

Extensive brain calcifications, leukodystrophy, and formation of parenchymal cysts:

A new progressive disorder due to diffuse cerebral microangiopathy

P. Labrune, MD; C. Lacroix, MD; F. Goutières, MD; J. de Laveaucoupet, MD; P. Chevalier, MD; M. Zerah, MD; B. Husson, MD; and P. Landrieu, MD

Article abstract—A new cerebral disorder, described in three unrelated children, has recognizable clinical, radiologic, and neuropathologic findings. The onset occurs from early infancy to adolescence with slowing of cognitive performance, rare convulsive seizures, and a mixture of extrapyramidal, cerebellar, and pyramidal signs. CT shows progressive calcifications in the basal and cerebellar gray nuclei and the central white matter. MRI reveals diffuse abnormal signals of the white matter on T₂-weighted sequences. A special feature is the development of parenchymal cysts in the cerebellum and the supratentorial compartment, leading to compressive complications and surgical considerations. Neuropathologic examination of surgically removed pericyclic samples reveals angiomatous-like rearrangements of the microvessels, together with degenerative secondary changes of other cellular elements. Both the anatomic findings and the course of the disease suggest a constitutional, diffuse cerebral microangiopathy resulting in microcystic, then macrocystic, parenchymal degeneration.

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The finding, on cerebral imaging, of multiple calcifications in central nuclei and of abnormal signals on the white matter is relatively unusual in children, but this occurs in a variety of situations, both congenital and acquired (reviewed in reference 1). Because systemic disease is not usually present and pathologic examination is not performed, most of these lesions remain obscure in origin. We report three children presenting with such calcifications, in whom the slow clinical course, the extension of the calcifying changes to the white matter, and the cystic evolution of the lesions make it possible to delineate a specific syndrome.

Case reports. *Case 1.* This girl, the first daughter of healthy, unrelated parents, was born after an uneventful pregnancy. At 4 years of age, a skull radiograph fortuitously showed intracranial calcifications judged to be located in choroid plexi. At 11 years of age, she had a first generalized seizure. Examination noted only a slow speech pattern and speech therapy was pursued for several years. Neurologic, ophthalmologic, and psychological examinations were considered normal. CT and MRI were done (figures 1A, 2A and B). During the following months she developed a progressive ataxia. At 12 years, she was readmitted with signs of high intracranial pressure due to

a voluminous cerebellar cyst that sequential imaging showed to have developed within the previous year (figure 3A). The cyst was surgically removed and clinical improvement ensued. During the following 2 years, recurring tonic-clonic seizures required anticonvulsant therapy (valproate and vigabatrin), cerebellar ataxia slowly worsened, and intellectual performance declined. At 14 years, symptoms of intracranial hypertension, deterioration of visual condition, slight right hemiparesis, and left third-nerve palsy led to the discovery of a new, expanding interventricular cyst. Numerous surgical procedures were performed during the following months: puncture of the cyst under stereotaxic conditions, ventriculoscopic perforation of the cyst into the left ventricular cavity, direct surgical approach to break down the cyst into the ventricle with the aid of a balloon, placement of a lumboperitoneal shunt (soon complicated by infection), and finally placement of a ventriculoperitoneal shunt. At 15 years, the girl is bedridden but capable of communicating with her close relations, and her condition is slowly ameliorating. She is handicapped by severe bulbar symptoms and by blindness with bilateral optic atrophy, probably related to both the natural progression of the disease and past periods of uncontrolled intracranial hypertension.

Case 2. This boy was born after an uneventful pregnancy. The parents are unrelated and healthy. A brother was stillborn and had cephalic dysmorphism but this was not

From the Department of Pediatrics (Drs. Labrune and Chevalier) and the Department of Radiology (Dr. de Laveaucoupet), Hôpital Beclère, Clamart; the Unit of Pediatric Neurology (Dr. Goutières) and the Department of Neurosurgery (Dr. Zerah), Hôpital Necker-Enfants Malades, Paris; the Laboratory of Neuropathology (Dr. Lacroix, Dr. Landrieu), the Department of Pediatric Radiology (Dr. Husson), and the Department of Pediatric Neurology (Dr. Landrieu), Hôpital de Bicêtre, France.

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Address correspondence and reprint requests to Dr. P. Labrune, S de Pédiatrie, Hôpital A, Beclère 92140, Clamart, France.

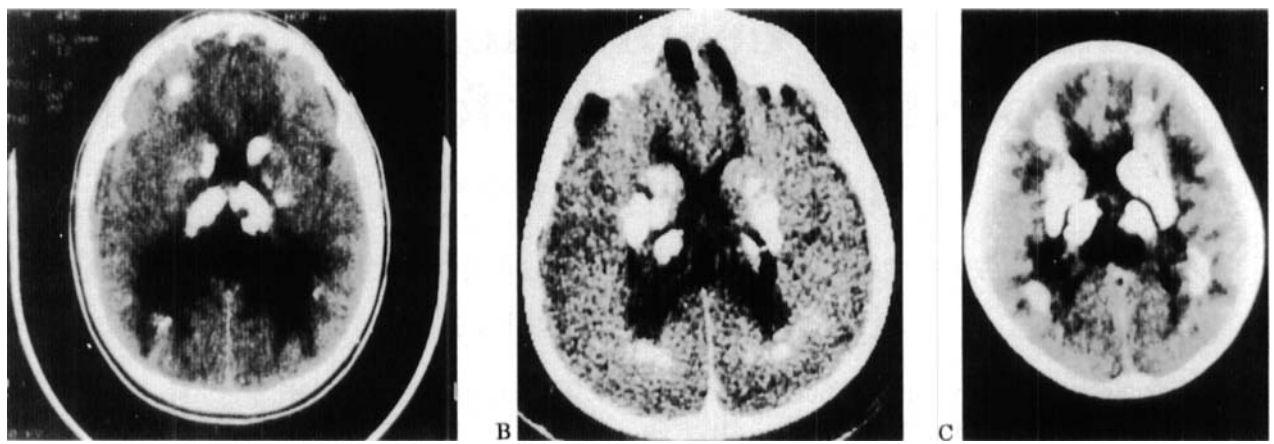


Figure 1. Brain calcifications. Brain CT examination in the three patients: (A) patient 1; (B) patient 2; (C) patient 3. Extensive calcifications are seen in the periventricular white matter and in the basal ganglia. Note also the diffuse hypodense lesions in the periventricular white matter.

investigated further. An older sister is clinically normal. He was admitted at 5 years of age for an acute ataxic syndrome, which resolved in a few days. At that time CT revealed brain calcifications (figure 1A), and MRI was performed (figure 2C). He had been followed since infancy for developmental delay and the Denver test showed a homogenous level of 3.5 years. He had infrequent, generalized, tonic-clonic seizures since 4 years of age, treated with valproate. From birth, he had multiple cafe au lait spots that increased with time. Axillar freckling was present at 5 years, confirming the von Recklinghausen trait. After 18 months follow-up, the patient developed a slight, progressive left-sided hemiparesis due to a right paraventricular, progressively expanding cyst. Surgery has not been performed.

Case 3. This girl, the only child of healthy, unrelated parents, was born after normal pregnancy. At 3 months of age she experienced right-sided convulsive seizures over a 4-day period and was given phenobarbital for 6 months. CT was normal. At 3 years and 10 months of age, bilateral intracranial calcifications were fortuitously discovered on a skull radiograph. Clinical examination was normal and IQ was 107. CT then confirmed extensive brain calcifications (figure 1C). Starting at 5 years of age, learning performance slowed down and speech retardation developed. After 5 years and 10 months of age, progressive right-sided hemiparesis and dystonia, dysarthria, and expressionless

face appeared. At 7 years mental performance was that of a 4-year-old. Optic fundi were normal. When 8 years old, her condition suddenly worsened, with signs of intracranial hypertension, cerebellar ataxia, brainstem dysfunction with permanent gaze deviation to the right, left horizontal nystagmus, swallowing difficulties, and peripheral left facial nerve palsy. A large cerebellar cyst was discovered that was adjacent to the floor of the fourth ventricle and produced obstructive hydrocephalus. In addition, two supratentorial cysts were bulging in both occipital horns (figure 3B). Surgical puncture of the posterior fossa cyst showed a 3,500 mg/dL protein-rich fluid containing a few macrophages. The clinical condition improved, but 3 months later worsened again. Empiric treatment with prednisone did not help. At 9 years of age, a second episode of increased intracranial pressure led to the surgical opening of the cerebellar cyst in the fourth ventricle and of the right lateral ventricular cyst in the occipital horn. Her status continued to deteriorate despite correct CSF shunting and at 14 years of age she was wheelchair-bound with quadriplegia, bilateral dystonia, anarthria, peripheral facial diplegia, and palatal myoclonus. However, she remained alert and communication by gesture remained possible.

Laboratory investigations. In all three patients, routine biologic investigations, including phosphocalcium me-

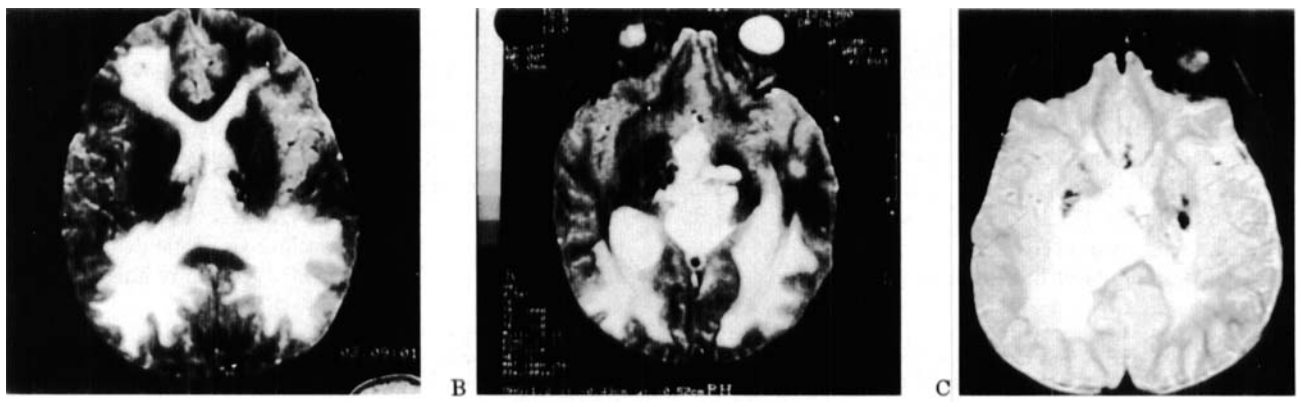


Figure 2. Leukodystrophic changes. MRI T_2 -weighted sequences in (A and B) patient 1 and (C) patient 2. Hypersignal is seen in the periventricular white matter, mainly in the posterior area.

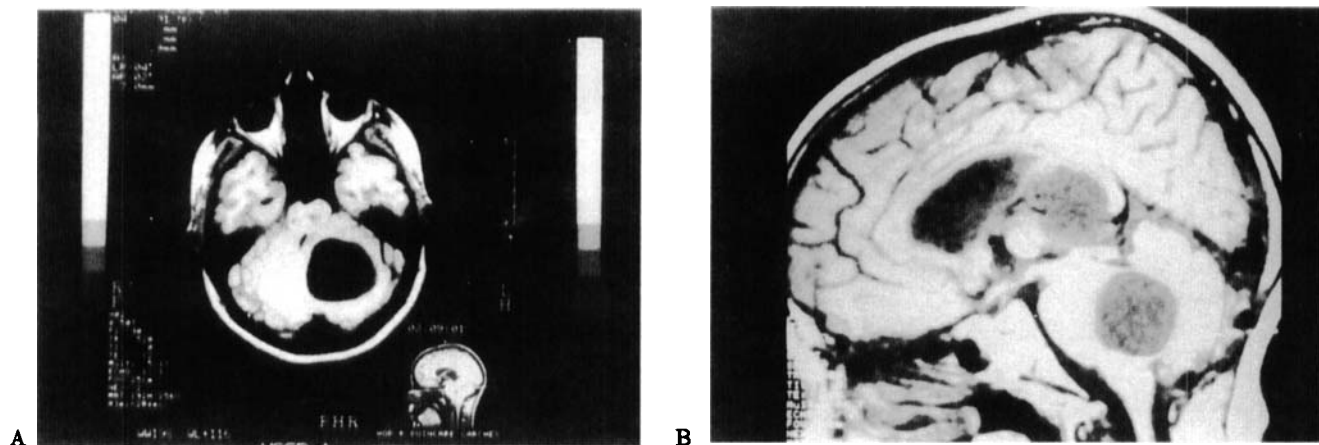


Figure 3. Cystic degeneration. Brain MRI showing cystic lesions in the patients. (A) patient 1 (age 12). Voluminous cerebellar cyst with mass effect on the fourth ventricle. (B) T_1 -weighted sequence in patient 3. A large posterior fossa cyst compresses the fourth ventricle (not apparent at this level) and the brainstem. There is a large supratentorial cyst bulging in the lumen of the lateral ventricle.

tabolism and studies for systemic inflammatory signs and for abnormal substrates in urine, blood, and CSF lactate and pyruvate, were normal or negative. Routine CSF analysis was normal in patients 1 and 2 and showed 310 mg/dL protein and 1 WBC/mm³ in patient 3. CSF electrophoresis of proteins showed normal profile in the three patients. CSF myelin basic protein could not be measured in any patient. Tests for serum and CSF antibodies for cytomegalovirus, rubella, human immunodeficiency virus, and toxoplasmosis in patients 1 and 3 and for varicella zoster, measles, herpes, mumps, and HTLV1 in patient 3 were negative. In patient 3, muscle histochemistry was unremarkable and respiratory chain functions were normal in both muscle and lymphocytes. In patient 2 and his parents, a molecular investigation of the NF1 locus using 2 CA repeat markers showed no gross rearrangement.

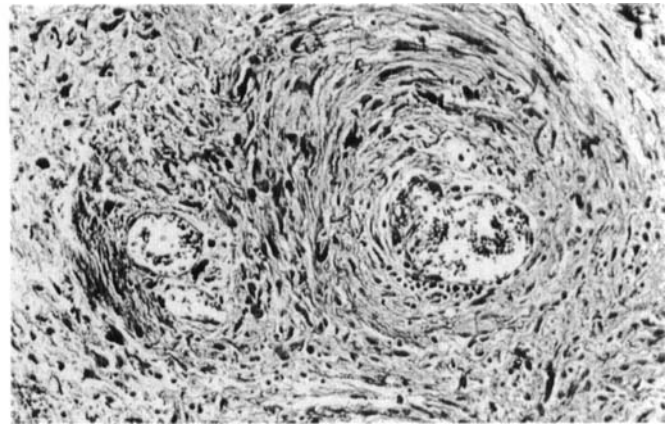
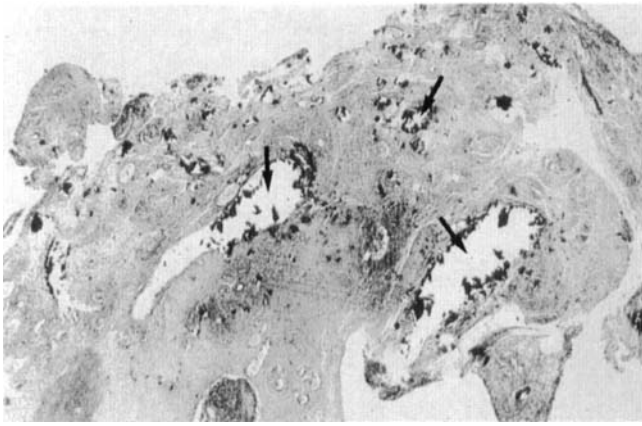
Cerebral imaging. In all three patients, brain CT showed extensive calcifications in the basal ganglia and the periventricular white matter (figure 1). Calcifications were also prominent in the centrum ovale (patients 1 [figure 1A] and 3 [figure 1C]), cerebellar white matter or dentate nuclei (patients 1 and 3), and the ventral pons (patient 3). CT also showed marked hypodensity in the periventricular white matter (figure 1A and C). MRI studies gave similar results in the three patients; T_2 -weighted sequences showed a diffuse hypersignal in the periventricular white matter, mainly in the posterior areas (figure 2). The second hallmark of brain MRI was the formation of cystic lesions in the cerebellum (figure 3) and in the supratentorial region, mainly in the interhemispheric area (figure 3B). Arteriography was performed in patient 1 and was normal. No imaging was performed in the parents or siblings.

Pathologic data. In patient 1, different samples were taken during the surgical operation around the cerebellar cyst. The cortex had no abnormalities. The specimen of white matter showed demyelination and astrocytic changes such as microcystic degeneration. The most prominent finding was the angiomatous changes in the vascularity of the parenchyma: numerous small, tortuous blood vessels, either contiguous or separated by areas of nervous

tissue, exhibited normal endothelial lamina but irregular, often calcified wall (figure 4A). They were surrounded by many whirled and irregular Rosenthal fibers, eosinophilic bodies, microcalcifications, and ferric iron deposits (figure 4B). Using an orcein technique, no elastic fibers were detected in the abnormal vessel walls, whereas some were present in the normal ones. Many of the Rosenthal fibers were stained by the glial acid fibrillar protein antibody. Neurofilament antibodies stained a few preserved axons between Rosenthal fibers. In some areas, dense hyaline deposits, showing no amyloid substance on Congo red staining, were associated with large, calcified blood vessels. The small samples obtained during ventriculocopy of the interventricular cyst showed only reactive gliosis and necrosis. Samples of the walls of the cerebellar and of the supratentorial cysts were obtained in patient 3. Similar exuberant proliferation of abnormal small vessels was present, associated with Rosenthal fibers, intense gliosis, and microcalcifications (figure 4C). No ultrastructural study could be performed.

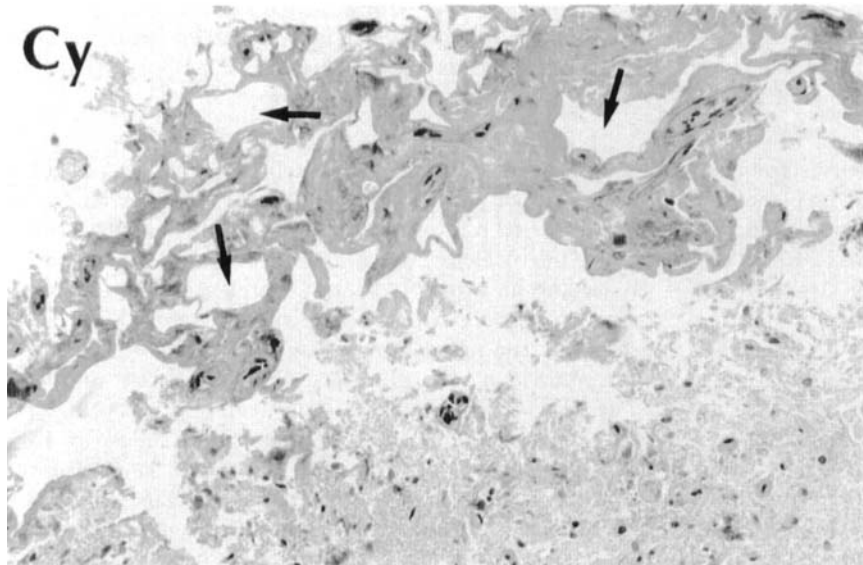
Discussion. Within the heterogeneous group of cerebral calcification disorders of childhood,¹⁻³ the present cases have features that delineate a separate condition: (1) onset with a slow, predominantly non-cortical cerebral degradation; (2) prominent calcifications of basal ganglia extending to cerebellar and brainstem nuclei, and to the white matter; (3) diffuse hyperintense signals of the white matter on T_2 -weighted MRI sequences; and (4) the development of parenchymatous cysts. These expanding cystic formations could possibly be due to a localized necrotic process leading to a progressive accumulation of increased osmotic fluid, a phenomenon encountered in other conditions exhibiting signs of slow astrocytic degeneration, especially in the cerebellum, such as astrocytoma, capillary hemangioblastoma, or Alexander disease.⁴

The more striking and probably primary pathologic rearrangements were those involving the microvessels, whereas perivascular foci of calcifications, hyaline deposits, and formation of Rosenthal fibers



A

B



C

Figure 4. Vascular abnormalities. (A) Patient 1. Calcified large angiomatous vessels (arrows) in the cerebellar white matter in the vicinity of the cyst. Bodian stain $\times 75$, before 31.6% reduction. (B) Patient 1. Cerebellar white matter with pseudoangiomatous blood vessels surrounded by numerous irregular Rosenthal fibers. Bodian stain $\times 60$, before 31.6% reduction. (C) Patient 3. Fibrous angiomatous-like vessels (arrows) in the white matter in contact with the cerebellar cyst (Cy). H-E stain $\times 600$, before 8.3% reduction.

appeared compatible with secondary changes. There being no evidence for an inflammatory or tumoral angiopathy, a dysplastic, angiomatous-like process appears likely. That no anomalies were visible on the different angiographic sequences confirms that the dystrophic process is limited to the small vessels. Classical or rare angiomatous dysplastic syndromes can be ruled out, such as Von Hippel-Lindau disease and "familial noncalcified corticomeningeal angiomatosis with progressive demyelination of the white matter";^{5,6} these are clearly different both clinically and anatomically. In Sturge-Weber syndrome, the most common syndrome with cerebral angioma leading to progressive calcifications, the clinical and radiologic differences are obvious. The morphologic process also appears different, presenting with a juxtaposition of numerous microvenular structures predominating in the pia mater of certain cortical regions, in contrast with the present disorder, in which exuberant and irregular capillaries are diffusely proliferating in the deep structures of the brain. However, some pathogenetic mechanisms in Sturge-Weber syndrome could be relevant to the present condition, such as major blood stasis and alteration of wall permeability, resulting in hypoxic changes,

reactive gliosis, and calcium deposits.⁷ Such chronic processes probably also explain the secondary white matter changes observed in both disorders, accounting for, in the present cases, a high proton density on MRI, and demyelination on the neuropathologic examination.

The cystic complications of the disorder require delicate and repeated surgical interventions. Further pathologic studies, extending beyond the cystic wall, might better characterize this rare disorder.

Acknowledgments

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Stroke recurrence in patients with patent foramen ovale:

The Lausanne Study

J. Bogousslavsky, MD; S. Garazi, MD; X. Jeanrenaud, MD; N. Aebischer, MD; and G. Van Melle, PhD for the Lausanne Stroke with Paradoxal Embolism Study Group

Article abstract—Patent foramen ovale (PFO) is more common in patients with stroke than in matched controls, but the stroke mechanism and late prognosis are not well known. We studied features, coexisting causes, and recurrences of stroke in 140 consecutive patients (mean age 44 ± 14 years) with stroke and PFO admitted to a population-based primary-care center. We selected the patients from 340 patients (41%) aged ≤ 60 years with acute stroke. The initial event was brain infarction in 118 patients (84%) and TIA in 22 (16%). Intracranial embolic occlusions were present on angiography or transcranial Doppler in most patients admitted within 12 hours of onset, whereas a venous source was clinically apparent in only six patients (5.5%). Pulmonary embolism, Valsalva maneuver at onset, and coagulation abnormalities were rare, but one-fourth of the patients had an interatrial septum aneurysm (ISA) that coexisted with PFO. An alternative cause of stroke was present in only 22 patients (16%), usually cardiac (atrial fibrillation, severe mitral valve prolapse, akinetic left ventricular segment). During a mean follow-up of 3 years, the stroke or death rate was 2.4% per year, but only eight patients had a recurrent infarct (1.9% per year). This low rate of recurrence contrasted with the severity of initial stroke, which left disabling sequelae in one-half the patients. Multivariate analysis showed that interatrial communication, a history of recent migraine, posterior cerebral artery territory infarct, and a coexisting cause of stroke were associated with recurrence, whereas ISA and treatment type (coagulant or antiaggregant therapy, surgical closure of PFO) were not. However, given the low number of events, these findings must be taken with caution. In conclusion, our study shows that stroke associated with PFO with or without ISA is not commonly due to a coexisting cause of stroke. It is usually embolic, although a definite source cannot often be demonstrated. The presenting stroke is often severe, but recurrence is uncommon. The demonstration of factors associated with a higher risk of recurrence in subgroups of patients is critical for the long-term management of these patients.

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During the last decade, there has been a progressive emphasis on the role of interatrial septal abnormalities, including patent foramen ovale (PFO) and interatrial septum aneurysm (ISA), in the genesis of ischemic stroke in young adults.¹⁻⁶ Indeed, there is a significant association between PFO, ISA, and stroke of otherwise undetermined origin in case-control studies.⁷⁻⁹ Paradoxical embolism from a venous source through a right-to-left shunt is usually incriminated,^{1,5,8} but direct evidence for paradoxical embolism is commonly lacking,^{3,9,10} and systematic screening for deep venous thrombosis in the lower limbs or pelvis has led to extremely variable estimates.^{9,11} Despite these ongoing controversies, the possibility of paradoxical embolism is commonly re-

tained in young patients with ischemic stroke and PFO without another cause of stroke.^{5,6,9} Moreover, ISA may contribute to increased risk of paradoxical embolism in patients with PFO, and may even act as a direct source of embolism.^{9,12} For these reasons, patients with stroke and PFO or ISA are commonly given antithrombotic therapy (platelet antiaggregating drugs, anticoagulants) for secondary prevention.¹³⁻¹⁵ There has been advocacy for more invasive treatments, such as surgical or transcatheter closure of PFO, in selected cases.¹⁶⁻¹⁹ However, the natural history of patients with stroke and interatrial septum abnormality is not known, so that preventive therapy is based only on a *presumed* risk of stroke recurrence.

From the Department of Neurology (Drs. Bogousslavsky and Garazi), and the Division of Cardiology (Drs. Jeanrenaud and Aebischer), University Hospital; and the University of Social and Preventive Medicine (Dr. Van Melle), Lausanne, Switzerland.

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Address correspondence and reprint requests to Dr. J. Bogousslavsky, Department of Neurology, CHUV, CH-1011 Lausanne, Switzerland.

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P. Labrune, C. Lacroix, F. Goutières, et al.

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