencephalopathy, and microbleeds was reported.[42] Although none of the patients described in that article had cataract, it is possible that the patients who Vahedi and colleagues[42] reported also have a mutation in the *COL4A1* gene.

It is known that not all obligate carriers of familial porencephaly have evidence of porencephaly on neuroimaging.[22] This indicates that it is possible that leukoencephalopathy, lacunar infarcts, microbleeds, and macrobleeds are seen in patients with collagen IV A1

mutations in absence of porencephaly. Mutations in *COL4A1* and perhaps also mutations in *COL4A2,* encoding collagen IV A2, and other genes encoding vascular basement membrane-associated proteins may be responsible for recurrent hemorrhagic and ischemic strokes in adults. An even more likely possibility is that polymorphisms in such genes, which are not disease causing in themselves, are risk factors predisposing to hemorrhagic and ischemic stroke in adults and act in conjunction with other risk factors such as hypertension. Larger studies screening adults with stroke at a relatively young age or recurrent stroke in the presence of evidence of an underlying microangiopathy, as indicated by the presence of microhemorrhages on T2*-weighted MRIs, for mutations and polymorphisms in collagen genes or genes encoding other basement membrane proteins are warranted.

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