Early Angiographic and CT Findings in Patients with Hemorrhagic Infarction in the Distribution of the Middle Cerebral Artery

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Hemorrhagic infarction subsequent to ischemic brain damage, even if small, slight, or marbled, can be detected by CT. The mechanisms that give rise to this transformation in humans are not well elucidated. Previous reports indicate that hemorrhagic infarction is most common in embolic stroke and large infarcts, and can worsen the clinical state of ischemic patients. We examined 36 patients with supratentorial ischemic signs and symptoms within the first hours after onset. CT was used to judge if hypodensity on early CT studies might predict the development of hemorrhagic infarction. Angiography was used to observe the site of arterial occlusion, the state of collateral circulation, and the mechanisms of late reperfusion. Hemorrhagic infarction was present in 18 of our 36 patients. Angiography revealed occlusion of the middle cerebral artery or internal carotid artery (three cases) in all patients. Hypodensity was present on early CT studies in all of the 18 patients who developed hemorrhagic infarction.

The finding of hypodensity on CT studies performed soon after embolic ischemic stroke is strongly predictive of hemorrhagic transformation.

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Hemorrhagic infarction (HI) is thought to be more common in embolic than in thrombotic occlusions [1–3]. Furthermore, there is a direct relationship between the size of the ischemic area and the probability of hemorrhagic transformation [4]. HI stems from the malfunction of the endothelium and subsequent restoration of blood flow, either through fragmentation of the embolus or through collateral perfusion. Early CT detection of a parenchymal hypodensity provides important clues to the site of arterial occlusion and may predict the severity of chronic brain damage [5].

The aim of the present study was to evaluate the possibility of a correlation between hypodensity on early CT studies and HI transformation of an ischemic area. To this end, we obtained sequential CT scans in a group of patients with ischemic stroke. Angiography was performed in the acute phase in order to verify the presence of arterial occlusion and to evaluate the early collateral blood supply (CBS).

Subjects and Methods

We studied 36 patients with supratentorial ischemic stroke in the territory of the middle cerebral artery (MCA) as shown by follow-up CT [5]. All patients had had an unenhanced CT study within 4 hr after onset of symptoms and a follow-up CT study 1 week later. Four-millimeter-thick slices were used in the examination of the posterior fossa up to the chiasmatic cistern, and 8-mm-thick slices were used above that level. Angiography was performed during the acute stage also, that is, within 6 hr of ictus. Angiography was repeated in three cases because of clinical indications. The CT study performed within 4 hr of ictus allowed us to evaluate early changes due to ischemia.

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When a hypodensity was seen on early CT studies, the lesion was categorized as being in one of three areas: (1) lentiform nucleus, (2) lentiform nucleus plus cortex, or (3) cortex [5]. Early CT scans were also evaluated for the presence of hyperdense areas along the region of the main trunk of the MCA, which is considered a direct sign of an embolus [6].

Follow-up CT 1 week later allowed us to determine the frequency and location of HI. Lesions with clear areas of hyperdensity were considered HI, as were petechial hemorrhages with spotty and scattered hyperdense areas [7]. HI was anatomically classified as being located in one of the same three areas where hypodensities were seen on early CT scans.

Angiography performed within 6 hr after ictus showed the sites of vascular occlusions, which were classified as the bifurcation of the internal carotid artery (ICA), cervical ICA, carotid siphon, MCA proximal to the lenticulostriate arteries, MCA distal to the lenticulostriate arteries, trifurcation of the MCA, or peripheral branch of the MCA [8]. The collateral blood circulation was evaluated according to criteria that took into account the rapidity of filling and the number of branches visualized through cortical anastomoses [9–11].

Of the 36 patients studied, 23 were treated with anticoagulant therapy, which was initiated 2 to 4 hr following ictus. Three different antiocoagulant regimens were used: heparin, 10,000 UI IV bolus followed by 8000 UI IV three times a day for 3 days; calcium heparin, 5000 UI subcutaneously three times over 24 hr or dicumarol, one 4-mg tablet daily for 6 months.

Results

The CT and angiographic findings are summarized in Table 1. In the 36 patients with lesions localized to the vascular territory of the MCA, findings on CT performed within 4 hr of stroke were normal in 11 and abnormal in 25 [5]. Of these 25 patients, a slight hypodensity was seen in the lentiform nucleus in 14 cases, in the lentiform nucleus and cortical regions in five cases, and in the cortex only in six cases.

In the 14 patients in whom a hypodensity was seen in the lentiform nucleus on early CT studies, HI occurred subsequently in seven cases. In four of these cases, HI was seen in the lentiform nucleus (Fig. 1). Of these, angiography showed proximal occlusion of the MCA in one case, distal MCA occlusion in one, and occlusion at the trifurcation in the remaining two. CBS was present in all. Early CT scans showed hyperdensity in the MCA in all four patients, but this had disappeared on follow-up CT scans obtained 7 days later

TABLE 1: CT and Angiographic Findings in Patients with Ischemic Supratentorial Stroke

Location of Hypodensity on Early CT/Case No.	Location of Hemorrhagic Infarct on Follow-up CT	Location of Occlusion on Angiography	Collateral Blood Supply
Lentiform nucleus + cortex			
1	Lentiform nucleus + cortex	Carotid siphon	Absent
2	Lentiform nucleus + cortex	Proximal MCA	Absent
3	Lentiform nucleus + cortex	Proximal MCA	Absent
4	Lentiform nucleus + cortex	Distal MCA	Absent
5	Cortex	Proximal MCA	Absent
Lentiform nucleus			
6	Lentiform nucleus + cortex	Proximal MCA	Absent
7	Lentiform nucleus + cortex	Proximal MCA	Present
8	Lentiform nucleus + cortex	Proximal MCA	Absent
9	Lentiform nucleus	Trifurcation of MCA	Present
10	Lentiform nucleus	Trifurcation of MCA	Present
11	Lentiform nucleus	Distal MCA	Present
12	Lentiform nucleus	Proximal MCA	Present
13	None seen	Carotid siphon	Present
14	None seen	Proximal MCA	Absent
15	None seen	Cervical ICA	Present
16	None seen	Trifurcation of MCA	Present
17	None seen	Bifurcation of ICA	Present
18	None seen	Proximal MCA	Present
19	None seen	Trifurcation of MCA	Present
Cortex			
20	Cortex, diffuse	Distal MCA	Absent
21	Cortex, diffuse	Trifurcation of MCA	Absent
22	Cortex, partial	MCA branches	Present
23	Cortex, partial	Trifurcation of MCA	Absent
24	Cortex, partial	Trifurcation of MCA	Present
25	Cortex, partial	MCA branches	Absent
None seen			
26	None seen	MCA branches	Absent
27	None seen	MCA branches	Present
28	None seen	Trifurcation of MCA	Present
29	None seen	MCA branches	Present
30	None seen	MCA branches	Present
31	None seen	None seen	–
32	None seen	None seen	–
33	None seen	None seen	–
34	None seen	None seen	–
35	None seen	None seen	–
36	None seen	None seen	–

Note.—MCA = middle cerebral artery; ICA = internal carotid artery.

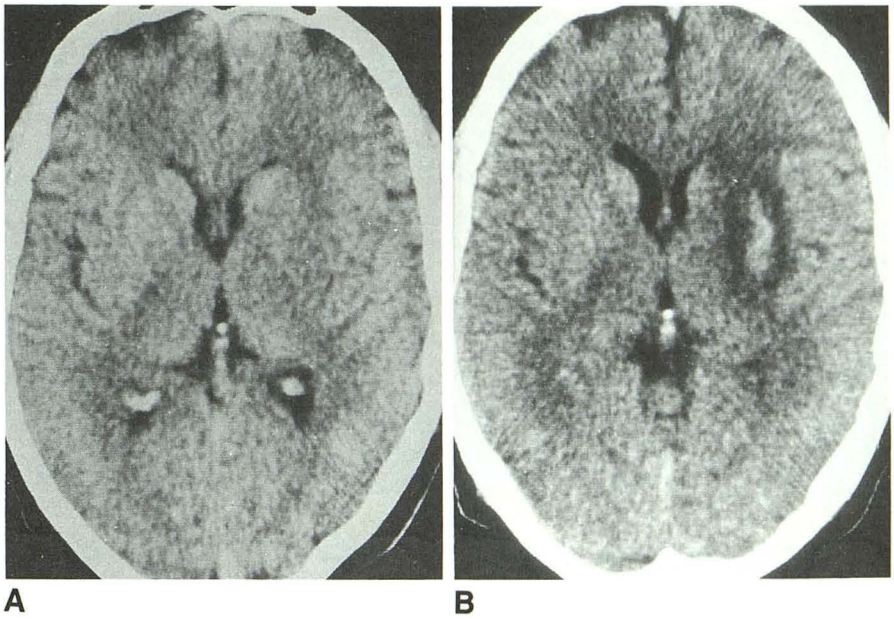

Fig. 1.—*A*, Early CT study shows hypodensity in left lentiform nucleus.
***B*, Follow-up study. Hemorrhagic infarction has developed at same site.**

in all cases. In the other three patients, HI was observed in the lentiform nucleus and cortex on follow-up CT. Angiography showed proximal MCA occlusion in all cases with no evidence of CBS in two of three. Hyperdensity in the MCA was evident in all on the early CT study, but had disappeared on the follow-up CT scan.

In seven patients with hypodensities in the lentiform nucleus on early CT studies, no evidence of HI was seen on follow-up CT. Angiography showed ICA occlusion in three cases (one cervical, one siphon, one bifurcation), all with good CBS; proximal MCA occlusion in two, with evidence of CBS in one of two; and occlusion at the trifurcation of the MCA in the remaining two, with good CBS in both. On the early CT scan, hyperdensity in the MCA was evident in all four patients with MCA occlusions and was still present in two on follow-up CT 1 week later.

In the group of five patients with an early hypodensity localized to the lentiform nucleus and cortex (Figs. 2A, 2B, and 3A), HI occurred in all. HI was observed in the lentiform nucleus and cortex (Figs. 2C–2F) in four patients. Of these, angiography showed proximal MCA occlusion in two (Fig. 2G), distal MCA occlusion in one, and occlusion at the carotid siphon in one. CBS was absent in all. In all of these patients, hyperdensity in the MCA was evident on early CT but had disappeared on the follow-up CT. HI involving the cortex diffusely was found in the fifth patient (Fig. 3B). In this case, angiography revealed proximal MCA occlusion with no evidence of CBS. Persistence of MCA occlusion was documented after 7 days both by MCA hyperdensity on follow-up CT and by repeat angiography, which also showed well-developed CBS (Figs. 3C and 3D).

In the group of six patients with hypodensity limited to the cortical region of the MCA on early CT studies (Figs. 4A and 4B), HI occurred in all. In four patients HI was observed to partially involve the cortical region (Figs. 4C and 4D). Angiography showed occlusion of the MCA at the trifurcation in two cases (Fig. 4E), with CBS in one case, and branch occlusions in the remaining two cases, with evidence of CBS in one. On the CT study soon after ictus, hyperdensity in the MCA was evident in one case and was still present on follow-up CT. In the last two patients with hypodensities limited to the cortical region, HI was observed throughout the cortex. Angiography showed distal MCA occlusion in one and occlusion at the MCA trifurcation in the other. CBS was absent in both. On CT soon after ictus, hyperdensity in the MCA was evident in one patient, but was no longer present on a follow-up CT scan.

In the group of 11 patients in whom no parenchymal hypodensity was seen on the early CT study, no HI was seen on follow-up CT. In five patients, angiography revealed MCA occlusion. Branch occlusions were seen in four of these and occlusion at the MCA trifurcation with good CBS was seen in one. On early CT, MCA hyperdensity was evident in two of these patients, and was still seen on follow-up CT in one. No arterial occlusions were seen on angiography in six of these patients.

Of the group of 18 patients in whom HI developed, only three were treated with IV heparin (one of these patients also received dicumarol). Thirteen of the patients with HI were treated with subcutaneous calcium heparin the first day only. The remaining two patients with HI received no anticoagulant therapy. Of the group of 18 patients in whom HI did not develop, four were treated with IV heparin (two of these also received dicumarol), two were treated with subcutaneous calcium heparin, one with dicumarol alone, and 11 did not receive anticoagulant therapy. In our opinion, these data suggest that there is not a strong correlation between development of HI and anticoagulant therapy and, as this topic was not of primary interest in this project, the role of anticoagulation in these patients will not be discussed further.

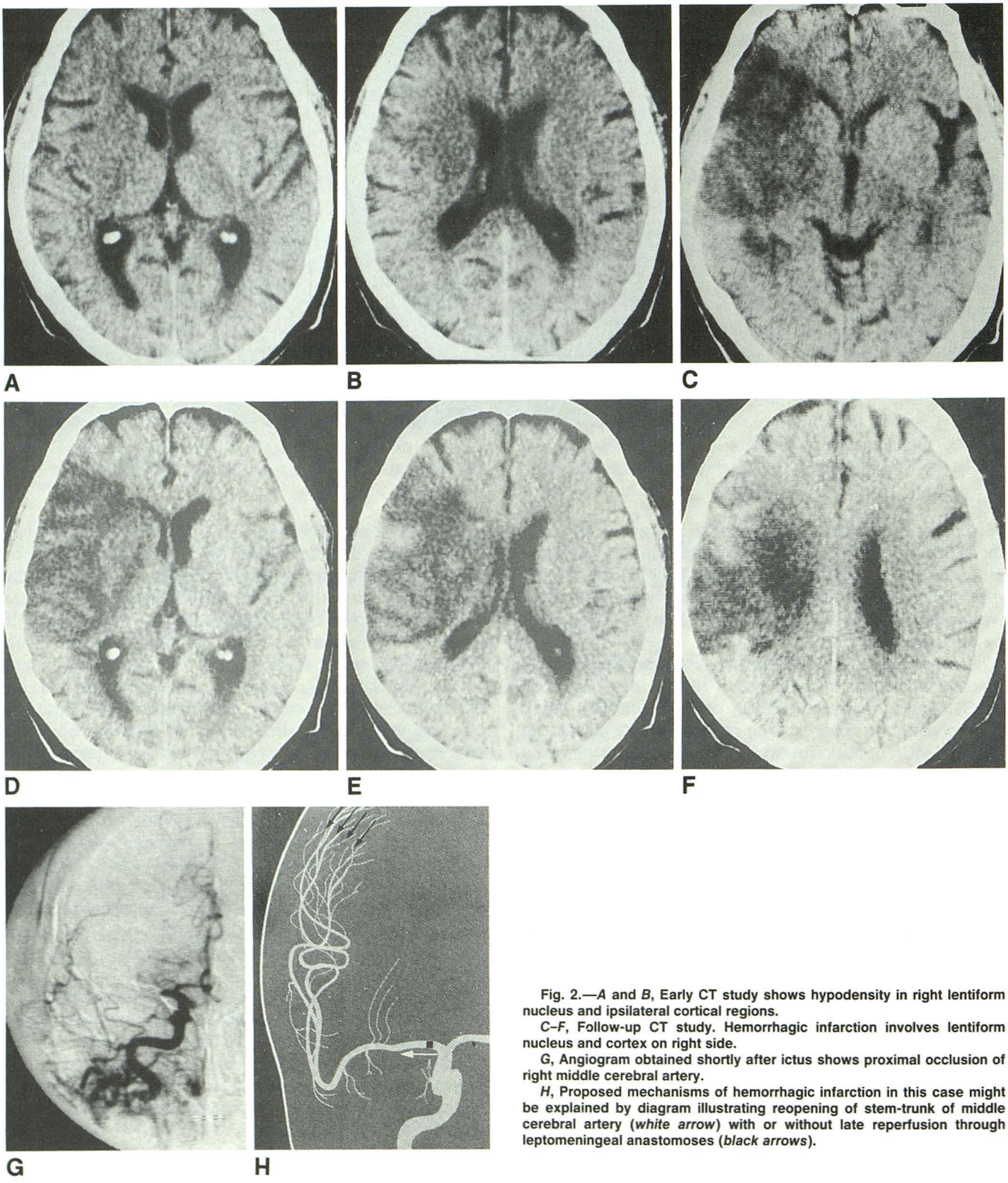

Fig. 2.—*A* and *B*, Early CT study shows hypodensity in right lentiform nucleus and ipsilateral cortical regions.

C–F, Follow-up CT study. Hemorrhagic infarction involves lentiform nucleus and cortex on right side.

G, Angiogram obtained shortly after ictus shows proximal occlusion of right middle cerebral artery.

H, Proposed mechanisms of hemorrhagic infarction in this case might be explained by diagram illustrating reopening of stem-trunk of middle cerebral artery (*white arrow*) with or without late reperfusion through leptomeningeal anastomoses (*black arrows*).

Discussion

Autopsy studies have demonstrated that hemorrhagic transformation of ischemic brain damage occurs in embolic strokes more often than in thrombotic strokes. Differing rates of HI have been reported: 54% [1], 65% [12], and 78% [13]. Previous CT studies have reported HI in 39% of 115 embolic strokes [14]; 43% of 65 strokes, both thrombotic and embolic

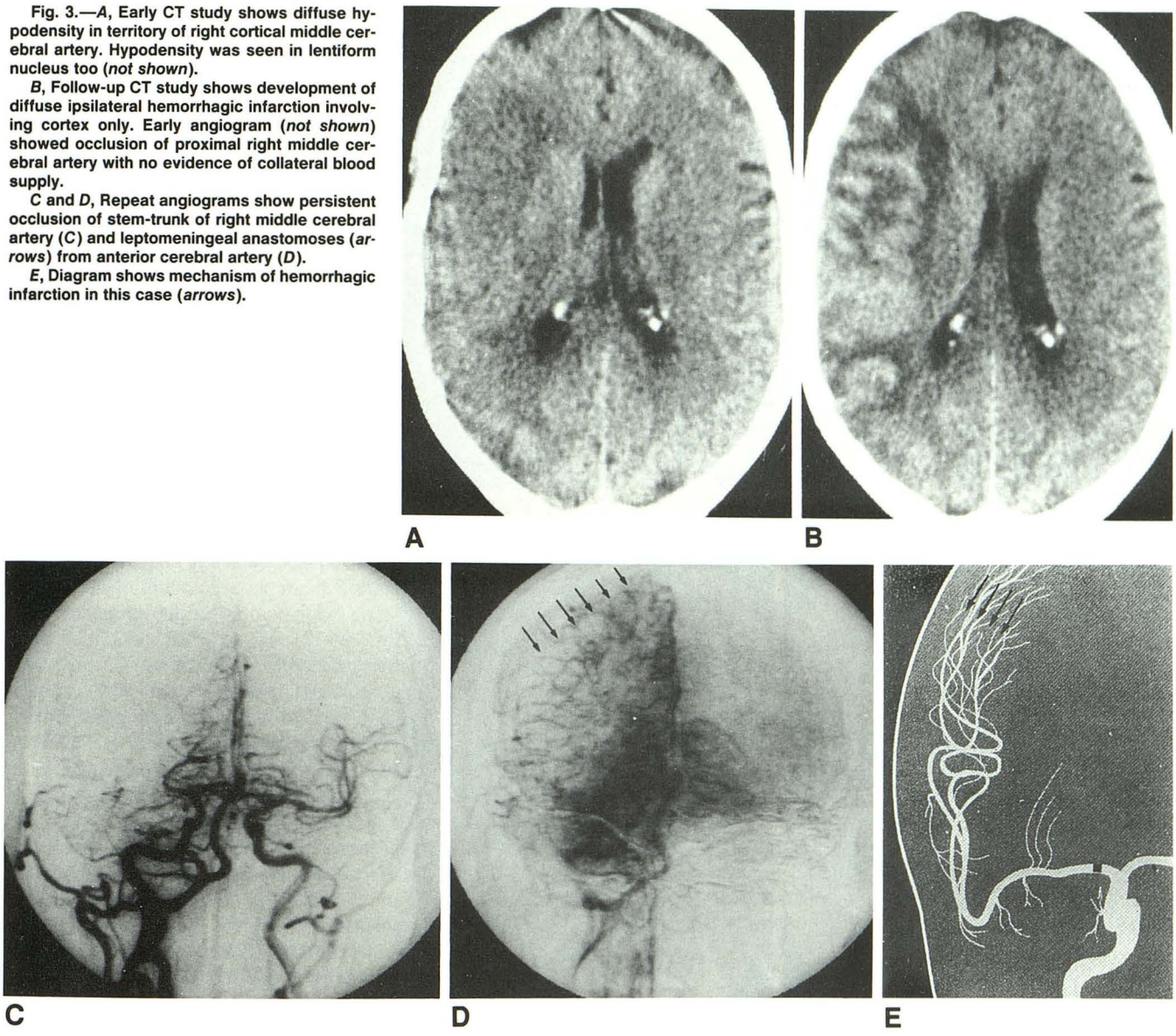

Fig. 3.—*A*, Early CT study shows diffuse hypodensity in territory of right cortical middle cerebral artery. Hypodensity was seen in lentiform nucleus too (*not shown*).

***B*, Follow-up CT study shows development of diffuse ipsilateral hemorrhagic infarction involving cortex only. Early angiogram (*not shown*) showed occlusion of proximal right middle cerebral artery with no evidence of collateral blood supply.**

***C* and *D*, Repeat angiograms show persistent occlusion of stem-trunk of right middle cerebral artery (*C*) and leptomeningeal anastomoses (*arrows*) from anterior cerebral artery (*D*).**

***E*, Diagram shows mechanism of hemorrhagic infarction in this case (*arrows*).**

[15]; and 40% of 65 embolic patients [7]. We found HI in 18 (50%) of 36 patients. Angiography performed within 6 hr of ictus revealed MCA occlusion at varying sites (Table 1).

It is presumed that the hemorrhagic transformation of a pale infarct results from two pathophysiological steps: (1) an ischemic insult of sufficient degree to damage the endothelial vascular wall and (2) the restoration of blood flow into the injured vascular territory. Reperfusion of an ischemic brain area can occur within 2 weeks from the stroke, either through the reopening of the major vessels that were formerly occluded [1, 6, 16] or by the development of CBS [13, 17]. Previous anatomic studies [18] have identified large and important arterial anastomoses on the surface of the brain between the three major cerebral arteries. These leptomeningeal arteries may be functionally effective during the first hours of ischemia [5]. Only cortical vascular territories can take advantage of this protective mechanism; in fact, deep vascular territories such as the lentiform nucleus supplied by lenticulostriate arteries (MCA terminal branches) have little possibility of such CBS [11]. Conversely, good collateral circulation was found to be essential for the transformation from ischemic infarction to HI in animal experiments [19, 20]. Therefore, pial collaterals seem to play two important roles: (1) protection of the brain tissue during the first hours after ischemic stroke and (2) later reperfusion of the injured vascular bed. Following the decrease in edematic compression, blood flow is reestablished in these small vessels, and, because of the local breakdown of the tight junctions in their endothelium, diapedesis of blood occurs. Only hemorrhagic transformation of cortical MCA infarcts may be explained by this pathophysiological mechanism; development of deep hemorrhagic infarction occurs primarily through the reopening of the previously occluded MCA and its perforating branches. Deep and cortical MCA hemorrhagic infarction could develop

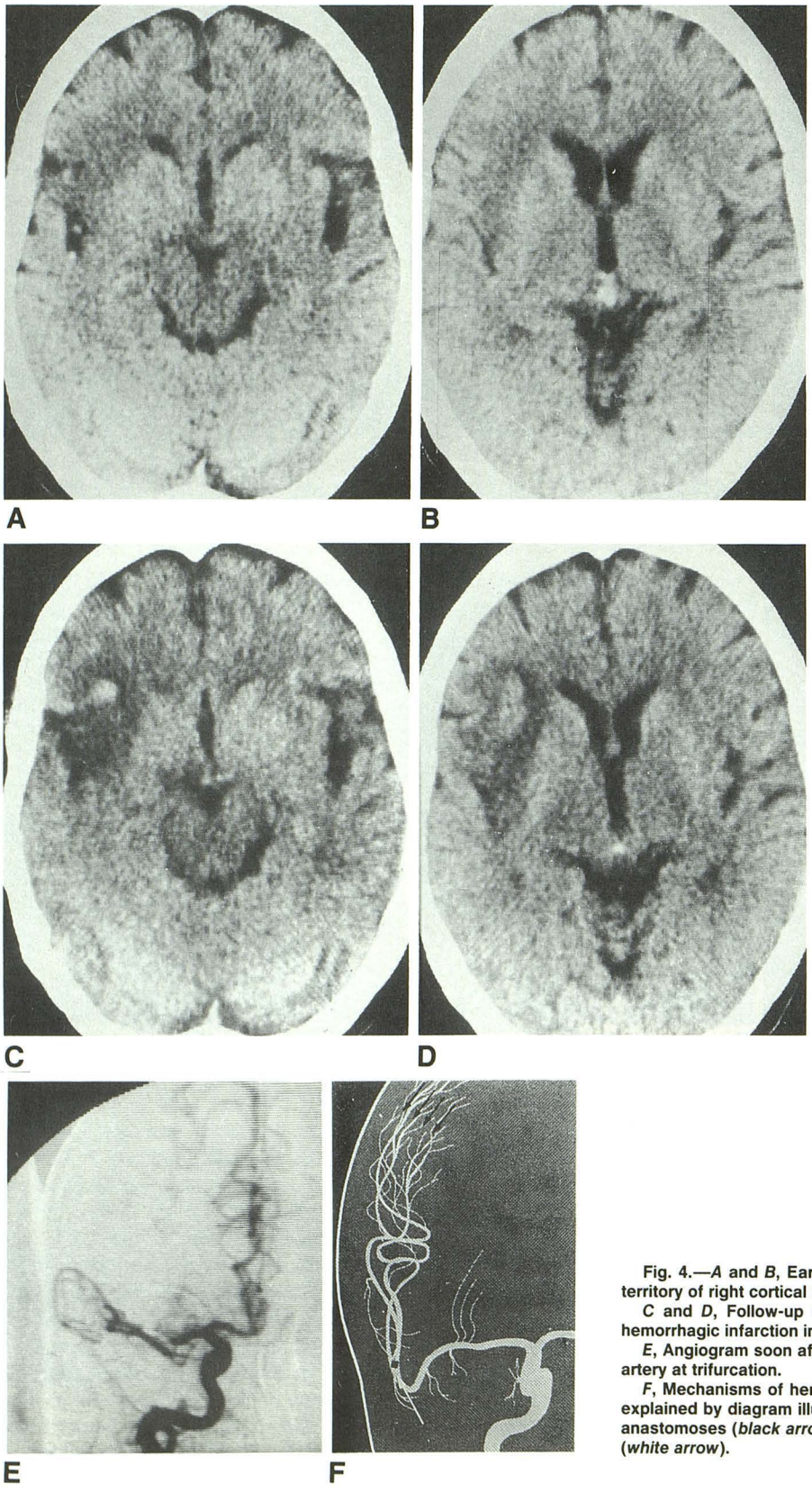

Fig. 4.—*A* and *B*, Early CT study shows hypodensity circumscribed in territory of right cortical middle cerebral artery.

C and *D*, Follow-up CT study shows development of circumscribed hemorrhagic infarction in same territory.

E, Angiogram soon after ictus shows occlusion of right middle cerebral artery at trifurcation.

F, Mechanisms of hemorrhagic infarction in this case probably can be explained by diagram illustrating late reperfusion through leptomeningeal anastomoses (*black arrows*), although recanalization cannot be excluded (*white arrow*).

in the same patient by a combination of these two mechanisms.

Our data seem to confirm this hypothesis. In fact, in those patients in our study in whom hypodensity localized only in the lentiform nucleus was seen on the early CT study, HI, when present, was always localized to the lentiform nucleus (Fig. 1). This confirms recanalization of the MCA stem, which was also documented by the disappearance, after 7 days, of the MCA hyperdensity detected on the early CT study. Furthermore, in those patients in whom hypodensity on early CT studies was localized to the lentiform nucleus and cortex, HI frequently developed in both anatomic structures (Fig. 2); the disappearance of the MCA hyperdensity in these cases indicates MCA recanalization. In the only patient in this group in whom HI developed that was localized only to the cortex (Fig. 3), persistence of the MCA occlusion was suggested by persisting MCA hyperdensity on follow-up CT and confirmed by repeat angiography. The cortical HI in this case resulted from late development of cortical CBS, as demonstrated by repeat angiography (Fig. 3). Finally, in patients in whom hypodensity was seen in the cortex on early CT scans, HI always developed in the cortical territories (Fig. 4). The presence of HI in these cases is most likely due to a late cortical reperfusion through leptomeningeal anastomoses (Fig. 4F).

In 18 (72%) of 25 patients in whom hypodensities were seen on CT scans soon after ictus, HI developed subsequently. This early CT finding, therefore, strongly predicts the hemorrhagic transformation of ischemic stroke (Table 1). In addition, HI failed to develop in any of the 11 patients in whom hypodensities were not seen on early CT studies.

When hypodensity is localized only to the lentiform nucleus on early CT scans, the subsequent HI always involves the lentiform nucleus owing to the reopening of a formerly occluded MCA. Hemorrhagic involvement of the cortex in these cases is dependent on the early or late development of leptomeningeal CBS. When hypodensity is localized to the cerebral cortex on early CT scans, HI always develops and involves the cortical territories owing to the late development of leptomeningeal CBS. Finally, when hypodensity is present in both the lentiform nucleus and cortex on early CT studies, HI always develops and frequently involves both territories owing to the reopening of the formerly occluded MCA. Our data confirm that hemorrhagic transformation is a rather common evolution of thromboembolic ischemic stroke. In these patients, hypodensity on early CT studies almost certainly predicts the development of HI. This predictive value may play an important role in the medical management of stroke patients.

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The reader's attention is directed to the commentary on this article, which appears on 1123–1126.