Response

We are grateful to Drs Norris and Bladin for their interest in our review of the relative merits of ticlopidine and aspirin,1 but we are not sure whether there is a baby in the bathwater at all. We feel less confident than they do that the point estimate of the overall advantage of ticlopidine over aspirin (8% with 3500 patients) would remain the same with greater numbers and would then reach statistical significance. This is what 95% confidence intervals (−4% to 19%) are all about: we simply don't know. By the way, we could not find a P of <.007 in the paper about the Ticlopidine Aspirin Stroke Study (nor indeed any significant difference for any outcome event that included more than stroke alone);2 is this perhaps a subgroup analysis that did not survive the final stages of publication? What the report does contain is a table of side effects, totalling 62% in the ticlopidine group and 59% in the aspirin group (with 1300 mg!). These proportions have not been weighted for severity, but this uncertainty can be interpreted both ways, as it can for efficacy.

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References

Presence of Ultrastructural Arterial Lesions in Muscle and Skin Vessels of Patients With CADASIL

To the Editor:

In the summary of the proceedings of the First International Workshop on CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy), we noted that remarkably similar lesions were observed in the small subcortical and leptomeningeal arteries in all cases of CADASIL studied.1 These lesions consisted of a nonatheromatous, nonamyloid angiopathy characterized by the presence within the media of a granular, electron-dense, osmiophilic material. Although these lesions were mostly localized to the brain,2 they have occasionally been found in the spinal cord3 and in other organs such as the spleen4 and heart,5 raising the possibility of a more generalized vascular disease, as already suspected by Sourander and Walinder.4

To further investigate this issue, we reexamined muscle (deltoid) biopsies performed in 6 patients belonging to our first study family (subjects III4, III5, III9, III21, III23, IV22; 4 males and 2 females aged 33 to 66 years),2 the family in which we located the responsible gene on chromosome 19.6 We also performed skin biopsies of 2 subjects of this family (III5, IV22). All these subjects were clinically affected except for subject III21, who was asymptomatic but had diffuse white matter signal abnormalities on magnetic resonance imaging.8 Only 3 subjects had vascular risk factors: III4 had hypertension, III19 had a high cholesterol level, and IV22 was a cigarette smoker. We have reported a lipidosis with a type I fiber predominance in muscle biopsies from subjects III4, III5, III19, and IV22.2 There was no morphological or functional mitochondrial abnormality. Vessels were not specifically investigated in that study.

The present ultrastructural study concentrated on the vessel walls of capillaries and arterioles whose diameters ranged from 10 to 50 μm (the electron microscope used was a Zeiss EM 10). In muscle vessels, the vascular basal lamina was thickened without lamellar pattern. In the basal layer, patches of granular and electron-dense material (Fig 1) were observed close to the cell membrane of vascular smooth muscle cells (VSMC). The VSMC were thin with multiple processes, large cell membrane infoldings, and several swollen mitochondria. Junctions between VSMC seemed loose. Endothelial cells were normal or turgescent.

In the skin vessels, where VSMC were present we observed identical granular osmiophilic material in the basal lamina, in contact with the cytoplasmic membrane of these cells (Fig 2). In capillaries, this material was also found in the basal lamina. This preliminary study reveals ultrastructural alterations in the wall of skin and muscle vessels that have not been reported so far in patients with CADASIL.2-5,8 No mention had been made of the skin in previous reports. In the only article specifically mentioning the smooth muscle arteries, these were said to be normal.8 The changes we observed are similar to those in the walls of the leptomeningeal and the small cerebral penetrating arteries in patients with CADASIL.2,5 The presence of a granular osmiophilic material was reported in the media of these arteries. In skin and
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.6 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.3,4

The pathophysiologic 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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References


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.3,5 Recent studies on epileptic seizures in the course of ICH+6 give no account of heralding seizures, and in our series of 82 consecutive cases of ICH no patient had seizures preceding the stroke.6 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), 19F-Tc-HMPAO (19F-Tc-hexamethylenepropyleneamine oxime)—single photon emission computed tomography, and Doppler sonography were normal. An electroencephalogram revealed slow and sharp waves over the entire 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 hemianopia; an MRI of the brain indicated a right occipital hemorrhage, which was confirmed by CT (Fig 1b). Transesophageal 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 hemianopia, 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.8,9 Obviously, neither explanation can directly relate epileptic seizures to hemorrhage. Cortical iron injection causes acute epileptiform activity in experimental models,10 and this finding has been claimed to account for posttraumatic and poststroke epilepsies.3,5 However, the relevance of this model to this case is questionable, because no hemorrhagic lesions (unless clinically silent) had ever occurred when seizures started.
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