Attenuated Corticomedullary Contrast: An Early Cerebral Computed Tomography Sign Indicating Malignant Middle Cerebral Artery Infarction

A Case-Control Study

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Background and Purpose—No neuroradiological markers have been characterized that support a timely decision for decompressive surgery in malignant middle cerebral artery (MCA) infarction (mMCAI). This case-control study was designed to analyze whether early cerebral CT (CCT) scanning provides reliable information for the prospective selection of stroke patients at risk of developing mMCAI.

Methods—Thirty-one pairs (n=62) were formed with cases (mMCAI) and controls (acute but not malignant MCA infarction) closely matched in terms of age, sex, and stroke etiology. CCT was performed within 18 hours of stroke onset and analyzed by a blinded neuroradiologist according to a defined panel of 12 CCT criteria.

Results—In terms of predicting mMCAI, the criteria of extended MCA territory hypodensities exhibited high specificity (100%, 93.5%, 100%, 96.7%, and 83.9%, respectively) but low sensitivity (45.2%, 58.1%, 12.9%, 19.4%, and 70.9%, respectively). Two criteria yielded high sensitivity (subarachnoid space compressed, 100%; cella media compressed, 80.6%) but low specificity (29% and 74.2%, respectively). The criterion of attenuated corticomedullary contrast yielded both high sensitivity (96.8%) and specificity (83.9%).

Conclusions—The analysis of CCT scans within 18 hours of stroke onset revealed an attenuated corticomedullary contrast as the crucial CCT criterion, which, with both sufficient sensitivity and specificity, predicted mMCAI with 95% certainty. (Stroke. 1999;30:1076-1082.)

Key Words: case-control study ■ cerebral infarction ■ middle cerebral artery ■ tomography, x-ray computed

Total middle cerebral artery (MCA) territory infarcts may be distinguished from the diverse group of ischemic MCA strokes. Epidemiological data indicate that this particular stroke type accounts for 3% to 15% of all ischemic supratentorial infarctions.1-3 This subgroup is characterized by a distinct pattern of etiological, pathomorphological, and clinical features. Internal carotid artery (ICA) occlusions, ICA dissections, and cardiogenic embolism are the most frequent causes, and the subsequent development of large space-occupying brain edema resulting in tentorial and foraminal herniation is usually responsible for the fatal course in the majority of patients.3,4 The mortality rate in such patients approximates 78%, which is 3 to 4 times higher than in the general ischemic supratentorial stroke population.3,4 In consideration of these characteristics, the term malignant middle cerebral artery territory infarction (mMCAI) was coined.4

Recent experimental and clinical series suggest that decompressive surgery might be a life-saving emergency measure, reducing mortality significantly without elevated morbidity.5-9 However, the rapid course of the space-occupying lesion requires urgent diagnostic and therapeutic decisions. Cerebral CT (CCT) is a mainstay in the emergency diagnostic workup of acute stroke patients and conveys important information within a few hours after the ictus.7-9 The initiation of thrombolytic intervention is guided by early CCT signs, among others.7-9 In contrast, no neuroradiological markers have been characterized that support the decision for decompressive surgery in a timely manner.

This case-control study was designed to analyze whether early CCT scanning provides reliable information for the prospective selection of acute ischemic stroke patients at risk to develop mMCAI.
Subjects and Methods

During a 3-year period between January 1993 and December 1995, 1230 patients with an acute ischemic stroke in the ICA territory were admitted to the neurological department of the University of Innsbruck. Among this population, 31 patients with mMCAI were selected for this study. The diagnosis of mMCAI was established on the basis of previously introduced clinical and neuroradiological characteristics: (1) hemiplegia, fixed head and eye deviation, and rapid deterioration of consciousness; (2) angiographically or sonographically documented ICA and/or MCA trunk occlusion; (3) space-occupying brain edema causing tentorial herniation within 24 to 96 hours after admission. Four patients whose exact time of stroke onset remained unclear were not eligible for this study. The same was true for any patient in whom neither angiographic nor sonographic tests were available. Thus, the entire percentage of mMCAI patients in the study period was 2.9% (n=36). This rate is substantially lower than the 15% reported in the community-based Oxfordshire Community Stroke Project but strikingly close to the more recent data of the Austin Hospital Stroke Registry (3%) and the Lausanne Stroke Registry (3.2%).

According to the principles of a case-control study, each mMCAI patient (case) was assigned a control. The latter were randomly selected acute MCA infarction (aMCAI) stroke patients without a malignant course. Thus, 31 pairs (n=62) were formed, with cases and controls closely matched in terms of age, sex, and stroke etiology (Table 1). The diagnosis of cardiogenic embolism was based on both a history of cardiac disease and the evidence of intracavitary thrombi by transthoracic and/or transesophageal echocardiography. Artero-thrombotic occlusions in patients with extended atherosclerosis and a vascular risk profile included both intracranial and extracranial (ie, artery-to-artery embolism) arterial occlusive diseases.

All patients underwent CCT scanning within 18 hours after stroke onset. A repeated CCT was performed 24 to 36 hours later. The follow-up CCT was performed to confirm the ischemic nature and the extent of the brain lesion but was not used for data acquisition. The initial CCT scans were evaluated by a neuroradiologist who was aware of the clinical diagnosis of an ischemic stroke but blinded in terms of the individual subsequent course of each patient (ie, mMCAI versus aMCAI) and was also unaware of the results of the repeated CCT scans. To achieve a quasi-standardized diagnostic procedure, the analysis of the CCT scans was performed according to a panel of 12 defined criteria, which are summarized in Table 2. These direct and indirect neuroradiological features are routinely used to recognize focal parenchymal ischemia (ie, MCA territory hypodensity, attenuated corticomedullary contrast [CMI]), edema formation (ie, compressed cell media and/or subarachnoid space [SAS], midline shift, hemispheric brain swelling), and vessel occlusion (hyperdense MCA sign). In part, they have been used in previous studies of early CCT changes in acute ischemic stroke. The predominant etiologies included embolism, local thrombosis, and dissection, with a nonsignificant imbalance between the study groups (Table 1). The overall mortality among cases was 65% compared with 5.2% among controls.

The results of the pairwise comparisons of the 12 defined CCT criteria are presented in the order listed in Table 2. The raw data are depicted as cross-tabulations in Table 3. Thirteen patients had their CCT scan 6 to 18 hours after stroke onset, and 49 patients had their CCT scan 6 to 18 hours after stroke onset; the respective figures are given separately in Table 3.

Nine initial CCT scans did not exhibit any hypodensity in the MCA territory (Table 3), which was associated with the subsequent development of mMCAI in only a single case (11.1%). In contrast, all 14 patients (100%) with a MCA territory hypodensity >67% on the initial examination suffered a malignant course. These 2 parameters were significantly different between cases and controls (P<0.001), which was not the case for the remaining 2 parameters of this group (ie, MCA hypodensity <33% and MCA hypodensity >33% but <67%).

Twenty patients presented initially with MCA territory hypodensity >50% (Table 3), which was followed by the development of mMCAI in 18 patients (90%). In contrast, only 12 of 33 patients (36.4%) with MCA territory hypodensity <50% were in the mMCAI group, and the remaining 21 were in the aMCAI group (P<0.001).

Twenty-five of 33 patients (75.8%) with unilateral compression of the cella media (Table 3) developed mMCAI, compared with only 6 of 29 patients (20.7%) without this CCT sign (P<0.001).

Fifty-three patients, including all 31 patients (58.5%) with mMCAI, exhibited a compressed SAS (Table 3) on the initial CCT scan. However, this finding was also associated with the
A midline shift (Table 3) was present in only 7 of 62 patients without compressed SAS and was associated with mMCAI in 6 of those (85.7%). It was absent in 35 patients and associated with mMCAI in 22 of those (63.2%). The hyperdense MCA sign (Table 3) was found in 27 patients with mMCAI but only 9 of those (33.3%) with aMCAI. This difference was not statistically different ($P=0.313$).

The hyperdense MCA sign (Table 3) was found in 27 patients and was associated with mMCAI in 22 of those (81.5%). It was absent in 35 patients and associated with mMCAI in only 9 of those (25.7%) ($P<0.001$).

Only 4 patients had a brain swelling (Table 3) of the entire affected hemisphere on the initial CCT scan, and all of them (100%) developed mMCAI. Among the remaining 58 patients without this CCT sign, 27 (46.6%) were also associated with mMCAI, but 31 patients (53.4%) were not. This difference was not statistically different ($P=0.039$).

Twenty-eight patients exhibited an attenuated CMC (Table 3), which was present at least throughout the entire MCA territory on the initial CCT scan. This was related to subsequent mMCAI in 27 (96.4%) of these cases. In contrast, only 4 of the 34 patients (11.8%) with an intact CMC developed a fatal mMCAI ($P<0.001$).

Sensitivity, specificity, predictive values, and the respective odds ratios (with 95% CIs) for the development of mMCAI are summarized in Table 4. CCT criteria exhibiting a specificity of $\geq80\%$ were extended hypodensities $>67\%$ (100%) and $>50\%$ (93.5%) of the MCA territory, hemispheric brain swelling (100%), midline shift (96.7%), and hyperdense MCA sign (83.9%) (Table 4). However, the respective sensitivities were low (45.2%, 58.1%, 12.9%, 19.4%, and 70.9%, respectively). In contrast, 2 criteria yielded high sensitivity (SAS compressed, 100%; cella media compressed, 80.6%) but low specificity (29% and 74.2%, respectively). The CCT criterion of attenuated CMC remained as the only radiological feature yielding both high specificity (96.8%) and sensitivity (87.1%). In a 2-tailed logistic regression analysis with the strongest correlating parameters (Spearman correlation factor $\geq0.6$ or $\leq-0.6$), an attenuated CMC remained as the critical criterion [$\text{Exp(B)}=90.8$; 95% CI, 5.8 to 1427.5], thereby suggesting that this sign on the initial CCT scan may predict the development of mMCAI with a 95% probability. The regression analysis yielded no further significant correlations.

A further subanalysis was performed with patients who underwent CCT scanning before or after 6 hours of stroke onset. This cutoff was chosen because of its critical therapeutic implications. Thirteen subjects (21%) were diagnosed within 6 hours, and the remaining 49 (79%) were diagnosed later. The distribution of the CCT criteria was not statistically different between both groups (Table 3).

The Figure shows representative CCT images of 3 patients with either mMCAI or aMCAI.

**Discussion**

This represents the first controlled study of early CCT signs associated with the subsequent development of mMCAI. From a panel of CCT criteria, a widespread attenuated CMC (ie, covering at least the entire MCA territory) has been identified as the most reliable neuroradiological feature. If present within 18 hours of stroke onset, this single CCT sign was strongly indicative (95% CI, 5.8 to 1427.5 in the logistic regression analysis) for the development of mMCAI with both high specificity (96.8%) and sensitivity (87.1%) (odds ratio, 202.5; 95% CI, 21.3 to 1925). This was in contrast to a number of other early CCT criteria (MCA $>67\%$, MCA $>50\%$, midline shift, hemispheric brain swelling), which were also highly specific ($>80\%$) for a subsequent mMCAI but exhibited insufficient sensitivity (Table 4). Two other CCT signs (compressed SAS, compressed cella media) were sufficiently sensitive (100%, 80.6%) but not specific (Table 4).

Most direct and indirect CCT signs of cerebral ischemia reflect common pathophysiological grounds. Ischemia-
induced energy breakdown of the cells is followed by an immediate transmembrane ionic shift and subsequent water accumulation. This in turn alters the x-ray attenuation in the affected tissue.8 Depending on the extent and severity of the stroke, increased radiolucency appears as hypodensity in subcortical or cortical areas or both.8 In our study, loss of the usual contrast between gray and white matter was termed attenuated CMC and considered to indicate cortical hypodensity. Reflecting impaired cortical perfusion, this CCT sign usually covered. Whether parenchymal hypodensity is accompanied by brain swelling as a reflection of edema depends primarily on the extent and severity of the affected tissue.8 Depending on the extent and severity of the stroke, increased radiolucency appears as hypodensity in subcortical or cortical areas or both.8 In our study, loss of the usual contrast between gray and white matter was termed attenuated CMC and considered to indicate cortical hypodensity. Reflecting impaired cortical perfusion, this CCT sign might reasonably be considered an early indicator of large territory infarction.19,23,24 The prognostic significance of this finding, however, is less unequivocally characterized. The majority of studies point to a close relation between the extent of middle cerebral artery (MCA) territory hypodensity and fatal outcome.19,21,25–28 This is in agreement with our results, in which the presence of the hyperdense MCA sign and fatal outcome was associated with a high specificity and positive predictive value for MCA territory infarction (98% and 83%, respectively) for MCA territory hypodensity (85.7% and 85.7%, respectively) for MCA territory hypodensity (98% and 83%, respectively). These data also supported our criterion of compressed cella media. This CCT finding showed sensitivity, specificity, and positive predictive value for MCA territory hypodensity (63.4% and 74.3%, respectively) and positive prediction (100%) for MCA territory hypodensity (63.4% and 74.3%, respectively) for MCA territory hypodensity (63.4% and 74.3%, respectively) for MCA territory hypodensity (63.4% and 74.3%, respectively) for MCA territory hypodensity (63.4% and 74.3%, respectively). The insuffi-
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cient sensitivity of 70.9% may reflect the limited prevalence of only 40% to 60% of this CCT sign in angiographically demonstrated MCA trunk occlusions,19,23–25,27,29–31 However, in one recent series, the prognostic value of the hyperdense MCA sign was strikingly low, with sensitivity, specificity, and positive predictive value of only 44%, 51%, and 32%, respectively. This discrepancy might be due to the different timing of CCT scanning (5 hours versus 18 hours after stroke onset), which clearly affects the prevalence of this finding.19,21,23,24,27,29,30,32

One possible weakness in the design of our study was the fact that the neuroradiologist was blinded to the subsequent course (ie, mMCAI versus aMCAI) of each patient but not to the clinical diagnosis of an ischemic stroke. This may have increased the number of positive findings on the initial CCT scans. However, the respective figures in our series correlate well with the results of a previous study in which 89% of all patients showed early CCT changes as early as 3 hours after stroke onset.19

Our study was primarily designed to identify early CCT criteria that may reliably be used to discriminate acute stroke patients with a malignant course from those with a nonmalignant course. Such criteria could be critical in supporting the decision of whether a patient with aMCAI should undergo decompressive surgery as a life-saving measure. Among our 31 patients with mMCAI, 11 patients underwent decompressive craniectomy after a median interval of 1.8 days (range, 0 to 6 days) after stroke onset, and the remaining 20 continued on full-scale intensive care. Three-month mortality among the operated patients was 41.6% compared with 80% in the conservatively treated group (overall mortality independent of therapy, 65.6%). These data correlate with the results of the only prospective controlled trial on hemicraniectomy in acute space-occupying ischemic stroke.6 This supports the notion that decompressive surgery may be a life-saving emergency measure in this particular stroke subtype. It was not the intention of this study to test therapeutic measures, but these data emphasize the clinical importance of the earliest possible and reliable neuroradiological features which, in association with clinical signs and symptoms, might be helpful for emergency differential diagnostic and therapeutic decisions. CCT scanning within 6 hours or 6 to 18 hours after stroke onset revealed no statistically significant differences in our series. However, the number of patients analyzed early was too small (n = 13) to allow reliable statistical analysis from this subgroup. In this regard, the retrospective analysis of the CCT scans must be critically noted, which we regarded as a sufficient approach to provide a first predicative data set.

Nevertheless, the results need to be confirmed in a prospective analysis, which might increase the sensitivity of time-related CCT changes.

It is noteworthy that our results might also be helpful in recognizing stroke patients who, despite suspicious clinical signs and symptoms, are not high-risk candidates for mMCAI if their CCT scans are lacking the required criteria. An intact CMC and a normal SAS in particular yielded high negative predictive values (Table 4). As a limitation, it must be noted, however, that no controlled data of the reliability of initial clinical signs and symptoms are available and that our study was not designed to address this question.

In conclusion, our results suggest that CCT scanning within 18 hours of stroke onset may help in the early identification of patients who may develop mMCAI. In particular, an attenuated CMC may be the crucial CCT criterion. Moreover, diagnostic reliability can be enhanced when the initial CCT scan is thoroughly screened for additional features, such as extended MCA hypodensity, hemispheric brain swelling, midline shift, and a hyperdense MCA sign.

References


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