

## Hemorrhagic Infarction: Guilt by Association?

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Efforts to clarify the natural prevalence, radiologic features, and clinical consequences of hemorrhagic infarction (HI), as seen on CT, are welcome. This information is especially important because HI has been viewed as an ominous sign of potential neurologic disaster and has prompted a reluctance to use anticoagulants. More recently, fear of hemorrhagic transformation has raised concern about the risks of using thrombolytic agents in the treatment of acute stroke.

In the CT-angiographic report in this issue of the *AJNR*, Bozzao et al. [1] found that 50% (18/36) of their patients with hemispheric infarcts had HI on the CT scans obtained on the seventh day after stroke. No HIs were present in any patients on the initial 4-hr CT scan, which is consistent with other reports that HI develops sometime after the first several hours. HI is usually detected by day 3 or 4 but can be found in serial CT studies as late as the second week after stroke [2–5]. The possibility that anticoagulants, given to most of these patients, may have contributed to the large number of HIs cannot be dismissed entirely, but the doses and duration of treatment were not excessive, and other reports [3, 6–9] of serial CT scans in patients who did not receive anticoagulants have shown a range of HI up to 43%. As expected, autopsy studies [10–13] of patients who had embolic strokes showed a higher prevalence of HI; 50–70%, consistent with the more severe nature of the pathologic changes in patients who died.

Bozzao et al. have shown that early hypodensity on the initial CT scan obtained within 4 hr of stroke was a predictor of HI in 72% (18/25) of their patients. HI did not develop in any of the remaining 11 who did not have early CT signs of

infarction. Yamaguchi et al. [14] found that hypodensity on the initial CT scan was associated with the later development of HI in 45 (40%) of 113 cases of cerebral embolism. Other CT studies have noted a relationship between the occurrence of HI and large infarcts with edema and mass effects [3, 7] and enhancement with contrast medium [3, 15]. Furthermore, Bozzao et al. noted a correlation between the site of cerebral arterial occlusion and subsequent HI. HIs deep in the hemisphere were associated with proximal occlusion of the middle cerebral artery (MCA), and this was followed later by fragmentation of the embolus (disappearance of the hyperdense MCA sign). In those HIs with mostly cortical distribution, collateral blood channels through leptomeningeal collaterals probably played the major role in producing HI via late cortical reperfusion. Several patients had HIs in deep and cortical territories, suggesting that both reperfusion of proximal MCA occlusion and cortical collaterals played some role.

These results support the well-known theory of “migratory embolism” proposed by Fisher and Adams [10] to account for HI, especially those deep in the hemisphere. This theory proposes that reperfusion bleeding occurs from injured capillaries after embolic obstruction clears and moves distally. The results also indicate that HIs with cortical distribution may occur from the effects of leptomeningeal collaterals when proximal occlusion of the MCA persists, a finding recorded by Ogada et al. [16]. Gomez et al. [17] recently have shown that sequential transcranial Doppler studies can indicate passage of embolic occlusions by changes in blood-flow velocities, making this imaging technique a safe and promising way to follow these patients. Hemorrhagic transformation was

This article is a commentary on the preceding article by Bozzao et al.

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seen on CT in two of the three patients in whom transcranial Doppler studies showed velocity changes consistent with recanalization.

Despite our improved understanding of the prevalence, timing, and pathogenesis of HI, the clinical importance has remained uncertain. Even the current report by Bozzao et al. provides no comment on the clinical outcome in their 18 patients with HI. *The occurrence of HI alone does not necessarily imply a serious complication.* Because, by definition, HI occurs within an area of infarcted tissue, the ischemic tissue damage itself accounts for the neurologic deficit, with little or no additional compromise associated with the hemorrhagic component. Several reports [3–5] have suggested that most patients are clinically stable or even improving when HI is discovered on CT. Among 47 patients reported by the Cerebral Embolism Study Group [5] 45 of 47 were stable or improving when HI was first noted; two (4%) had a worsening of their condition associated with HI. These limited observations strongly suggest *HI may be more of a CT curiosity than a dreaded complication.*

*The distinction between HI and parenchymatous hematoma is important in the assessment of intracranial bleeding, and both should not be casually grouped under the broad heading of HI.* It remains unsettled whether parenchymatous hematoma, in this setting, represents a severe form of multicentric bleeding from reperfusion of injured capillaries as in HI or is an expression of a different pathogenesis, such as rupture of one or more small arterioles. Parenchymatous hematoma has been regularly associated with clinical worsening in contrast with HI. CT patterns separating the two entities are not always distinctive, but parenchymatous hematomas generally show a more homogeneous high-density, well-demarcated region with associated mass effect and extension of blood into the ventricle, whereas HIs are more inhomogeneous, patchy, and gyriform in distribution, occurring within an area of infarction. Rarely, the hematomas occur outside the area of infarction.

How do these observations on HI relate to potential treatment strategies? The use of anticoagulants to prevent recurrent cardiogenic embolism is widely accepted, but the timing of administration after acute stroke is controversial. The data prompting immediate use of anticoagulants is based on the observations that early recurrent embolism (brain is the main site) occurs in 2–21% (average, 12%) of patients during the first 21 days [14, 18–24]. Several studies [19, 20, 22–25] have shown a reduction in recurrent embolism with the use of anticoagulation, from 18% for patients on no or delayed treatment compared with 2% for patients on immediate anticoagulation. However, the fear of converting a pale infarct to an HI or worse, a hematoma, has led many to delay anticoagulation. This concern has been fostered by anecdotal reports of the occurrence of hematomas in an area of infarct, with clinical deterioration, after early use of anticoagulation in acute embolic stroke [26–29]. No one factor has emerged to account for the formation of hematomas. Excessive anticoagulation, large infarcts, and uncontrolled hypertension have all been implicated, but none has occurred frequently enough to allow reliable prediction of this complication.

Limited observations have suggested that anticoagulation

has no serious consequences when used even in some patients who have HI present on CT [4, 19, 25]. We recently published a report on 10 patients with HI on CT who received heparin, warfarin, or both to prevent early recurrent embolism [30]. All these patients remained stable or improved, and serial CT scans showed that their HIs resolved. Further study is necessary to clarify the risks, if any, of anticoagulation in patients who have HI after acute cerebral embolism.

Intracranial bleeding has been a disturbing concern in recent studies of thrombolytic agents administered for acute stroke. The rationale for the use of these agents is based on the hypothesis, yet to be proved, that timely lysis of thrombus to restore circulation will result in reduced tissue injury and improved neurologic outcome, and that these will be achieved with an acceptably low risk of serious intracranial bleeding [31]. In trials of thrombolytic agents administered intraarterially and IV, parenchymatous hematomas have occurred relatively infrequently but often with serious effects, including death, whereas HIs have been more common but clinically benign.

Several investigators have administered intraarterial urokinase or streptokinase for acute stroke in the carotid [32–34] or vertebrobasilar [35] territories. Del Zoppo et al. [32] treated 20 patients with occlusions in the carotid territory with urokinase and found significant improvement in 12 of 18 patients in whom recanalization occurred. Four HIs, all asymptomatic, occurred in the recanalized group. Similarly, Mori et al. [33] found recanalization in 10 of 22 patients treated with urokinase for MCA occlusions, with one asymptomatic HI in the recanalized group and three parenchymatous hematomas in the nonrecanalized group. Theron et al. [34] treated 12 patients with carotid territory stroke with streptokinase. Three parenchymatous hematomas occurred in the eight patients who had recanalization. In patients with stroke in the vertebrobasilar territory, Hacke et al. [35] compared 43 patients treated with urokinase or streptokinase with 22 patients given conventional therapy with antiplatelet agents or anticoagulants. Ten of 19 patients treated with thrombolytic agents who had recanalization improved, compared with none of the other 24 who showed no recanalization. Patients treated with conventional therapy did poorly: 19 deaths occurred. One HI and three parenchymatous hematomas occurred in the treated patients (two each in the recanalized and nonrecanalized groups). The one patient with HI was asymptomatic, but three patients in whom pontine hematomas developed worsened, and two of the three died.

At least five preliminary studies of different design have used IV administered recombinant tissue plasminogen activator (rt-PA) early after acute stroke. In a study [36] in which angiography was not used, escalating doses of rt-PA (alteplase) given within 90 min of the onset of stroke and after normal findings on CT, 29 (39%) of 74 patients showed clinical improvement within 6 hr of treatment and smaller infarct volume on CT compared with 45 patients without early improvement. HI occurred in three (4%) of 74 patients who did not have clinical worsening, and three (4%) of 74 had parenchymatous hematomas with clinical deterioration, one distant from the original infarct. In a dose-finding safety study of rt-



PA (duteplase) [37], patients were treated within 8 hr of the onset of stroke and after a negative CT for intracranial bleeding and angiographic documentation of a vascular occlusion consistent with symptoms. No dose-recanalization response was found, but various degrees of recanalization were noted on repeat angiography. Of 104 patients receiving rt-PA, HIs developed in 21 (20%); four of these (19%) were associated with clinical worsening. Parenchymatous hematomas developed in 11 patients (11%), and six of these (55%) had clinical deterioration. Two of the hematomas occurred in an area distant from the initial infarct. HI and parenchymatous hematoma were significantly associated with time to treatment, if the time was longer than 6 hr, but not with rt-PA dose, recanalization, or CT abnormalities. Mori et al. [38] reported a limited two dose-placebo controlled trial of rt-PA (duteplase) given within 6 hr of acute stroke and after a negative CT for intracranial bleeding and angiographic evidence of vascular occlusion. Reperfusion occurred more frequently in the two treatment groups compared with control patients but did not reach statistical significance, except that in cases of MCA occlusions, the higher dose group had significantly more recanalizations than patients who received placebo. Neurologic outcome, as measured by a standard stroke scale, was better in the treated patients. HIs occurred in 8 (42%) of 19 treated patients and four (33%) of 12 control subjects with no clinical worsening. One parenchymatous hematoma occurred in each of the two treatment and placebo groups. Von Kummer et al. [39] treated 27 patients with angiographically proved occlusions in the vertebrobasilar or carotid territories with two different doses of rt-PA (alteplase). The higher dose was associated with more recanalizations, but no difference in outcome occurred between the two dose groups. Fatal parenchymatous hematomas occurred in two patients (7%), and six patients (22%) had HIs with no accompanying deterioration. Yamaguchi et al. [40], using three doses of rt-PA (duteplase), treated 58 patients who had angiographic evidence of embolic occlusions in the carotid territory. Twelve patients (21%) had HIs, but no information on clinical effects was reported. Taken together, these preliminary studies suggest that intracranial bleeding is associated with the use of all thrombolytic agents, but the magnitude of this risk remains unknown and will require further study.

HI is a natural and common tissue accompaniment of cerebral embolic infarction. Its clinical significance may have been exaggerated as a consequence of its association with the neurologic effects of the infarct itself. Future study in prospective, unselected patients is especially timely now that several treatments are being studied in patients who have had acute stroke. It is time for a realistic reappraisal of HI and its potential risks, within the perspective of potential benefits of newer treatments for stroke.

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