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AJNR Am J Neuroradiol 1998, 19 (5) 839-846
http://www.ajnr.org/content/19/5/839

AJNR Am J Neuroradiol 19:839–846, May 1998

The Predictive Value of Early CT and Angiography for Fatal Hemispheric Swelling in Acute Stroke

Thomas Kucinski, Christoph Koch, Ulrich Grzyska, Heinz-Jörg Freitag, Hannelore Krömer, Hermann Zeumer

PURPOSE: **Our goal was to analyze the predictive value of early CT and arteriographic morphologic criteria to achieve a more reliable prediction of fatal outcome in patients undergoing fibrinolytic stroke treatment.**

METHODS: **In 74 patients with acute carotid artery stroke, early signs of cerebral ischemia were determined by CT. The site of vascular occlusion was identified by digital subtraction angiography (DSA). The patients were subsequently treated by intraarterial (n = 68) or intravenous (n = 6) fibrinolysis by means of recombinant tissue plasminogen activator (rt-PA), urokinase, or rt-PA combined with lys-plasminogen and followed-up for a period of 3 months. CT and DSA data were compared with the clinical course, with special emphasis on signs of early fatal deterioration (ie, death by intracranial mass effect) as determined by corresponding CT and clinical observations, occurring within 7 days after stroke.**

RESULTS: **Seventeen patients died, all of intracranial mass effect, and all within a week after stroke. In nine of these fatalities, DSA revealed carotid "T" occlusion (CTO), which affected 19 patients. In five of the fatalities, a major early sign of ischemia (MESI, referring to cortical hypodensity in more than a third of the territory of the middle cerebral artery, as seen in 14 patients) was recognizable on the initial CT scan. This led to a higher predictive value and sensitivity of CTO relative to MESI for estimating early fatality.**

CONCLUSION: **CTO as determined by DSA is a substantially better predictor of fatal outcome in patients undergoing intraarterial thrombolytic therapy than is MESI as determined by CT.**

Both major studies dealing with the efficacy of fibrinolytic stroke treatment using intravenous recombinant tissue plasminogen activator (rt-PA)—ie, the European Cooperative Acute Stroke Study (ECASS) (1) and the National Institute of Neurological Disorders and Stroke (NINDS) study (2)—demonstrated the efficacy of fibrinolytic stroke treatment. In these studies, the rate of favorable outcome in treated patients was 12% and 15%, respectively, higher (as determined by modified Rankin scale) than in comparable groups who were administered placebos. But the NINDS study achieved the 15% mark under rather different study rules than those followed by the ECASS; specifically, in the NINDS study, initial CT examination was used only to exclude patients with hemorrhage, whereas in the ECASS, CT exclusion criteria were established to exclude poor-outcome candidates before treatment.

von Kummer et al (3) and the ECASS (1) found that hypodensity of more than one third of the middle cerebral artery (MCA) territory as established by CT is highly predictive of fatal outcome. We call such a finding a major early sign of ischemia (MESI). If all such cases had not been eliminated, a statistical difference between treated patients and those who received placebos would not have been found in the ECASS (1). Of the 31 patients in the treated group in whom protocol was violated in terms of MESI, 15 died within 7 days after admission, most by hemorrhage or space-occupying infarct edema. Building on these observations, we assumed that relying solely on early CT examinations (4–7), with their related difficulty in depicting and quantifying developing signs of ischemia in brain tissue, might not suffice in identifying patients likely to suffer a fatal outcome.

Received May 5, 1997; accepted after revision October 21.

This study was supported by a grant from Nycomed Imaging A/S.

From the Departments of Neuroradiology (T.K., C.K., U.G., H-J.F., H.Z.) and Neurology (H.K.), University Hospital Eppendorf, Hamburg, Germany.

Address reprint requests to Thomas Kucinski, MD, Department of Neuroradiology, University Hospital Eppendorf, Martinistrasse 52, D-20246 Hamburg, Germany.

In our group of stroke patients, all of whom were intended to be treated by intraarterial fibrinolysis, we performed both CT and digital subtraction angiography (DSA) before treatment. We thus tested the hypothesis that information on the vascular status of stroke patients would provide a higher predictive value for death from hemispheric brain swelling than would MESI alone as seen on CT scans.

Methods

Between May 1989 and March 1996, 114 patients suffering from a sudden neurologic deficit of the carotid artery distribution were admitted to our clinic for intraarterial cerebral DSA. Of these patients, 74 met the following inclusion criteria for the present study: 1) clinical symptoms indicating acute stroke involving the carotid artery distribution; 2) DSA findings indicative of extracranial or intracranial arterial vessel occlusion, related to current stroke symptoms; 3) subsequent fibrinolytic stroke treatment (8–11) within 6 hours of symptom onset; 4) an initial low-artifact CT scan, obtained before DSA, that excluded hemorrhage; and 5) at least one interpretable follow-up CT study. The resulting group consisted of 51 men and 23 women with a mean age of 53 ± 14 years (range, 19 to 76 years).

The unenhanced initial CT scans were evaluated retrospectively and independently by two neuroradiologists who were unaware of actual clinical symptoms, neurologic outcome, or follow-up CT results. Early CT findings of ischemic injury were interpreted as a slight hypodensity of the lentiform nucleus (12), the insular cortex (13), or the remaining hemispheric cortex (4–6), which was divided into three segments in a manner similar to the procedure used in (1) (ie, roughly localized to the frontal, temporal, and parietal supply of the MCA). CT scans at the level of the lentiform nucleus and at the cella media were chosen as reference standards (14). Hypodensity of the hemispheric cortex exceeding 33% of the MCA territory was considered a MESI. An additional sign of early ischemic alteration was hemispheric swelling as indicated by an effacement of the cerebral sulci, asymmetry of the basal cisterns, or ventricular compression (6). Cortical hypodensity within regions of the anterior cerebral artery (ACA) or posterior cerebral artery territory as well as a hyperdense MCA sign (15–18) were sought.

In a second session, after reviewing the follow-up CT studies and ascertaining the site of vessel occlusion that had subsequently been established by angiography, the two neuroradiologists reexamined the initial CT scans for signs of early ischemia. The follow-up CT scans were usually obtained 24 to 36 hours after onset of stroke and at any time required by the clinical situation. If hyperdense lesions occurred within the region of infarct or elsewhere, they were classified as hemorrhagic transformation, which corresponds to petechiae within the margins of the infarcted area, and parenchymal hemorrhage, which represents a blood clot with additional space-occupying effect (1, 19). Presence of subarachnoid and intraventricular blood was recorded separately.

Intraarterial DSA was performed via femoral approach, such that each carotid artery and, in most cases, the vertebral artery could be examined if symptoms or examination results indicated their involvement. Local intraarterial fibrinolysis was carried out as described elsewhere (8–11, 20–22), with urokinase (750,000 to 1,000,000 IU), plasmin (a combination of rt-PA [10 mg] and lys-plasminogen [2500 IU/h]) or rt-PA (80 mg) alone. Six patients with inaccessible emboli received an intravenous infusion of 80 mg rt-PA. Fibrinolysis was used for a maximum of 2 hours and was ended either upon complete recanalization of occluded vessel segments or when maximal doses were administered within the 2-hour period. Recanalization was judged to be complete if all occluded vessels were reopened and anterograde flow to all distal segments was established. It was considered to be incomplete if one or more distal vessels remained occluded. Except for the six patients with inaccessible emboli, the location of vessel occlusion was based on superselective evaluation with a coaxial microcatheter system.

Six different types of occlusion were seen: 1) occlusion of the internal carotid artery (ICA) in the neck associated with an MCA embolism (ICA/MCA); 2) occlusion of the intracranial bifurcation of the ICA (carotid "T" occlusion, CTO); 3) multiple MCA and ACA occlusion not involving the carotid "T" but rather peripheral branches of the MCA/ACA; 4) MCA trunk occlusion proximal to the medial lenticulostriate arteries (MCA trunk); 5) MCA trifurcation lateral to the medial lenticulostriate arteries (MCA trifurcation); and 6) single or multiple MCA branch occlusion with free trifurcation (MCA branch).

After the initial neurologic examination, the patients were observed for clinical signs of elevated intracranial pressure in an intensive care unit until at least the first day after the insult. Intracranial mass effect of space-occupying infarct edema was considered the cause of death if clinical and neuroradiologic (CT) observations were in agreement and if death occurred within the first week after stroke. Final clinical follow-up was carried out over a 3-month period after admission.

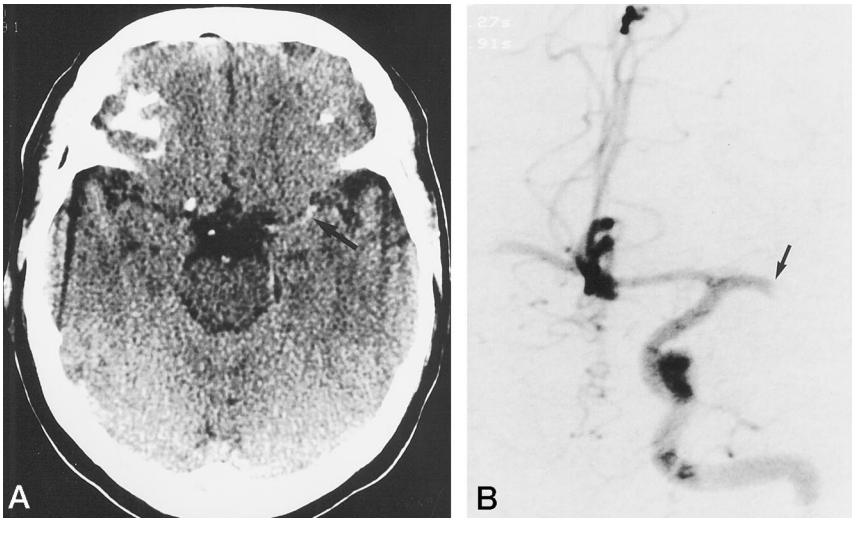

FIG 1. *A*, Early CT scan shows a hyperdense MCA sign (*arrow*) on the left 120 minutes after onset of a severe right-sided hemiparesis.

B, DSA shows a trunk occlusion of the MCA (*arrow*).

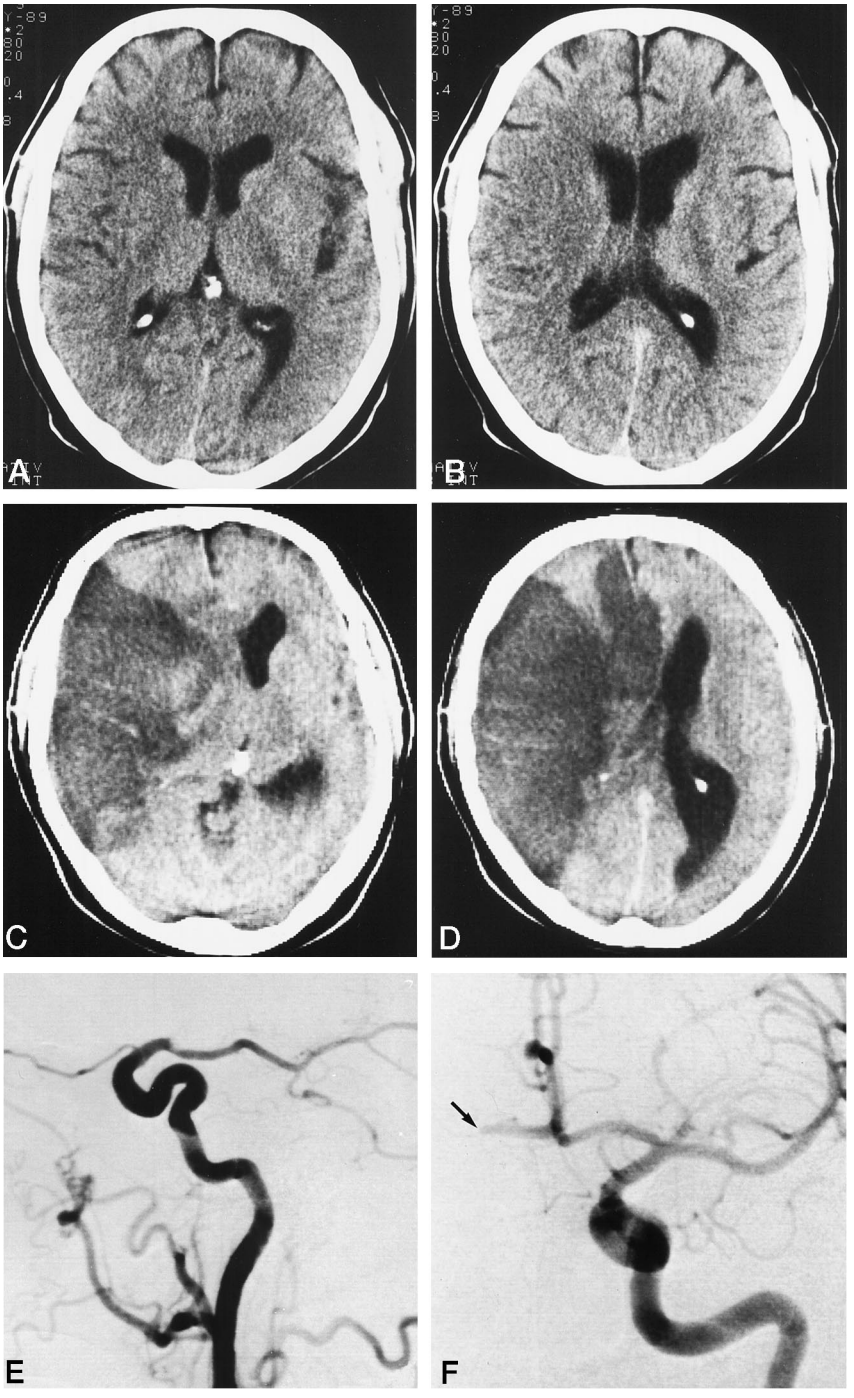

FIG 2. *A* and *B*, Initial CT study of a patient with left-sided hemiplegia and impaired level of consciousness lasting 105 minutes shows hypodensity of the lentiform nucleus, insular ribbon, and temporal hemispheric cortex on the right.

C and *D*, Follow-up CT examination 3 days later shows space-occupying infarction of the MCA territory with hemorrhagic transformation of the lentiform nucleus and additional partial infarction of the ACA territory.

E, DSA of the right carotid artery indicates CTO by a lack of flow of contrast medium distal to the posterior communicating artery.

F, Injection into the left carotid artery shows cross-filling of the A1 segment of the left ACA and a characteristic failure of distal opacification (*arrow*), proving CTO. The patient died 2 days later with clinical signs of elevated intracranial pressure.

For statistical analysis the unpaired *t*-test, the χ^2-test (95% odds ratio confidence intervals [CI]) (23), and the two-tailed Fisher's exact test for 2×2 tables were applied.

Results

Early signs of ischemic brain damage were seen on CT studies at a mean of 2 hours after initial stroke (range, 0.75 to 4.5 hours) in 84% of all stroke patients. Selected examples of early CT findings and corresponding DSA images are shown in Figures 1 to 3.

In Table 1, mean age, sex distribution, mean time between initial stroke and early CT, frequency of general early CT signs, occurrence of MESI, and fatal swelling are presented for each type of vessel occlusion in those patients with MESI. No significant difference was found between MESI, CTO, and non-CTO relative to age or time of assessment of early CT. Sex differences were considered a statistical artifact. Almost no patient, regardless of the type of carotid occlusion, was without early signs of infarct. Hypodensity of the lentiform nucleus and insular cortex were common findings in proximal MCA occlusions, but not in peripheral intracranial occlusions of the MCA branch or in multiple peripheral MCA/ACA embolisms, in both of which early infarct signs were found less often (Tables 1 and 2).

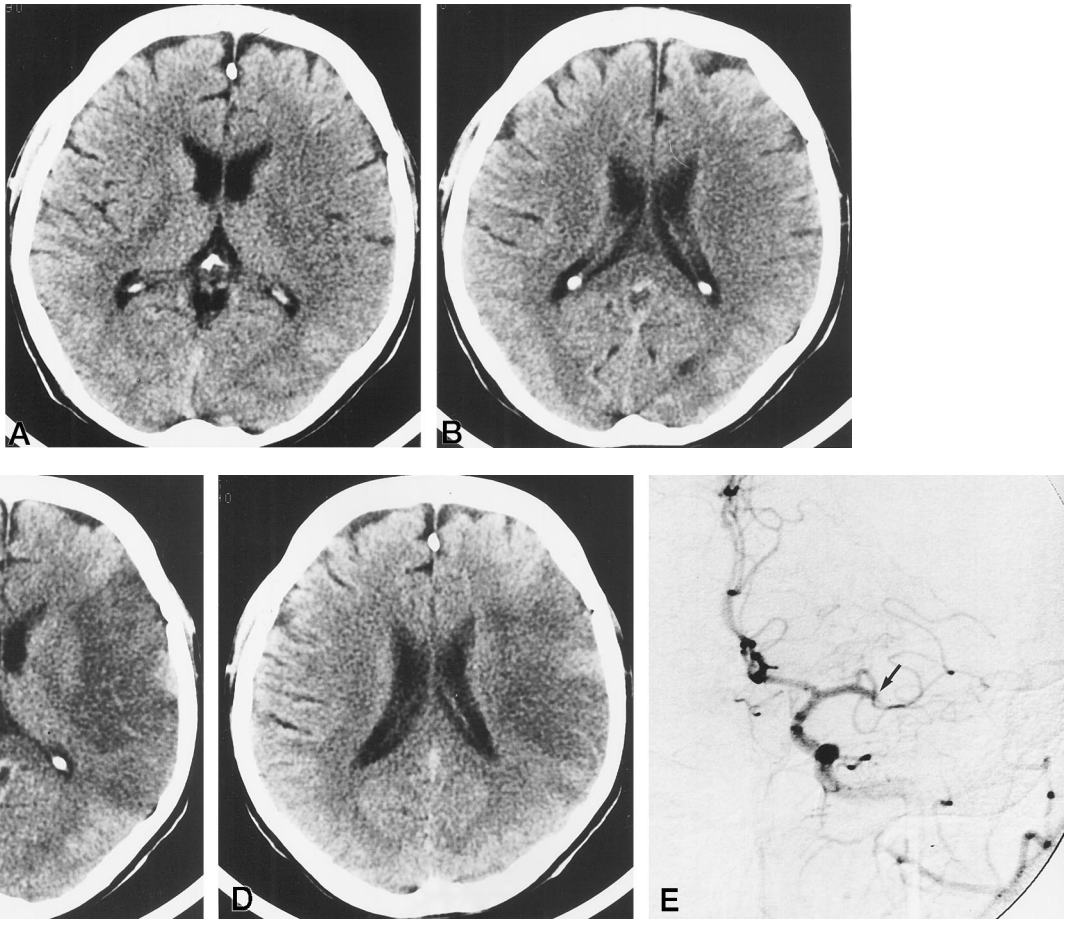

FIG 3. *A* and *B*, CT study in a patient 135 minutes after the onset of hemiparesis and aphasia shows hypodensity of the left insular, frontal, and temporal hemispheric cortex judged as a MESI. Effacement of cerebral sulci indicates early hemispheric swelling.
C and *D*, CT study 1 day later shows nearly total infarction of the hemispheric cortex of the MCA territory.
E, Angiography of the right carotid artery proved occlusion of the MCA (*arrow*) distal to the medial lenticulostriate arteries (MCA trifurcation), allowing opacification of two minor branches of the MCA. The patient survived with severe disability.

TABLE 1: Early CT signs and fatal swelling in classification of vessel occlusion

Diagnosis	No. of Patients	Mean Age, y	Sex Distribution M/F	Time from Stroke to Early CT, h	General Early CT Signs	MESI	Fatal Swelling
					No. (%)	No. (%)	No. (%)
MESI	14	53	13/1	2.4	14 (100)	14 (100)	5 (36)
CTO	19	57	15/4	1.9	18 (95)	4 (21)	9 (47)
Non-CTO*:							
ICA/MCA	6	60	4/2	3.1	6 (100)	1 (17)	2 (33)
MCA/ACA	6	54	3/3	1.8	3 (50)	0 (0)	2 (33)
MCA trunk	16	52	11/5	2.3	15 (94)	6 (38)	2 (13)
MCA trifurcation	21	49	12/9	1.7	17 (81)	1 (5)	2 (10)
MCA branch	6	56	6/0	1.8	3 (50)	2 (33)	0 (0)
Total non-CTO	55	54	36/19	2.1	44 (80)	10 (18)	8 (15)

Note.–MESI = major early sign of ischemia (hypodensity on early CT exceeding 33% of MCA territory); CTO = carotid "T" occlusion; ICA/MCA = occlusion of the internal carotid artery (ICA) associated with middle cerebral artery (MCA) embolism; MCA/ACA = multiple MCA and anterior cerebral artery (ACA) embolism; MCA trunk = trunk occlusion of MCA; MCA trifurcation = occlusion of MCA at trifurcation; MCA branch = single or multiple MCA branch occlusions.

* Site of vessel occlusion (other than CTO) defined by intraarterial DSA.

TABLE 2: Early ischemic signs and outcome CT

Occlusion	No.	Early Signs on CT MCA Cortex		Infarct on Follow-up CT MCA Cortex		Hemorrhage		
		Max 33%*	MESI	Max 33%	>33%	HT	PH	Other†
CTO	19	15	4	6	13	8	1	0
ICA/MCA	6	5	1	3	3	0	0	0
MCA/ACA	6	6	0	3	3	1	1	1
MCA trunk	16	10	6	8	8	4	1	1
MCA trifurcation	21	20	1	15	6	8	1	5
MCA branch	6	4	2	2	4	1	0	0
Non CTO	55	45	10	31	24	14	3	7

Note.—HT = hemorrhagic transformation; PH = parenchymal hematoma; see Table 1 for other abbreviations.

* Number of patients without hypodensity or with hypodensity in maximal 33% of usually MCA-supplied hemispheric cortex.

† Subarachnoid or intraventricular hemorrhage.

TABLE 3: Carotid "T" occlusion (CTO) versus fatal swelling

CTO	Fatal Swelling		
	Yes	No	Total
Yes	9	10	19
No	8	47	55
Total	17	57	74

Note.—Positive predictive value (PPV) was 9/19 = 0.47; negative predictive value (NPV) was 47/55 = .85; sensitivity was 9/17 = .53; specificity was 47/57 = .83.

TABLE 4: Major early sign of ischemia (MESI) versus fatal swelling

MESI	Fatal Swelling		
	Yes	No	Total
Yes	5	9	14
No	12	48	60
Total	17	57	74

Note.—Positive predictive value (PPV) was 5/14 = .36; negative predictive value (NPV) was 48/60 = .80; sensitivity was 5/17 = .29; specificity was 48/57 = .84.

Fatal swelling and resultant early death occurred at a mean of 5 days, no death occurred later than 7 days after stroke. In each fatal case, CT and clinical signs of elevated intracranial pressure corresponded, so all deaths were considered to be due to intracranial mass effect of brain edema. Fatal swelling resulted in 47% of all CTO cases (Fig 2), which yielded a positive predictive value for CTO (Table 3) in contrast to all non-CTO cases, in which early death due to increased intracranial pressure only reached 15%, the negative predictive value being .85, sensitivity .53, and specificity .83 (Table 3). The odds ratio for CTO patients to sustain fatal swelling was 5.3 (CI 1.7 to 16.2) ($P \leq .01$; Fisher's exact test for 2×2 tables). MESI were not significantly related to malignant infarcts in the ICA territory stroke, because of a relatively lower positive predictive value (.36) and sensitivity (.29) than those for CTO (Table 4). The odds ratio for patients with MESI to die of intracranial mass effect was 2.2 ($P \leq .29$). Negative predictive value (.80) and specificity (.84) hardly differed from those for CTO.

TABLE 5: Predictivity levels of other early CT signs of fatal swelling

	Lentiform Nucleus	Insular Cortex	Swelling	HMCAS
PPV	0.23	0.27	0.29	0.24
NPV	0.78	0.89	0.80	0.78
Sensitivity	0.65	0.88	0.47	0.47
Specificity	0.37	0.30	0.65	0.54
Odds ratio	1.1	3.2	1.6	1.1
95% CI	0.3–3.3	0.7–14.7	0.6–4.9	0.4–3.2
P	1.00	0.21	0.40	1.00

Note.—PPV = positive predictive value; NPV = negative predictive value; HMCAS = hyperdence middle cerebral artery sign.

In non-CTO cases, death was predominantly related to combined findings of ICA/MCA or MCA/ACA occlusion (Table 1). In patients with more distally located occlusions (MCA trunk and MCA trifurcation), fatal swelling was a rare finding, even in the presence of MESI (Fig 3): it was never observed with MCA branch occlusions. Negligible predictive value concerning poor outcome was found for other early infarct signs (Table 5), such as hypodensity of the lentiform nucleus or insular cortex, swelling, and a hyperdense MCA sign (Fig 1).

Secondary parenchymal hemorrhage occurred in a single patient with CTO, who survived. The only parenchymal hemorrhage with lethal mass effect occurred in a patient in whom multiple MCA/ACA emboli preceded hemorrhage. Hemorrhage of any kind, however, was most frequent in patients with CTO (47%), although the predictivity did not prove statistically significant (odds ratio 2.0; $P \leq .27$). MESI was an even less sufficiently reliable predictor of hemorrhagic transformation or parenchymal hemorrhage (29%; odds ratio 0.7; $P \leq .76$). Additional intraventricular or subarachnoid hemorrhages were rare (Table 2); three such cases (two intraventricular, one subarachnoid) were associated with death, including the aforementioned case involving an intraventricular hemorrhage additional to parenchymal hemorrhage. Hemorrhage occurred significantly more frequently ($P \leq .01$) in patients who died (65%) than in those who survived (26%). Similarly, a significant differ-

ence ($P \leq .001$) was found between the mean age of all patients who died of fatal swelling (61 years) and those who survived (51 years).

Either complete or incomplete recanalization after intraarterial (n = 68) or intravenous (n = 6) application of fibrinolytic drugs was achieved in 61% of the cases. In cases of CTO, the recanalization rate was only 37% (only one complete), in non-CTO occlusions 69% ($P \leq .02$). Successful recanalization was followed by death in only 13% of patients, but when recanalization failed, fatal swelling occurred in 61% ($P \leq .02$).

Discussion

Previous investigators have found that fibrinolytic stroke treatment (1, 2, 8–11, 20–22) is only useful if it serves to reestablish normal blood flow to brain regions that have at least temporarily remained undamaged owing to a transiently sufficient collateral blood supply. The damage incurred by early loss of tissue attenuation and slight mass effect as a consequence of increasing water content of brain tissue due to intracellular cytotoxic edema and extracellular fluid elevation (24, 25) is considered irreversible (4, 5). Thus, CT signs of ischemia (5–7, 12, 26, 27) show the core of the infarcted tissue at a moment when treatment is still possible. To ameliorate the indication for fibrinolytic treatment and to improve patient selection, we investigated the positive predictive value of early infarct signs of fatal hemispheric swelling. Early infarct signs, however, are only an indirect clue to the existence of poorly collateralized vascular territories.

Of the six occlusion types seen in the present study, those occurring exactly at the "T" of the ICA proved most detrimental (see Table 1). These CTOs not only disrupt blood flow into the M1 and A1 segments of the ACA and MCA (Fig 2E) but also prevent cross flow to the ischemic MCA territory (Fig 2F). They are not equivalent to other types of ICA occlusion (such as dissection, atherosclerotic plaque, or balloon placement) in more proximal sections of the ICA, in which cross flow is sustained. Such occlusions are far better tolerated clinically.

In cases of CTO, the ACA territory on the occlusion side can only be supplied via the anterior communicating artery. The ischemic MCA territory can only be supplied with blood that has already passed the ACA peripheral vessels against an increased peripheral resistance within the leptomeningeal collateral anastomoses. Subsequently, the flow capacity of the contralateral A1 segment and the anterior communicating artery is insufficient to provide an adequate leptomeningeal collateral blood supply to the most distal MCA territory.

We examined early CT and angiographic findings for sites of intracranial vessel occlusion to determine their power in predicting early fatal outcome. CTO was found to offer a better indication of impending brain swelling associated with herniation and death. Other investigators (28–30) also found a high correlation between CTO and poor clinical outcome (not always fatal). In contrast to other observations (1, 28), we found the predictive value of MESI (based on early hypodensity exceeding 33% of the MCA territory) not to be a statistically significant indicator of poor outcome. This discrepancy may be due to the number of patients in our study, since tentatively adjusting the findings of MESI (depicted in Table 4) to the number of patients recruited in the ECASS trial reveals a significant odds ratio for fatal outcome.

In the evaluation of early CT findings related to MESI, one must take into account that not only detection but especially a dependable quantification of subtle parenchymal hypodensity is difficult in the emergency setting. Consequently, the determination of clearly definable ischemic brain regions must be improved. Assuming a time-dependent evolution of early ischemic brain lesions (4, 13), the earlier a patient is examined the more difficult the CT quantification.

Although the hyperdense MCA sign has been reported to indicate major infarcts in stroke patients (15–18, 31), in the present study, as observed in 59% of all cases, this sign was not predictive of fatal outcome. Any prediction of outcome, especially fatal outcome, based only on that sign is uncertain (4, 18). This is not surprising, since a hyperdense MCA sign at CT is only indicative of vessel occlusion and provides no information on the status of brain tissue or vascular collateralization. Independently recorded early CT signs, such as obscuration of the lentiform nucleus or the insular cortex and early mass effect, also did not prove significantly predictive of fatal swelling.

Opinions on the predictivity of MESI for an approaching hemorrhagic infarction (6, 19, 32, 33) are controversial. We did not establish a significant predictive value of MESI for hemorrhage. In our study collective, different kinds of hemorrhage appeared on 35% of all follow-up CT scans. A parenchymal hemorrhage with significant mass effect was only seen in 5% of our patients. Our data, which were obtained from patients who had received intraarterial fibrinolytic treatment, correspond well with results from the placebo groups of both the ECASS (1) and the Multicenter Acute Stroke Trial-Europe (34) as well as with cohorts from other trials (19, 33).

Owing to violation of the inclusion criteria in the ECASS "intent to treat" group, hemorrhage-related deaths were significantly associated with MESI (1, 3). Although our study does not statistically support the contention that MESI must be followed by parenchymal hemorrhage, a trend in the relationship between hemorrhage and poor outcome is clear: patients with CTO had the highest probability of hemorrhage (47%) (eight hemorrhagic transformations and one parenchymal hemorrhage of 19), and the change from a hemorrhagic transformation to a parenchymal hemorrhage was small. This is important because of the ECASS finding that fibrinolysis does not increase the frequency of hemorrhages at all but does increase their size (1). We found that hemorrhage in general was frequently related to death within 7 days after

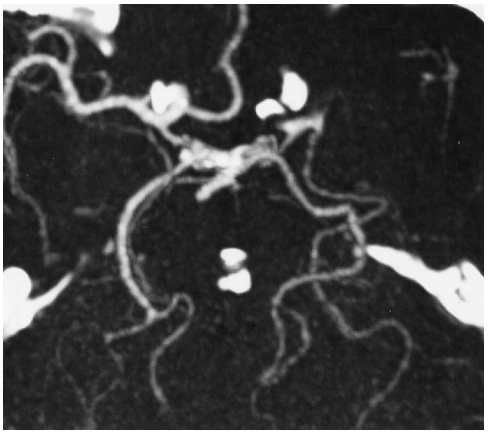

FIG 4. Maximum intensity projection reconstruction of CT angiogram after intravenous bolus injection of 120 mL of contrast material shows a left-sided CTO 210 minutes after onset of right-sided hemiplegia. Note that left C1, M1, and A1 vessel segments are missing, whereas the C2 segment of the ICA is filled by the posterior communicating artery. On the basis of this finding and an anticipated poor prognosis, intraarterial DSA and fibrinolysis were not performed. The patient died 3 days later.

stroke. Although this is a common observation (33), the exact relationship between non–space-occupying parenchymal hemorrhages (hemorrhagic transformation) and fatal outcome remains to be clarified. Similarly, since our results indicate a highly significant relationship between patient age and early deterioration, causality, which may have affected the high death rate in the somewhat older CTO patient group, remains unclear.

In contrast to the study protocols employed in the NINDS (2) and ECASS (1) trials, in which patients were treated with intravenous rt-PA, our protocol provided for the acquisition of angiographic data before treatment with intraarterial fibrinolysis. The diagnosis of CTO does not necessarily depend on DSA; it can be detected easily and without delay by means of CT angiography (an example is shown in Fig 4). Hence, in evaluating possible intravenous fibrinolytic stroke treatment, angiographic information may be gained by means of CT angiography, MR angiography, or even transcranial Doppler sonography. Only DSA, however, can show CTO with excellent leptomeningeal collateral flow into the MCA trunk, such as was observed in one patient who had a favorable outcome after successful recanalization.

Conclusion

We found that CTO was highly predictive of fatal brain edema and indicated a trend toward increased hemorrhage. The significantly lower CTO recanalization rate in connection with fatal outcome further supports the conclusion that fibrinolysis is not useful and possibly even dangerous in such cases. Whether fibrinolysis or early decompressive craniectomy (35, 36) should be chosen for patients at high risk for brain swelling is being evaluated. We propose selecting patients by CTO rather than submitting them to fibrinolytic treatment until more specific outcome predictors, such as functional tests relying on perfusion parameters (37–40), have been validated and made clinically applicable.

Acknowledgment

We thank Dr. Jarold Knispel, Hamburg, for his editorial assistance.

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