

muscle vessels, we observed identical material localized within the laminar layer at the basement of the VSMC or scattered between the VSMC. In capillaries, despite the absence of elastica lamina, this granular material is also present, which suggests that this material does not originate from the elastica lamina as previously thought.⁸ The primary phenomenon might involve the VSMC, which are strikingly altered in skin and muscle vessels as well as in brain arteries in patients with CADASIL.^{2,4}

The pathophysiological significance and the specificity of these ultrastructural arterial lesions, particularly of the granular material, are unknown. The sensitivity and specificity of their presence in skin and muscle vessels should be evaluated in a case-control study. If the present results are confirmed, ultrastructural study of skin punch or muscle biopsy might be of crucial diagnostic value in patients with CADASIL, particularly in atypical or sporadic cases.

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Marie-Magdeleine Ruchoux, MD, PhD
Laboratoire de Neuropathologie
CHRU
Lille

Hugues Chabriat, MD
Marie-Germaine Bousser, MD
Service de Neurologie

Marielle Baudrimont, MD, PhD
Service d'Anatomie Pathologique
Hôpital Saint Antoine

Elisabeth Tournier-Lasserre, MD
INSERM U25
Faculté de Médecine de Necker
Paris, France

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Epileptic Seizures Heralding Intracerebral Hemorrhage

To the Editor:

The term "vascular precursor epilepsy" indicates seizures caused by cerebrovascular disease and occurring prior to a stroke,^{1,2} thus

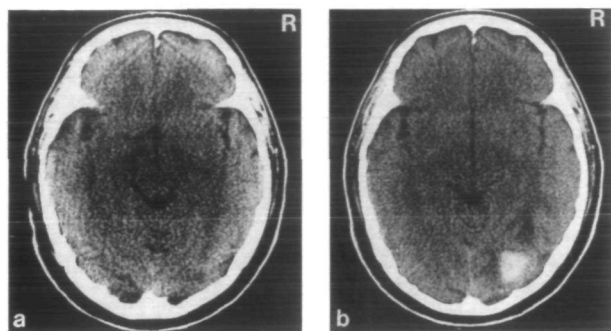
being a warning sign of a major cerebrovascular event. Although this definition includes no assumption about the type of stroke the seizures precede, it is generally assumed that seizures may herald ischemic but not hemorrhagic strokes.^{3,4} In fact, only very few and poorly documented cases of seizures occurring prior to a primary intracerebral hemorrhage (ICH) have been reported.^{1,5} Recent studies on epileptic seizures in the course of ICH⁶⁻⁸ give no account of heralding seizures, and in our series of 82 consecutive cases of ICH no patient had seizures preceding the stroke.⁹ However, we recently observed a patient whose new-onset seizures, having occurred prior to an ICH, suggested a relation between the two clinical entities.

A 55-year-old man began to experience sudden visual sensations of moving spots of light and more complex and formed visual hallucinations (geometric figures and written words) in his left visual field, where he also saw the objects distorted. The symptoms resolved completely within a few minutes, but the spells recurred several times daily; on the day after onset one of them rapidly progressed to a generalized tonic-clonic seizure. He was taken to an emergency unit, where an immediate computed tomographic (CT) scan revealed no brain lesions, and then to the neurology department of the University of Genova. On admission he reported mild hypertension, but no history of epilepsy, migraine, stroke, or head trauma. Physical and neurological examinations were unremarkable except for a blood pressure of 170/110 mm Hg. Findings on repeat CT scan with contrast enhancement (Fig 1a), magnetic resonance imaging (MRI), ^{99m}Tc-HMPAO (^{99m}Tc-hexamethylpropyleneamine oxine)—single photon emission computed tomography, and Doppler sonography were normal. An electroencephalogram revealed slow and sharp waves over the right occipital region. The patient was diagnosed as having cryptogenic late-onset partial seizures (visual) with secondary generalization, and antiepileptic treatment with carbamazepine and phenobarbital was started. Two months later, he came to the hospital again because of another spell of visual hallucination followed by sustained left hemianopsia; an MRI of the brain indicated a right occipital hemorrhage, which was confirmed by CT (Fig 1b). Transfemoral four-vessel angiography showed neither arteriovenous malformations nor signs of cerebral neoplasm, and the final diagnosis was lobar primary ICH. The patient improved, and serial CT scans showed a gradual resorption of hemorrhage without evidence of underlying lesion; he was put on antiepileptic and antihypertensive treatment and discharged from the hospital. During a 5-year follow-up his neurological status has been unchanged, indicating only mild left hemianopsia, and repeat neuroimaging revealed no further lesions of the brain. He is now seizure-free but still on antiepileptic treatment.

The patient had new-onset epileptic seizures prior to an ICH. An extensive neurological evaluation was done both at the onset of seizures and after the stroke. When epilepsy was the only symptom, the absence of any structural lesions of the brain warranted a diagnosis of cryptogenic late-onset seizures. After the hemorrhage, appropriate investigations and follow-up ruled out arteriovenous malformations and other underlying lesions, thus confirming the diagnosis of primary ICH.

Epilepsy and ICH were related in time (2 months) as well as in space (right occipital lobe); a coincidental association is therefore unlikely, despite the high frequency of both diseases in later life.

The mechanisms by which seizures should herald an ICH are hard to conceive. In the case of cerebral infarction, ischemia may account for both seizures and stroke, or a silent ischemic lesion could be responsible for seizures occurring before a symptomatic stroke.^{9,10} Obviously, neither explanation can directly relate epileptic seizures to hemorrhage. Cortical iron injection causes acute epileptiform activity in experimental models,¹¹ and this finding has been claimed to account for posttraumatic and poststroke epilepsy.^{6,7} However, the relevance of this model to this case is questionable, because no hemorrhagic lesions (unless clinically silent) had ever occurred when seizures started.



Findings on computed tomography 8 days after the onset of seizures, showing the absence of any structural lesions of the brain (a), and immediately after the stroke, showing a right (R) occipital hemorrhage (b).

This case raises the more general issue of the frequency, characteristics, and mechanisms of transient episodes preceding an hemorrhagic stroke. Indeed, transient neurological deficits, possibly resulting from a concurrent cerebral ischemia related to the underlying vascular disease, have been reported to herald an ICH in about 7% of patients.¹² Taking for granted that a subclinical cerebral ischemia can trigger epileptic seizures,¹³ we suggest that the same determinants might be responsible for both paralytic and irritative manifestations, although seizures are less common than transient neurological deficits, and both are more likely to occur before a cerebral infarction than before a cerebral hemorrhage. As to the latter, the role of amyloid angiopathy should be emphasized, as well as that of atherosclerotic disease, because amyloid angiopathy may be responsible for both ischemic and hemorrhagic damage in the same patient.^{14,15}

In fact, our patient bears some similarities to another patient, described by Smith et al,¹⁴ in whom surgery revealed pathological features of amyloid angiopathy, and even more with patient 3 in the report by Greenberg et al.¹⁵ The latter patient, who was clinically diagnosed as having amyloid angiopathy, presented with transient visual spells regarded as epileptic seizures possibly due to a small hemorrhage that may have heralded a larger one¹⁵; this hypothesis, however, was not verified because neuroimaging was available only after the stroke. In our patient there was no CT or MRI evidence of hemorrhage at the time of seizures, which indirectly favors the role of an ischemic mechanism rather than that of petechial hemorrhages.¹⁵ He may have amyloid angiopathy, although a 5-year follow-up indicated neither recurrences of ICH nor dementia.¹⁶ The existence of a cryptogenic hamartoma too small for angiographic detection, though unlikely, cannot be definitely ruled out since pathological findings were not available.

In conclusion, the occurrence of seizures prior to a stroke does not necessarily imply that a cerebral infarction has taken place. In fact, seizures heralding ICH, though uncommon, do occur. Although the mechanism is still obscure, the triggering role of a subclinical ischemia related to the underlying vascular disease should be considered, at least in principle.

Leonardo Cocito, MD
Raffaella Nizzo, MD
Nicoletta Bisio, MD
Emillo Favale, MD

Clinica Neurologica dell'Università di Genova
Genova, Italy

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Silent Infarctions in First-Ever Stroke Patients

To the Editor:

We read with interest the article by Jørgensen et al¹ about silent infarction in acute stroke patients and wish to congratulate the authors for this very important and stimulating contribution. They are kind enough to quote our own work on the same topic,² making interesting comparisons; however, they make two small mistakes that we would like to correct.

(1) They write that we defined a poor outcome as "death or persistence of physical handicap." Actually, we defined handicap (both physical and functional) in terms of the Rankin Scale, a validated method for measuring the outcome of stroke.² We agree that "smaller differences in outcome may not be recognized with these end points," but this is probably also a problem with the Barthel Index, which Jørgensen et al used.

(2) They write that "only 56% of the patients had CT [computed tomographic] scan," but in fact all 209 patients we studied were scanned within 30 days after stroke. They represent 56% of the registered stroke cases in the Studio Epidemiologico sull' Incidenza delle Vasculopatie Acute Cerebrali (SEPIVAC) study, and 96% of the patients with a definite cerebral infarction; these figures are available in our paper. We could not have discussed silent infarctions in patients without a CT scan.

Apart from these two points, we fully agree with the conclusion by Jørgensen et al¹: in community-based studies (ie, in the "real world") there is no evidence at all that the presence of these silent lesions contribute to a worse prognosis of patients with a first-ever ischemic stroke.

Stefano Ricci, MD
Maria Grazia Celani, MD
Enrico Righetti, MD
Clinica Neurologica