Interobserver Agreement in Assessing Early CT Signs of Middle Cerebral Artery Infarction

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PURPOSE: To assess the reliability of detecting signs of hemispheric infarction on CT scans obtained within 6 hours of the onset of symptoms. **METHODS:** A neuroradiologist selected 12 normal and 33 abnormal CT studies showing the hyperdense middle cerebral artery sign (HMCAS) (n = 10), brain swelling (n = 22), and parenchymal hypodensity (n = 33) from two series of 750 patients with recent onset of middle cerebral artery stroke. These selections served as the reference source for a nonblinded analysis of the initial and follow-up CT scans. Six neuroradiologists then reviewed the CT scans twice, first blinded then not blinded to clinical symptoms. They assessed the signs of infarction for each hemisphere separately and estimated the volume of abnormal parenchymal hypodensity in increments of 20% within the territory of the middle cerebral artery. **RESULTS:** Unblinding the reviewers did not change interobserver agreement significantly. The chance adjusted agreement was moderate to substantial: κ = .62 (95% confidence interval [CI], .46 to .78) and κ = .57 (95% CI, .33 to .81) for the HMCAS of the right and left hemisphere, respectively; κ = .59 (95% CI, .47 to .71) and κ = .56 (95% CI, .38 to .74) for focal brain swelling of the right and left hemisphere, respectively; and κ = .58 (95% CI, .50 to .66) and κ = .55 (95% CI, .32 to .67) for parenchymal hypodensity of the right and left hemisphere, respectively. Weighted κ was .65 and .57 for the estimation of the hypodense tissue volume in the right and left hemisphere, respectively. Agreement with the reference source ranged from 73% to 93% for all variables and both hemispheres. **CONCLUSION:** Even with no clinical information, neuroradiologists can assess subtle CT signs of cerebral infarction within the first 6 hours of symptom onset with moderate to substantial interobserver agreement.

Index terms: Arteries, cerebral, middle; Brain, computed tomography; Brain, infarction

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For the last 20 years computed tomography (CT) has been used to examine stroke patients to rule out such competing diagnoses as cerebral ischemia, intracranial hemorrhage, brain neoplasm, encephalitis, and abscess. More recent experience has shown that modern CT technology can further directly depict sequelae of brain ischemia within the first 6 hours after stroke (1–9). Therefore, CT is still widely considered to be the first diagnostic step for patients with acute focal central neurologic deficit (10, 11). Identification of ischemic brain tissue by CT enables the positive diagnosis of cerebral ischemia and delineates that volume of brain tissue prone to die (2, 7). The relation between the volume of identified ischemic brain tissue and the severity of clinical symptoms may show the chances of successful recanalization for a given patient (12). If this volume consists of the major part of a vascular territory, any attempted recanalization is useless and probably harmful (13).

Early CT signs of brain tissue ischemia are subtle, however, and sometimes difficult to detect (8, 14). To study the reliability of early CT

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diagnosis of cerebral ischemic infarction we invited six neuroradiologists to take part in a study of interobserver agreement.

Subjects and Methods

A neuroradiologist selected early diagnostic and follow-up CT scans from 14 institutions taking part in two trials on early treatment of hemispheric stroke that required CT to check inclusion criteria and the extent of infarction within the first 6 hours of symptom onset. This investigator selected 45 of 750 CT scans with the goal being to obtain a representative variety of normal and abnormal findings. Angiography had been performed in 20 of these patients and had shown occlusion of the intracranial internal carotid artery (n = 8) and of the middle cerebral artery (MCA) trunk (n = 12). All patients had had a stroke of the MCA. Section thickness of the CT scans varied from 5 to 10 mm. All scans were unenhanced. The reference neuroradiologist analyzed the initial and follow-up CT scans before the test with knowledge of the patients' clinical history and current clinical and angiographic findings; his interpretations thus became the reference source. Twelve (27%) of the 45 CT scans showed normal findings, 22 (49%) showed focal brain swelling, 33 (73%) showed parenchymal hypodensity, and 10 (22%) showed the hyperdense MCA sign (HMCAS). The reference neuroradiologist estimated the volume of parenchymal hypodensity as less than 20% of the MCA territory in seven patients (16%), as 20% to 40% in 14 patients (31%), as 41% to 60% in five patients (11%), as 61% to 80% in two patients (4%), and as more than 80% in five patients (11%). The 45 CT scans of 45 patients were then presented to six board-certified neuroradiologists in a randomized fashion. All neuroradiologists are faculty members of academic departments of neuroradiology.

The six readers reviewed the CT scans individually in two sequential sessions and were initially not aware of the patients' clinical symptoms or of the number of CT scans with normal findings; however, they knew that the cohort was a stroke population. After the first review, lasting 2 hours, and an intermission of 30 minutes, the reviewers reexamined the same scans in different sequence during the subsequent 2 hours after having been informed as to the side of hemiparesis. They were not allowed to communicate with one another. Each reader had to fill in a form answering questions concerning whether and where focal brain swelling was present, whether and where brain parenchyma was abnormally hypodense, and whether and where the MCA was hyperdense (dichotomous rating). Each variable was assessed for each hemisphere separately. Brain swelling was defined as a circumscribed effacement of cortical sulci, compression of ventricles, and/or shift of midline structures. Parenchymal hypodensity was defined as increased radiolucency of brain structures relative to other parts of the same structure or to its contralateral counterpart that could be recognized visually. The HMCAS was defined as a part of the MCA that was denser than other parts of the vessel or of its counterpart and denser than any visualized vessel of similar size, as shown by unenhanced CT in which density could not be attributed to calcification.The readers were asked to estimate the extent of abnormal hypodensity in relation to the MCA territory in increments of 20% (ordinal rating). Before they began their interpretations, readers were given instructions on completing the data sheet, informed of its definitions, and shown two CT scans as examples.

The description of interobserver agreement includes agreement rates and κ for blinded and nonblinded interpretations of the CT scans. A multiple observer κ coefficient with standard error was calculated for dichotomous ratings according to Fleiss (14) for all six observers combined. Approximate 95% confidence intervals were calculated from $\kappa \pm 2 \times$ standard error. In addition, the range of all pairwise κ coefficients is given. In the case of the ordinal rating of the extent of hypodensity, we calculated pairwise weighted κ (with squared weights) by the method given by Fleiss (14). For overall weighted κ we used its equivalence to the intraclass correlation coefficient, which was calculated by applying variance components analysis to the category scores (0 to 5).

In agreement with others (15, 16), we considered a κ of more than .40 and less than or equal to .80 as moderate to substantial, as suggested by Landis and Koch (17).

Agreement rates for dichotomous variables are given for total agreement (all six observers agreed) and for clear agreement (at least five of six observers agreed). For the ordinal rating of the extent of hypodensity we calculated pairwise agreement for all pairs of observers who agreed that a certain extent of hypodensity was visible. Disagreement by one or two categories, respectively, was also considered.

Results

Unblinding did not significantly affect agreement rates or κ values. We therefore only present the results of the blinded CT reading. Interobserver agreement of all six neuroradiologists in assessing CT signs of brain infarction varied from 49% to 71%, with the lowest values achieved for the assessment of parenchymal hypodensity in the right hemisphere (Table 1). Clear agreement of five of the six neuroradiologists was considerably better, varying from 78% to 93%. The chance adjusted agreement among all six neuroradiologists was moderate to substantial for the HMCAS, focal brain swelling, and parenchymal hypodensity in both hemispheres, with κ varying from .55 to .62 (Table 1).

The neuroradiologists agreed substantially in estimating the extent of parenchymal hypodensity with ordinal κ = .65 for the right and ordinal κ = .57 for the left hemisphere (Table 2). Complete pairwise agreement for the identical per-

TABLE 1: Interobserver agreement and κ for dichotomous ratings

	Agreement Rate, %		κ	
	Six of Six Observers	At Least Five of Six Observers	All Observers, κ (95% CI)	Pairwise (Minimum, Maximum)
HMCAS				
R	71	82	.62 (.46–.78)	(.44, .81)
L	69	93	.57 (.33–.81)	(.20, .91)
Swelling				
R	60	82	.59 (.47–.71)	(.38, .79)
L	64	84	.56 (.38–.74)	(.42, .76)
Hypodensity				
R	49	84	.58 (.50–.66)	(.40, .77)
L	56	78	.55 (.43–.67)	(.32, .76)

Note.—HMCAS indicates hyperdense middle cerebral artery sign; CI, confidence interval.

TABLE 2: Interobserver agreement and κ for ordinal rating of extent of hypodensity

	Ordinal κ		Pairwise Agreement,* %		
	All Observers	Pairwise (Minimum, Maximum)	Complete,	±1 Category	±2 Category
R	.65	(.44, .80)	23	61	91
L	.57	(.37, .77)	26	60	86

* Pairwise agreement was calculated only for pairs of observers who agreed that hypodensity was visible. The value given is the percentage of complete agreement (or including disagreement by at most one or two categories).

TABLE 3: Agreement between reference source and single observers or majority rating (five best observers)

	Percentage of Agreement							
	Observer						Mean	Majority
	1	2	3	4	5	6		
HMCAS								
R	76	87	84	87	84	82	83	89
L	78	87	93	91	91	91	89	93
Swelling								
R	80	87	82	87	82	76	82	82
L	78	84	82	89	87	87	84	87
Hypodensity								
R	78	82	80	73	82	76	78	84
L	73	76	84	80	69	87	78	87
All variables, mean	77	83	84	84	83	83	82	87

Note.—HMCAS indicates hyperdense middle cerebral artery sign.

centage of MCA territory's being hypodense was rather low, varying from 23% to 26%. Agreement increased considerably if disagreement by at most one or two categories was allowed.

Agreement between individual observers and the reference neuroradiologist was rather homogeneous, varying from 69% to 93% for all variables and both hemispheres (Table 3). A ranking of observers was attempted in two ways. First, for each variable, we analyzed how often there was a clear majority vote, wherein only one observer disagreed with the others. Combining all variables, we found that observer 3 showed the highest conformity with the majority vote and observer 1 had the highest number of discordant votes. Second, we counted the number of agreements of each observer with respect to the reference source. With all variables combined, it is again observer 3 (and observer 4) who agreed most often and observer 1 who agreed least often.

Table 3 also includes the number of agreements between the majority vote and the reference source. Here we considered a simple majority based on five observers in order to achieve unequivocal majority votes. After identifying and excluding the least consistent rater (observer 1), we found the majority vote agreed more with the reference source than did the best single observer.

Discussion

Whereas the older literature suggests that CT is not helpful in assessing ischemic tissue changes during the first 12 to 24 hours after the onset of symptoms, more recent studies have demonstrated that CT can show signs associated with brain ischemia within the first 6 hours after stroke (1–9). These include the HMCAS or hyperdensity of other cerebral vessels, focal brain swelling, and/or parenchymal hypodensity.

The HMCAS is not literally an early CT sign of ischemic infarction but rather a highly specific but not very sensitive CT sign of MCA occlusion (7, 18). Selection of patients and number of patients studied clearly affect the prevalence of the HMCAS: in the first 6 hours after ischemic stroke, CT detected HMCAS in 35%, 50%, and 47% of patients with angiographically proved MCA occlusion (7, 19, 20). The prevalence of the HMCAS on CT scans was low in patients selected for hemorrhagic and nonhemorrhagic stroke (27%), in patients with MCA infarctions (30%), and in patients with hemispheric infarctions (17%) (13, 19, 21). In consecutively selected patients, HMCAS was associated with a higher rate of early parenchymal hypodensity and hemorrhagic transformation and with the development of large infarctions (19–22). Some studies have found that HMCAS is associated with poor clinical outcome (23–28).

So far, the prognostic value of early focal brain swelling in brain ischemia has been studied only in patients with MCA occlusion (7): the positive predictive value for fatal outcome was 70%.

The clinical significance of parenchymal hypodensity as depicted by CT within the first 6 hours of symptom onset has been studied in only a few instances. It has been suggested that early (<4 hours) positive CT findings predict hemorrhagic transformation of ischemic brain tissue and final brain damage (2, 4). In a study of thrombolytic therapy, four of 10 patients had early CT signs of infarction within 3 hours of stroke. None of them showed arterial recanalization and only one improved clinically, whereas four of six patients with no early CT findings had excellent or good outcomes (29).

The size of an ischemic lesion on initial CT scans obtained within 48 hours of stroke onset correlated positively with the neurologic deficit at 1 week and 3 months after stroke (30). A study of patients with MCA occlusion showed that early parenchymal hypodensity covering more than an estimated 50% of the MCA territory is associated with a mortality of 85% (7).

All these studies underline the clinical significance of early CT findings after stroke. In addition, a recently terminated international stroke study showed that thrombolysis may be beneficial, if patients with a parenchymal hypodensity exceeding 33% of the MCA territory are excluded (13).

As far as the reliability in detecting these findings by CT in acute stroke, Tomsick et al (16) studied the limits of detectability of the HMCAS in selected CT scans performed within 90 minutes of symptom onset, a period during which the frequency of brain swelling and parenchymal hypodensity caused by ischemia may be low. These investigators found an overall agreement with a reference source of 91% for the blinded readings and 87% for the nonblinded readings. The κ values for interobserver agreement were .38 and .53, respectively.

Like Tomsick et al (16), we asked six neuroradiologists to serve as observers and we compared their ratings with that of a reference neuroradiologist. Because 6 hours is a widely accepted period for therapeutic decisions in acute stroke, we gathered 45 CT scans obtained within this time frame and studied interobserver agreement in detecting brain swelling and parenchymal hypodensity in addition to the HMCAS. We repeated the test after unblinding the reviewers to the clinical signs and symptoms and allowing a short intermission. Because of this study design, we cannot entirely exclude the possibility that the reviewers' exhaustion or memories of their blinded interpretation influenced the second reading. This may explain why unblinding did not significantly enhance interobserver agreement and why knowing the involved hemisphere did not significantly affect the readers' sensitivity.

The overall and chance adjusted agreement as presented in Tables 1 to 3 for blinded interpretations suggest that neuroradiologists can assess the signs of ischemic brain infarction and the HMCAS on CT scans obtained within 6 hours of stroke with moderate to substantial interobserver agreement. As compared with an

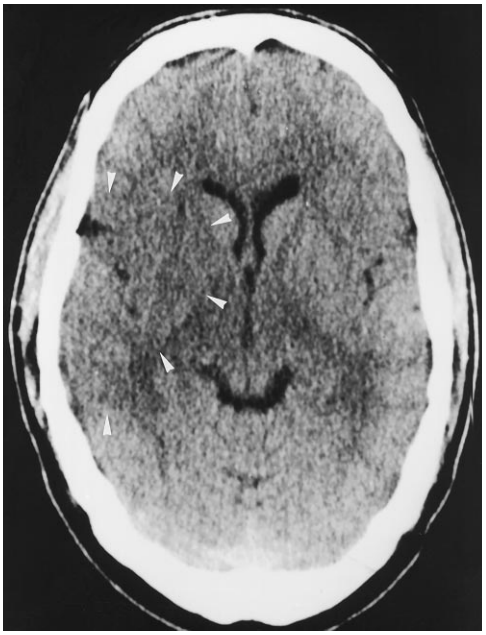

Fig 1. Twenty-year-old man with left-sided hemiparesis of 3 hours' duration. CT scan shows parenchymal hypodensity of the right insular cortex, putamen, pallidum, and temporal lobe with blurred margins (*arrowheads*). Interpretation by the reference neuroradiologist for all sections was as follows: "Parenchymal hypodensity of right lentiform nucleus and insular cortex covering 20% to 40% of the middle cerebral artery territory, slight tissue swelling with compression of right ventricle. No hyperdense middle cerebral artery sign."

observer who is aware of the patient's clinical history and symptoms and who has already seen follow-up scans that might have shown the well-demarcated infarction or no abnormality at all, the blinded observer may misinterpret signs of infarction in up to 31% of scans. If identical scans are presented to a group of neuroradiologists (such conferences occur seldom in daily clinical practice but may play a role in major clinical trials), the strategy of obtaining a majority vote may enhance the sensitivity of CT signs of infarction over that achieved by even the best individual reader.

Detecting subtle parenchymal hypodensity may be one problem; estimating its extent, another. The borders of this area may be too shallow to perform exact measurements (Fig 1). Because parenchymal hypodensity after cerebral ischemia represents the increase in tissue water content as a sequela of no or low perfusion in an arterial supply area, its extent follows certain patterns. Knowledge of the major cerebral arterial distribution areas should enable an experienced neuroradiologist to recognize this pattern of parenchymal hypodensity and thus its extent. One study revealed excellent interobserver agreement, with $\kappa = .78$ between two experienced neuroradiologists in classifying patterns of cerebral infarctions on CT scans obtained 2 hours to 3 months after stroke (31). Determining the hypodense tissue volume in partitions of the MCA territory may be advantageous with regard to therapeutic consequences: If the whole volume of MCA tissue distribution has already become hypodense after proximal MCA occlusion, the chances for recanalization to be beneficial may be considerably lower than in patients with the same type of arterial occlusion but only small hypodense tissue volume (32). In the investigation presented here, we asked the observers to estimate the volume of parenchymal hypodensity in rather small partitions of 20% of the MCA territory to study the limits of volume estimation. Although the chance adjusted agreement of all six neuroradiologists was substantial, the percentage of agreement in the same volume category was low, with 23% and 26% for the right and left hemisphere, respectively. Our observations suggest that categories representing larger partitions of the MCA territory (for example, one third or one half) are more reliable to assess.

In summary, our study suggests that neuroradiologists without any clinical information can reliably determine from the CT scan obtained within the first 6 hours of stroke whether the HMCAS is present and whether and to what extent the MCA territory has become hypodense or swollen in the majority of patients. This information seems of utmost importance for patient management, since the HMCAS is highly specific for an MCA occlusion and defines the vascular territory at risk from hypoperfusion. Parenchymal hypodensity and focal brain swelling represent ischemic edema and thus define the volume of the most ischemic brain tissue prone to die that is not treatable by recanalization and reperfusion.

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