Sensitivity and Prognostic Value of Early CT in Occlusion of the Middle Cerebral Artery Trunk

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PURPOSE: To investigate the incidence and prognostic value of local brain swelling, the extent of parenchymal hypodensity, and the hyperdense middle cerebral artery sign as shown by CT within the first 5 hours after the onset of symptoms in patients with angiographically proved middle cerebral artery trunk occlusions. **METHODS:** Fifty-three patients were studied prospectively with CT 46 to 292 minutes (median, 120; mean, 134 ± 59) after symptom onset and scored clinically at admission and 4 weeks later. All patients were treated with recombinant tissue plasminogen activator (30 to 100 mg). **RESULTS:** Early CT showed parenchymal hypodensity in 43 patients (81%), local brain swelling in 20 patients (38%), and hyperdensity of the middle cerebral artery trunk in 25 patients (47%). Hypodensity covering more than 50% of the middle cerebral artery territory had an 85%, local brain swelling a 70%, and the hyperdense middle cerebral artery sign a 32% positive predictive value for fatal clinical outcome. Specificity of these findings for fatal outcome was 94%, 83%, and 51%, respectively, and sensitivity was 61%, 78%, and 44%, respectively. **CONCLUSIONS:** Early CT in acute middle cerebral artery trunk occlusion is highly predictive for fatal clinical outcome if there is extended hypodensity or local brain swelling despite aggressive therapeutic attempts such as thrombolysis or decompressive surgery.

Index terms: Arteries, cerebral, middle (MCA); Arteries, stenosis and occlusion; Brain, computed tomography; Brain, ischemia; Brain, infarction

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Among the most serious conditions in cerebrovascular disease are the occlusions of the middle cerebral artery (MCA) trunk and of the basilar artery. Whereas basilar occlusion directly causes impairment of brain stem functions, MCA trunk occlusion may lead to extended space occupying "malignant" ischemic brain edema, consequent uncal herniation, and finally incarceration of the midbrain. Mortality in patients with MCA occlusion is between 5% and 45% (1–3). Several attempts have been made to prevent malignant ischemic brain swelling, such as embolectomy, bypass surgery, and most recently thrombolytic recanalization (4, 5). To reduce intracranial pressure, decompressive surgery has been performed in some of these patients (3, 6). A precondition for the effectiveness of these therapeutic measures, however, is to select the patients early after the onset of symptoms. Emergency computed tomography (CT) is still the first diagnostic step after physical examination in patients with acute focal neurologic deficits. In contrast to the older literature, recent studies reported positive CT findings in 56% to 95% of patients with hemispheric ischemic stroke in the first 6 hours after symptom onset (7–10). In one recent study of patients with hemispheric stroke, CT showed ischemic alterations of the brain parenchyma earlier than did magnetic resonance (11). We studied in a selected group up of patients with acute severe hemispheric ischemic stroke caused by MCA trunk occlusion whether CT can predict life-threatening ischemic brain edema and poor clinical prognosis early; that is, when therapeutic decisions have to be made.

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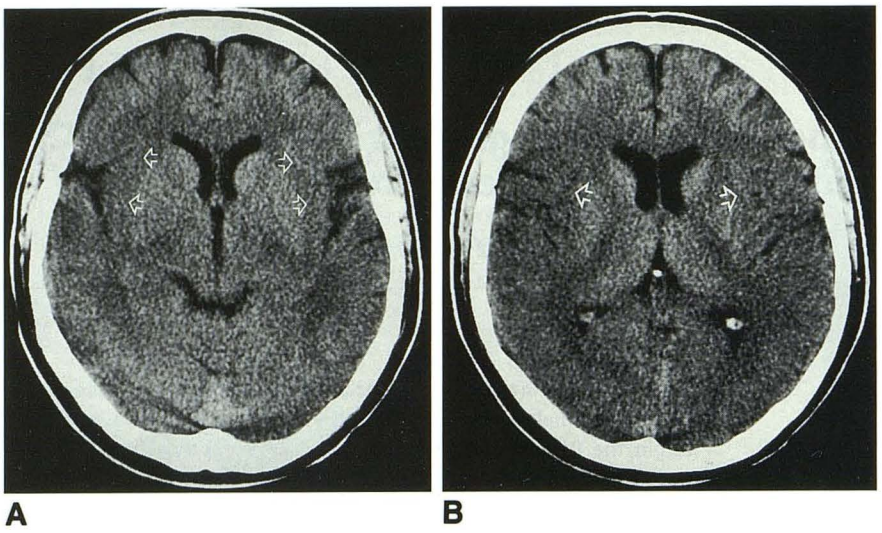

Fig. 1. Noncontrast CT performed 46 minutes after sudden onset of left-sided hemiparesis shows decreased density of right frontal insular cortex (*arrows*) compared with left side (*arrows*) in a 37-year-old man with angiographically proved distal MCA trunk occlusion. Parenchymal hypodensity covers less than 50% of the MCA territory.

A. Scan at lower level of basal ganglia. *B.* Scan at upper level of basal ganglia.

Methods

From February 1988 to August 1992, we recruited for thrombolytic therapy 119 consecutive patients with an acute stroke who were admitted to our hospital within 4 hours after the onset of symptoms. By following a standardized protocol, each patient's pathologic status was documented by neurologic examination (at admission and after 4 weeks) as well as by serial CT and by angiography, enabling prospective analysis of the prognostic value of early CT findings. Inclusion criteria for this study were 1) a precisely defined and witnessed onset of hemiparesis within the last 5 hours before the first cranial CT was performed (patients with symptom onset during sleep were excluded); 2) a technically satisfactory CT scan without evidence of cerebral hemorrhage; 3) an MCA trunk occlusion on the side contralateral to the hemiparesis shown by digital subtraction angiography within 2 hours after the first CT scan; 4) at least one additional CT during follow-up; 5) informed consent obtained from the patient or his or her relatives.

A total of 53 patients, 19 women and 34 men (28 to 78 years old; median age, 59), met the inclusion criteria and were selected for the study. Thirty patients had isolated MCA trunk occlusions; that is, an occlusion of the M1 segment corresponding to type 1 and 2 of Bozzao et al (9), or pattern 1 and 2 of Saito et al (3). In an additional 21 patients the occlusion extended from the intracranial internal carotid artery into the MCA trunk, and 2 patients had additional anterior cerebral artery occlusion. Patients with extracranial occlusions were excluded. The first CT study was performed 46 to 292 minutes (median, 120; mean, 134 ± 59) after symptom onset. Twenty-five CT studies were obtained during the first 2 hours after symptom onset, 18 CT studies during the third hour, 7 CT studies during the fourth hour, and 3 CT studies during the fifth hour. All CT scans were unenhanced and obtained on a Picker 1200 SX (Picker International, Highland Heights, OH) scanner with a section thickness of 8 mm throughout the brain. The CT scans were examined prospectively by a neuroradiologist who was aware of the clinical status of the patient. The interpreter determined the presence or absence of a hyperdense MCA sign (HMCAS) (12–16) (that is, a unilateral tubular structure denser than brain in the basal sylvian fissure), focal brain swelling (effacement of sulci, compression of ventricle), and midline shift. The scans were evaluated further for regions of parenchymal radiolucency with an arterial distribution, searching for early signs of cerebral ischemia such as obscuration of the lentiform nucleus (10) or insular cortex (8). The size of a hypodense area was called small if it covered less than 50% of the presumed MCA territory, large if 50% to 90%, and total if more than 90% (Fig. 1 to 3). Follow-up CT scans were performed 1 to 120 days after the stroke.

The collateral blood supply was assessed semiquantitively and prospectively from the digital subtraction angiogram after the symptomatic carotid artery and the ipsilateral vertebral artery had been visualized. It was graded as scarce when no collaterals or only a few collaterals with slow flow were seen, and good if there were many leptomeningeal collaterals from the anterior and posterior cerebral artery. In patients with distal inter-

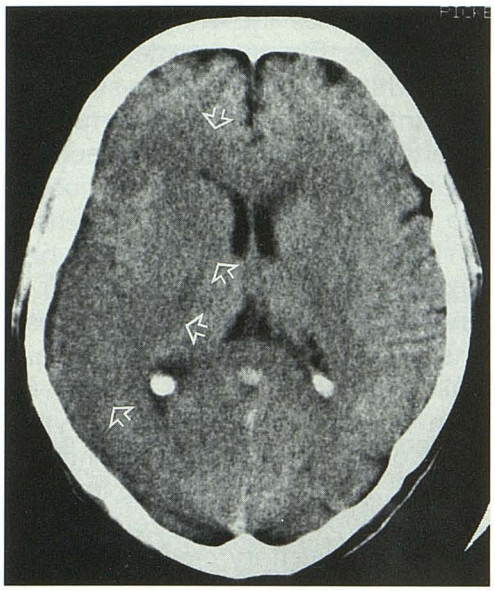

Fig. 2. Noncontrast CT performed 140 minutes after sudden left-sided hemiparesis shows effacement of right-sided sulci and scattered areas of parenchymal hypodensity sparing the insular cortex in a 46-year-old man with angiographically proved MCA trunk occlusion. Parenchymal hypodensity covers more than 50% of the MCA territory.

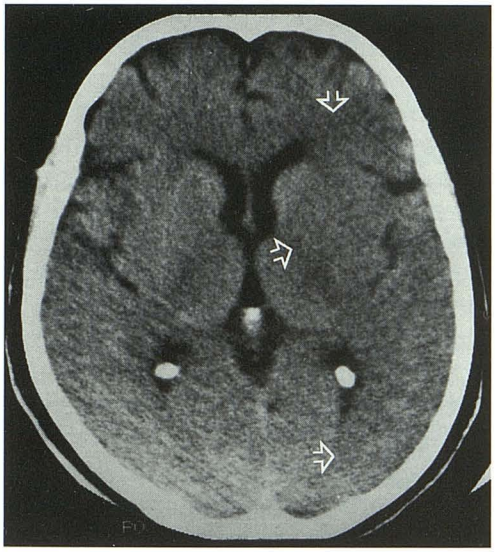

Fig. 3. Noncontrast CT performed 113 minutes after sudden right-sided hemiparesis in a 62-year-old woman with angiographically proved MCA trunk occlusion shows extensive parenchymal hypodensity covering nearly 100% of the MCA territory.

nal carotid artery occlusion, the contralateral common carotid artery was also injected to visualize collateral flow into the A1 segment of the symptomatic side.

At admission and after 4 weeks, a neurologist scored disability and neurologic dysfunction in each patient by using the Oxford Handicap Scale (17) and the Scandinavian Stroke Scale, which is 0 in dead patients and gives 58 points if the patient is asymptomatic (18).

The patients were treated with intravenous (n = 46) or intraarterial (n = 7) recombinant tissue plasminogen activator (30 to 100 mg) within 6 hours after symptom onset; glycerol was given additionally if signs of increased intracranial pressure were present. Partial or complete recanalization of the MCA trunk was shown in 11 patients immediately after recombinant tissue plasminogen activator treatment by a second angiogram and in 18 patients 1 day later by transcranial Doppler ultrasound. Seven patients underwent decompressive craniectomy because their infarctions were accompanied by massive space-occupying effects. The effects of treatment on the extent of ischemic brain damage in this group of patients will be described elsewhere.

The data were analyzed with the χ^2 test and Fisher Exact Test for differences in proportions.

Results

At admission, all patients presented rather uniformly with severe hemispheric symptoms that scored on the Scandinavian Stroke Scale between 4 and 20 points in 26 patients (49%) and between 21 and 30 points in 23 patients (43%). Only four patients (8%) had a better score than 30. Disability was graded 5 in 46 patients (87%), 4 in 6 patients (11%), and 3 in 1 patient on the Oxford Handicap Scale.

The CT findings at varying intervals after the onset of symptoms are shown in Table 1. The earliest finding was a slightly decreased attenuation of the insular cortex in a CT study performed 46 minutes after the patient had collapsed with a sudden hemiparesis (Fig 1). The incidence of hypodensity increased during the first 2 hours up to 100%. All CT scans performed after the 124th minute after symptom onset showed some de-

TABLE 1: CT findings at varying intervals after symptom onset

Interval (min)	No. of Patients Studied	Findings (n)			
		Hypodensity		Swelling	HMCAS
		Small	Large		
<60	3	1	1	0	0
60–119	22	7	8	9	13
120–179	18	14	2	5	7
180–239	7	6	1	5	4
240–292	3	2	1	1	1
Total	53	30	13	20	25

gree of parenchymal hypodensity. The area of hypodensity was small in 30 patients (57%), large in 8 patients (15%), and totally covered the MCA territory in 5 patients (10%). The extent of hypodensities did not correlate with the time of their detection by CT ($P > .2$). All 43 infarctions except 5 covered the lentiform nucleus. Twenty-one small hypodensities (70%) but only 2 large hypodensities (25%) were not accompanied by local brain swelling, whereas all total hypodensities showed local brain swelling ($P < .05$). The incidence of local brain swelling did not increase during the first 5 hours after the onset of symptoms ($P > .1$). None of the early CT scans showed a midline shift. The HMCAS was present in 25 patients (47%).

Collateral flow was good in 23 patients and scarce in 30 patients. Large or total hypodensity in early CT had a positive predictive value for scarce collaterals of 85% (11 of 13), a negative predictive value of 53% (21 of 40), a sensitivity of 37% (11 of 30), and a specificity of 91% (21 of 23). Patients with additional internal carotid artery and anterior cerebral artery occlusions did not have larger hypodensities ($P > .6$).

The follow-up CT scans showed areas of parenchymal hypodensity in all 53 patients except two in whom recanalization of the MCA was achieved within 6 hours after symptom onset and collateral flow was good. In 8 of 10 patients with normal early CT scan, the follow-up CT showed small (n = 4), large (n = 2), or total (n = 2) areas of MCA territory hypodensity. The 30 patients with small infarctions in the first CT scan had small (n = 16), large (n = 8), and total (n = 6) infarctions in the follow-up CT. Follow-up CT showed an increase in size in 6 of 8 large infarctions. Altogether, follow-up CT showed an increase of the hypodense area in 28 patients (53%) but never a decrease or disappearance of parenchymal hypodensity. Follow-up CT revealed involvement of the lentiform nucleus by the hypodense area in 46 patients. There was local brain swelling in 49 patients, 20 of whom also had a cerebral midline shift to the contralateral side. Hemorrhagic transformation was detected by follow-up CT in 21 patients (40%). Ten of these patients had their first CT within 2 hours postictus, 5 patients during the third hour, and 6 between 180 and 292 minutes postictus. The HMCAS was no longer visible in 16 patients and appeared newly in 1, so that follow-up CT scans showed this sign in 10 patients.

Table 2 correlates the early CT findings and clinical outcome. Eighteen patients (34%) died, 17 patients within 4 days after the stroke because of "malignant" ischemic brain edema, 1 patient 24 days after decompressive craniectomy from renal failure. Clinical outcome was poor (Oxford Handicap Scale: 4 and 5) in 16 patients (30%), whereas 19 patients (36%) improved neurologically (Oxford Handicap Scale: 1 to 3). Clinical outcome did not correlate with the presence of hypodensity or HMCAS but with the presence of local brain swelling ($P < .05$) in early CT. The correlation between the extent of hypodensity and clinical outcome was highly significant ($P < .005$) (Table 3): all 13 patients in whom the parenchymal hypodensity covered more than 50% of the MCA territory died (n = 11) or had a poor clinical outcome (n = 2). Sensitivity, specificity, and predictive value of early CT findings are listed in Table 4. In 5 patients with parenchymal hypodensity exceeding 50% of the MCA territory, decompressive craniectomy was performed, although without preventing poor (n = 1) or fatal (n = 4) outcome. The negative CT results in two patients with fatal outcomes were obtained at 61 and 116 minutes after symptom onset.

TABLE 2: Early CT findings for clinical outcomes

Outcome[a]	No. of Patients Studied	Findings (n)		
		Hypodensity	Swelling	HMCAS
Good	19	14	4	8
Poor	16	13	2	9
Dead	18	16	14[b]	8
Total	53	43	20	25

[a] Good designates Oxford Handicap Scale score of 1 to 3; poor indicates scores of 4 and 5.

[b] $P < .05$, Fisher Exact Test.

TABLE 3: Extent of hypodensity for clinical outcomes

Outcome[a]	Hypodensity (n)[b]			
	Absent	Small	Large	Total
Good	5	14	0	0
Poor	3	11	2	0
Dead	2	5	6	5
Total	10	30	8	5

[a] Good indicates Oxford Handicap Scale score of 1 to 3; poor indicates scores of 4 and 5.

[b] Absent, no hypodensity visible; small, area of hypodensity was smaller than 50% of the MCA territory; large, 50% to 90%; total, >90%; $P < .005$, Fisher Exact Test.

TABLE 4: Sensitivity, specificity, and predictive value of early CT findings for fatal outcome

	Findings			
	Hypodensity		Swelling	HMCAS
	Any	Large/Total[a]		
Sensitivity, %	89 (16/18)	61 (11/18)	78 (14/18)	44 (8/18)
Specificity, %	23 (8/35)	94 (33/35)	83 (29/35)	51 (18/35)
Positive predictive value, %	37 (16/43)	85 (11/13)	70 (14/20)	32 (8/25)
Negative predictive value, %	80 (8/10)	83 (33/40)	88 (29/33)	64 (18/28)

[a] Large/total, hypodensity larger than 50% of the MCA territory.

Discussion

The main findings in this series of patients with angiographically proved MCA trunk occlusions are as follows: 1) Sensitivity of CT for parenchymal hypodensity increased up to 100% during the first 2 hours after the onset of symptoms. 2) Sensitivity of the HMCAS for MCA trunk occlusion was relatively low (47%). 3) Large or total hypodensity and focal brain swelling were highly specific (94% and 83%) and predictive (85% and 70% likelihood), but only moderately sensitive (61% and 78%) findings for fatal outcome. 4) Specificity of large or total hypodensity for scarce collateral flow was high (92%). 5) The presence of hypodensity of any extent and the presence of HMCAS had a low predictive value of 37% and 32%, respectively, for fatal clinical outcome.

To our knowledge, surprisingly few patients with angiographically proved MCA trunk occlusion have been studied by early CT, despite the clinical significance of this condition. Tomura et al (10) reported the cases of 7 patients with embolic MCA trunk occlusion studied by CT between 55 and 285 minutes after the onset of symptoms. In all of these patients CT showed an obscured outline or partial disappearance of the lentiform nucleus; in 5 patients local tissue density was slightly decreased, but no patient had an effacement of cortical sulci. In the series of 36 patients reported by Bozzao et al (9), 12 patients had MCA trunk (type 1 and 2) occlusion. In all of these patients, CT performed within 4 hours after symptom onset showed hypodensity of the lentiform nucleus or the cortex, and sulcal effacement in one. Recently, Horowitz et al (7) published a series of 50 patients with CT and angiographic findings (n = 38) within the first 5 hours of stroke. The series included 9 patients with MCA trunk occlusion, 7 of whom showed CT abnormalities. Truwit et al (8) published CT findings in MCA strokes less than 6 hours old but reported no angiographic data. They observed parenchymal hypodensity in one of two patients within 1 hour after symptom onset, in 7 of 8 patients during the second hour, in all 3 patients during the third hour, in 7 of 8 patients during the fourth hour, and in all 4 patients thereafter.

These observations and our series of 53 patients suggest that, contrary to earlier reports (19, 20), neuroradiologists can now detect very early stages of ischemic brain edema thanks to improved CT scanner technology. In our study the interpreter of the CT scans was not aware of the result of angiography. We elected not to blind the neuroradiologist to the clinical data, because we think that good communication between the neurologist and the neuroradiologist is very important, particularly in emergencies, that it will enhance her or his awareness of the potential changes, and that it should be the "gold standard" in clinical practice. This fact may have increased the proportion of positive findings. To test the limits of detectability of early ischemic alterations in a blinded, then unblinded analysis, and to look for interobserver reproducibility under somewhat artificial conditions will be the subject of another study.

Obviously, the frequency of positive findings depends on the degree of ischemia; that is on the site of arterial occlusion and on the development of collateral blood supply (9). Confirming other observations (9, 10), the lentiform nucleus was most frequently involved in our series indicating its poor collateral blood supply. Our findings confirm that ischemic infarctions are detected before local brain swelling or midline shift occurs. This means that CT can show ischemic infarction in the stage of watershift from the extracellular to the intracellular space before there is a significant breakdown of the blood-brain barrier and before brain water content increases considerably.

In describing our findings, we did not differentiate between obscuration of the lentiform nucleus (10), loss of the insular ribbon (8), or other

forms of gray matter hypodensity, because the underlying pathophysiology is considered to be identical. It was shown that the localization of hypodensity depends on the site of arterial occlusion (9). If parenchymal hypodensity in early CT scans reflects early cellular water influx into the cells, then it may represent a region of irreversible brain damage. In agreement with this hypothesis, Bozzao et al (9) could show that very early CT findings in supratentorial ischemic strokes predicted the brain damage that finally develops. We confirmed this by correlating the findings of early and later CT scans and clinical outcome. No area of parenchymal hypodensity shown by early CT decreased in size or became normal, but new areas of hypodensity or an increase of hypodense areas were seen in 28 patients (53%) when the CT scan was repeated. In correspondence to data from positron emission tomography (21), this suggests that consecutive factors other than the primary disturbance of cerebral blood flow caused by MCA trunk occlusion contribute to the final size of ischemic necrosis, and explains that poor clinical outcome was observed in patients with only small or even no area of parenchymal hypodensity shown by early CT. We speculate that secondary events are among these factors diminishing oxygen supply to surrounding brain tissue, such as a decrease of perfusion pressure (caused by the increased tissue pressure), a decrease of arterial blood pressure, or a decrease of arterial oxygen content. To identify these events individually will help to improve the management of acute ischemic stroke.

To search for early radiolucency *and* to determine and classify its extent is a new attempt to obtain more information from CT in acute stroke patients. Being aware that volumetry of very subtle findings is difficult at best (and dangerously time consuming in emergency situations), we decided to classify visually the hypodensities prospectively as "absent, small, large, and total." Our results show that even this rough estimate can be of predictive value in these patients. If early parenchymal hypodensity covered more than 50% of the MCA territory, mortality was as high as 85% (because of malignant brain edema) and outcome was poor in survivors, which means that this finding is highly specific for poor and fatal clinical outcome despite the aggressive therapeutic attempts that were made. Moreover, lack of large or total hypodensity in early CT does not exclude the possibility of fatal outcome in patients with MCA trunk occlusions. Because local brain swelling was associated with more extended infarctions, the high specificity and predictive value of this finding for fatal outcome is not unexpected. Patients with large or total hypodensity, local brain swelling, or hemorrhagic transformation in follow-up CT had their first CT no later than did patients without these alterations. Therefore, delayed diagnostic CT and delayed treatment within the first 6 hours after symptom onset is not responsible for clinical outcome in this group of patients.

Decompressive craniectomy could significantly reduce mortality of 15 patients with severe ischemic brain edema in an open uncontrolled study (Rieke et al, unpublished data) in which surgery was performed within 24 to 96 hours after stroke onset, after detection of a space-occupying large infarct. Of our patients with extended early hypodensity, 5 were operated upon but did not improve. Our data raise the question whether patients with extended early hypodensity should be excluded from decompressive craniectomy or should be operated on earlier. Another question is whether thrombolytic therapy is of any clinical benefit in patients with early large hypodensities. This will be the subject of another work.

The prevalence and sensitivity of the HMCAS in our series (47%) correspond to the findings of Tomsick et al (15), who observed this sign in 4 of 8 patients with occlusions of the M1 segment. In another series, 9 of 13 patients (69%) with angiographically proved MCA trunk occlusion had the HMCAS (14). Because we showed that MCA trunk occlusion alone does not predict the extent of ischemic brain infarction and clinical outcome, HMCAS was correspondingly of low prognostic value in this selected group of patients. Even in unselected patients with a first cerebrovascular event, HMCAS did not always predict poor prognosis (16).

In conclusion, the early appearance of a parenchymal hypodensity in CT is a highly significant predictor of ischemic brain damage. If parenchymal hypodensity covers more than 50% of the MCA territory, fatal ("malignant") brain edema will occur with a likelihood of 85%. The HMCAS is of *low* prognostic value. CT is well suited to study the development of ischemic brain damage and its predictive value for poor and fatal clinical outcome. Early CT findings seem to be important when stroke patients are selected for therapeutic trials.

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Please see the Commentary by Tomsick on page 16 in this issue.