Stress-Related Primary Intracerebral Hemorrhage
Autopsy Clues to Underlying Mechanism

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Background—Research into the causes of small-vessel stroke has been hindered by technical constraints. Cases of intracerebral hemorrhage occurring in unusual clinical contexts suggest a causal role for sudden increases in blood pressure and/or cerebral blood flow.

Case Description—We describe a fatal primary thalamic/brain stem hemorrhage occurring in the context of sudden emotional upset. At autopsy, the brain harbored several perforating artery fibrinoid lesions adjacent to and remote from the hematoma as well as old lacunar infarcts and healed destructive small-vessel lesions.

Conclusions—We postulate that the emotional upset caused a sudden rise in blood pressure/cerebral blood flow, mediating small-vessel fibrinoid necrosis and rupture. This or a related mechanism may underlie many small-vessel strokes.

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Key Words: hypertension ■ intracerebral hemorrhage ■ lacunar infarction ■ small-vessel disease

Research into the cause of primary (ie, nontraumatic) intracerebral hemorrhage (PICH) is hampered by the fact that vessel rupture destroys, or at least modifies, the underlying vessel wall pathology. In 1988, Caplan1 reviewed reports of PICH occurring in unusual circumstances, most often in patients with no evidence of prior hypertension, suggesting that acute elevations in blood pressure or cerebral blood flow could cause vessel rupture. He pointed out that such uncommon examples might shed light on the pathogenesis of the generality of PICH. We describe a case of thalamic/brain stem PICH after acute emotional upset and suggest a possible causal relationship mediated by a specific small-vessel-lesion fibrinoid necrosis.

Case Report
An 84-year-old man, with a history of hypertension treated with methyldopa, was generally upset because his wife, who had become seriously ill, was admitted to the hospital. Two days after her admission, he got up as usual but was then told by a relative that his wife had died. He went to the bathroom but returned complaining of pins and needles affecting the left arm. He collapsed with a severe left-sided weakness and was helped to bed by the same relative. He rapidly became drowsy.

On his arrival at the hospital, he was rated Glasgow Coma Scale 10 (E3V2M5) and had Cheyne-Stokes breathing. Blood pressure was 198/102 mm Hg, and his pulse was 62 bpm and regular. He had 2-mm reactive pupils, dysconjugate gaze paresis, a left upper motor neuron facial weakness, and a complete left hemiparesis. Investigations revealed normal urea and electrolytes, full blood count, and erythrocyte sedimentation rate. ECG showed marked left ventricular hypertrophy. CT revealed a right thalamic/midbrain hemorrhage. He was treated with supportive care, and when his condition deteriorated, a repeat CT scan showed extension of the bleed into the ventricles. Surgical intervention was considered inappropriate. He died 5 days after admission.

Autopsy Findings
Full autopsy was performed the day after death. Relevant findings included an enlarged heart (470 g) with concentric left ventricular hypertrophy, together with hypertensive/ischemic nephrosclerosis. The cause of death was confirmed as bilateral lower lobe bronchopneumonia.

The fresh brain weighed 1400 g. Coronal brain slice examination showed a right thalamic intracerebral hemorrhage 25 mm in maximal dimension, with extension into the midbrain and upper pons (Figure 1). There was no evidence of underlying vascular malformation, tumor, or vasculitis. The brain also harbored multiple long-standing, small, deep (lacunar) infarcts: 1 in the contralateral thalamus, 2 in the contralateral putamen, and 4 in the ipsilateral putamen. In addition, there were a number of areas in the basal ganglia and thalami of so-called incomplete lacunar infarction.2

There was widespread concentric small-vessel wall thickening, perivascular space dilatation, and focal perivascular...
hemosiderin deposition. There was, in addition, acute fibrinoid necrosis of small vessels, with red blood cell extravasation, adjacent to the hematoma (Figure 2A). Distinct fibrinoid vessel wall changes, with focal martius, scarlet, and blue (MSB) staining and patchy foam cell infiltration, were also seen remote from the hematoma in perforating vessels in the right cerebellar white matter (Figure 2B) and in the right and left basal ganglia. Old, healed, disorganized small-vessel lesions with mural foam cell infiltration were seen in the same brain areas.

Discussion

We suspect that this man’s blood pressure suddenly rose when he was informed of his wife’s death. Emotional or physical stress can cause such circulatory changes, mediated in part by catecholamine secretion. If so, this case supports Caplan’s hypothesis1,4 that acute rises in blood pressure or cerebral blood flow may cause rupture of perforating cerebral vessels. He reviewed cases of PICH occurring in the context of emotional stress, exposure to cold weather, severe dental pain, sympathomimetic drug use or abuse, and trigeminal stimulation.1,4 He suggested that this may happen in patients without evidence of prior long-standing hypertension in vessels presumed therefore to have been structurally normal, although he did emphasize that the same mechanism is also common in brains that do harbor chronic hypertensive vessel changes. The neuropathological findings in the present case provide a link between a clinical situation that could cause a sudden perturbation of cerebral hemodynamics and a specific cerebral vessel lesion, namely, fibrinoid necrosis.

Multiple foci of vessel wall fibrinoid necrosis with petechial red blood cell extravasation were seen in the immediate vicinity of the hematoma. This is a common autopsy finding in PICH brains5–7; in this context, fibrinoid necrosis is reactive to the bleed and may be related to small-vessel spasm. More significantly, focal segmental fibrinoid vessel wall changes were also observed remote from the hematoma, in contralateral basal ganglia and cerebellar white matter, both well-documented predilection sites for PICH. It is not currently possible to date fibrin deposits accurately, but MSB stains relatively recently deposited fibrin a red color, before its postulated transition to pale blue–stained collagen.3 Therefore, it is not possible to say whether the fibrinoid lesions noted distant from the hematoma in this case were caused by the emotional stress or if they predated it. However, the important point is that the cerebral vessels in this case were clearly susceptible to developing fibrinoid vessel lesions, which are widely held to be the common pathological substrate of hypertensive-type PICH.5–9 Therefore, we postulate that in this case, such a lesion was mediated in the thalamus by stress-mediated hypertension/hyperemia, with subsequent vessel rupture and fatal hemorrhage.

This brain also harbored old lacunar infarcts, strengthening the observed association between PICH and lacunar infarcts as well as the notion that they are caused by the same or a closely related small-vessel lesion,5,6,9,10 In its acute form, this lesion is characterized by fibrinoid vessel wall destruction; in its healed form, by a complex disorganized lesion, with or without aneurysmal dilation, which Fisher11 termed “lipohyalinosis.” It remains unclear why some vessels affected by fibrinoid necrosis rupture, some occlude (and cause lacunar infarction), and some heal without obvious sequelae. Also unclear is the reason for the apparent rarity of multiple synchronous intracerebral bleeds. We did not observe similar vessel changes in organs remote from the brain, in keeping with the idea that cerebral vessels are in some way “uniquely susceptible” to the development of fibrinoid necrotic lesions.5,7,8

Taken together, these observations suggest that sudden alterations in cerebral blood flow or pressure may cause...
fibrinoid necrosis and sometimes vessel rupture. Such changes in blood flow/pressure must occur repeatedly in all individuals to some extent, perhaps more often and to a greater degree in hypertensive individuals, but they are usually accommodated by rapid compensatory mechanisms. Altered cerebral vasomotor reactivity or autoregulatory control, which may accompany the aging process, and chronic hypertension could thus predispose an individual to vessel rupture (or occlusion), as could genetically determined variability in vessel responsiveness. There is clearly potential here for a complex dynamic interplay between local cerebral hemodynamics, vessel wall structure, and function, both acquired and inherited, in the pathogenesis of these lesions and their related stroke subtypes.

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**References**

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