Association of Hyperdense Middle Cerebral Artery Sign With Clinical Outcome in Patients Treated With Tissue Plasminogen Activator

Claude Manelfe, MD; Vincent Larrue, MD; Rüdiger von Kummer, MD; Luigi Bozzao, MD; Peter Ringleb, MD; Stefano Bastianello, MD; Françoise Iweins, MSc; Emmanuel Lesaffre, PhD

Background and Purpose—The hyperdense middle cerebral artery sign (HMCAS) is a marker of thrombus in the middle cerebral artery. The aim of our study was to find out the frequency of the HMCAS, its association with initial neurological severity and early parenchymal ischemic changes on CT, its relevance to clinical outcome, and the efficacy of intravenous recombinant tissue plasminogen activator (rtPA) in patients with the HMCAS.

Methods—Secondary analysis of the data from 620 patients who received either rtPA or placebo in the European Cooperative Acute Stroke Study I (ECASS I), a double-blind, randomized, multicenter trial. The baseline CT scans were obtained within 6 hours from the onset of symptoms. Functional and neurological outcomes were assessed using the modified Rankin Scale and the Scandinavian Stroke Scale at day 90.

Results—We found an HMCAS in 107 patients (17.7%). The initial neurological deficit was more severe in patients with the HMCAS than in those lacking this sign ($P<0.0001$). Early cerebral edema and mass effect were also more common in patients with the HMCAS ($P<0.0001$). The HMCAS was related to the risk of poor functional outcome (grade of 3 to 6 on the modified Rankin Scale) on univariate analysis: 90 patients (84%) with the HMCAS and 310 patients (62%) lacking this sign were dependent or dead at day 90 ($P<0.0001$). However, this association was no longer significant in a logistic model accounting for the effect of age, sex, treatment with rtPA, initial severity of neurological deficit and early parenchymal ischemic changes on CT. Patients with the HMCAS who were given rtPA had better neurological recovery than those who received placebo ($P=0.0297$).

Conclusions—The HMCAS is associated with severe brain ischemia and poor functional outcome. However, it has no significant independent prognostic value when accounting for the effect of initial severity of neurological deficit and of early parenchymal ischemic changes on CT. Patients with the HMCAS may benefit from intravenous rtPA. (Stroke. 1999;30:769-772.)

Key Words: stroke assessment ■ stroke outcome ■ stroke, acute ■ thrombolytic therapy ■ tomography, x-ray computed
placebo-controlled, randomized trial with eligibility based on clinical symptoms and CT, performed between December 1992 and March 1994 at 75 centers in 14 European countries. Six hundred twenty patients with a moderate to severe acute hemispheric ischemic stroke received either rtPA (1.1 mg/kg IV) or placebo within 6 hours after onset of symptoms.

All patients had a pretreatment noncontrast CT (baseline or day 0), a second CT at 24±12 hours (day 1 CT), and a third between days 6 and 8 (day 7 CT). The CT scans were performed according to guidelines of the study protocol. Section thickness was 3 to 5 mm for the base of the brain, including the chiasmal cistern region, and 8 to 10 mm for the upper brain. Window width levels were those used in conventional brain studies. Patients with spontaneous intracranial hemorrhage and those with major early infarct signs on CT such as diffuse swelling of the affected hemisphere, parenchymal hypodensity, and/or effacement of cerebral sulci in more than 33% of the MCA territory had to be excluded.

All CT scans were reviewed by an independent CT reading panel. The 3 neuroradiologists on the panel (R. v. K., C.M., and L.B.) were blinded to clinical data and to treatment groups but not to follow-up CT scans. A CT scan was defined as “not readable” when gray and white matter attenuation could not be differentiated. A CT scan was defined as “poor” when gray and white matter could be differentiated with difficulty because the CT window was too large or because of the presence of motion artifacts. CT scans with some motion or beam-hardening artifacts but with good contrast between gray and white matter were considered to be of “moderate” quality. All remaining CT scans were defined as “good.” Each CT scan was evaluated for parenchymal hypodensity and mass effect (effacement of cortical sulci or ventricular compression) as a percentage of the MCA territory in 3 categories (none; ≤33%; >33%). Parenchymal hypodensities in the territory of the anterior, posterior, and choroidal cerebral arteries were assessed separately.

The HMCAS was defined as an MCA denser than its counterpart and denser than any other visualized artery or vein. The HMCAS was categorized according to its location and extent as “proximal” (MCA trunk or basal M1 segment), “distal” (beyond MCA bifurcation or M2 and M3 segments) or both (Figure). The HMCAS was interpreted as “present” or “absent,” and doubtful cases were considered to be absent HMCASs. When the panelists disagreed with each other, they came to a final judgment during a consensus meeting.

The neurological severity of stroke was graded by use of the Scandinavian Stroke Scale. The functional outcome at day 90 was assessed with the modified Rankin Scale. Poor outcome was defined as grades 3 to 6 on this scale.

Statistical analysis of categorical data was performed with Fisher’s exact test or a χ² test when appropriate. For continuous data, we used a t test and ANOVA tables. A Wilcoxon (or Kruskal-Wallis) test was used to test differences between subgroups. Finally, to assess the independent contribution of the HMCAS to the risk of poor outcome at day 90, we used logistic regression analysis. Treatment with rtPA, age, and sex were forced into the model. Results are expressed as adjusted odds ratio and corresponding 95% confidence intervals. Significance was set at P < 0.05. All tests were 2-sided and computed with the software SAS upgrade 6.11 and 6.12 (SAS Institute, Inc).

Results
According to the judgment of the CT reading panel, good-quality CT scans were obtained in 166 patients (27%), moderate-quality scans were obtained in 314 patients (51%), and poor-quality scans were obtained in 123 patients (20%). Poor-quality CT scans were mainly due to motion artifacts and/or inappropriate window setting. CT scans were unreadable in 8 patients and were not available in 9 other patients. Fifty-two patients with major early infarct signs, erroneously included in the trial, were kept in the analysis. Thus, 603 patients remained for analysis with a complete set of CT scans.
An HMCAS was found on baseline CT scan in 107 patients (17.7%). The hyperdensity was proximal in 36 patients (33.6%), distal in 14 (13.1%), and present in both segments in 57 (53.3%). The HMCAS was seen in 61 patients who received placebo and in 46 patients who were given rtPA. The HMCAS subsisted in 58 of 106 patients on the day 1 CT scan (55%) and in only 22 of 86 patients on the day 7 CT scan (26%). Patients with the HMCAS had a more severe neurological deficit at entry. Cerebral edema or mass effect were also more common on baseline CT scan in these patients (Table 1).

An HMCAS on baseline CT scan was significantly associated with poor clinical outcome at day 90 on univariate analysis: 90 patients with the HMCAS (84%) and 310 patients lacking this sign (62%) were dependent or dead (Rankin grade ≥3 to 6) at that time ($P<0.0001$). Table 2 describes the results of the logistic regression. There was a small but significant association of poor outcome with increasing age. Also, a lower baseline score on the Scandinavian Stroke Scale was significantly associated with poor outcome. The existence of a cerebral edema or mass effect on the baseline CT scan was significantly associated with poor outcome, whereas the HMCAS per se was not.

Among patients with the HMCAS, those who were given rtPA had better neurological recovery than those who received placebo. Mortality at day 90 was not significantly increased in the rtPA-group (Table 3).

### Discussion

We found a lower proportion of patients with the HMCAS than in previous studies. The difference may be explained by some methodological reasons. Patients with very severe stroke, in whom the HMCAS might have been more common, were excluded from ECASS I. Furthermore, most patients who participated in ECASS I were enrolled between 3 and 6 hours from the onset of symptoms. This may have decreased the apparent frequency of the HMCAS, because previous studies and our own data have demonstrated the vanishing nature of the HMCAS. Finally, the quality of some CT scans in ECASS I may have been insufficient to detect the HMCAS in some cases. More specifically, previous studies have demonstrated that reduction of section thickness improves the detectability of a clot within the MCA by reducing partial volume averaging that would make the detection of the HMCAS more difficult.

We cannot exclude the possibility that the members of the CT reading panel were biased because of knowledge of the follow-up scans when they assessed the baseline scans. This may have increased the frequency of the HMCAS if one admits that parenchymal edema on follow-up scans may have stimulated the readers to look for the HMCAS on baseline scans. On the other hand, doubtful cases may have been classified as absent HMCAS if the follow-up scans were normal. Thus, the setting of the ECASS I CT reading panel was different from that in real life when a stroke has just occurred and only the first CT scan has been obtained.

We found that the HMCAS was significantly related to initial neurological severity and to early parenchymal ischemic changes on CT. These relationships reflect the specificity of the HMCAS for MCA occlusion and the heterogeneity of vascular occlusive processes in patients lacking this sign, who may only have distal branch occlusion or even no detectable arterial occlusion at all.

The relationship of the HMCAS to functional outcome has been disputed. Using a logistic model including neurological severity and early parenchymal ischemic changes on CT as explanatory variables, we failed to find a significant independent effect of the HMCAS on functional outcome. It should be noted that only 87 patients were enrolled in the ECASS within 3 hours from the onset of symptoms. Therefore, the possibility remains that the HMCAS could have independent prognostic value in patients who are seen very early, before parenchymal changes develop.

### Table 1. Baseline Characteristics of Patients and Extent of Early Parenchymal Ischemic Changes

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>With HMCAS (n=107)</th>
<th>Without HMCAS (n=496)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean±SD age, y</td>
<td>63.6±12.5</td>
<td>65.8±11.2</td>
<td>0.07</td>
</tr>
<tr>
<td>Male</td>
<td>69 (65)</td>
<td>309 (62)</td>
<td>0.74</td>
</tr>
<tr>
<td>Mean±SD baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scandinavian Stroke Scale Score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypodensity or mass effect on baseline CT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>19 (18)</td>
<td>317 (64)</td>
<td></td>
</tr>
<tr>
<td>≥33% or less</td>
<td>68 (64)</td>
<td>147 (30)</td>
<td>0.0001</td>
</tr>
<tr>
<td>&gt;33%</td>
<td>20 (19)</td>
<td>32 (7)</td>
<td></td>
</tr>
</tbody>
</table>

The Scandinavian Stroke Scale score is 2 in a maximally impaired patient and 56 in a normal person. The extent of parenchymal ischemic changes was estimated as a percentage of the territory of the MCA. Values in parentheses are percentages.

### Table 2. Logistic Model of Association of Baseline Variables With Poor Functional Outcome (Grades 3 to 6 on the modified Rankin Scale at day 90)

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (by year)</td>
<td>1.03</td>
<td>1.01–1.05</td>
<td>0.0015</td>
</tr>
<tr>
<td>Male</td>
<td>0.81</td>
<td>0.53–1.24</td>
<td>0.3297</td>
</tr>
<tr>
<td>Treatment with rtPA</td>
<td>0.59</td>
<td>0.39–0.89</td>
<td>0.0130</td>
</tr>
<tr>
<td>Scandinavian Stroke Scale score (by point)</td>
<td>0.91</td>
<td>0.89–0.93</td>
<td>0.0001</td>
</tr>
<tr>
<td>Hypodensity or mass effect on CT</td>
<td>2.51</td>
<td>1.61–3.96</td>
<td>0.0001</td>
</tr>
<tr>
<td>HMCAS</td>
<td>1.52</td>
<td>0.80–3.02</td>
<td>0.2167</td>
</tr>
</tbody>
</table>

### Table 3. Neurological Recovery in Patients With HMCAS

<table>
<thead>
<tr>
<th>rTPA Group (n=46)</th>
<th>Placebo Group (n=61)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean±SD baseline Scandinavian Stroke Scale score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>22.1±9.7</td>
<td>24.4±9.9</td>
<td>0.33</td>
</tr>
<tr>
<td>No. of dead patients at day 90</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>Mean±SD Scandinavian Stroke Scale score at day 90 in survivors</td>
<td>45.9±11.5</td>
<td>39.5±13.4</td>
</tr>
</tbody>
</table>

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this limitation borne in mind, our findings suggest that the HMCAS is significantly related to the severity of brain ischemia but does not by itself indicate an increased risk of poor clinical outcome.

The efficacy of intravenous thrombolytic treatment in patients with the HMCAS has been questioned. A study using cerebral angiography before and after intravenous rtPA has documented immediate recanalization in only 23 (38%) of 60 MCA stems or divisions (M1 or M2) compared with 8 (47%) of 17 recanalizations of MCA branch(es). More aggressive approaches, such as intra-arterial administration of the thrombolytic drug or mechanical dissolution of the clot have been proposed for these patients.

In ECASS I, patients with the HMCAS who where given rtPA had better neurological recovery than those who received placebo. The benefit did not occur at the expense of increased mortality. This result should be viewed with caution, owing to the small sample size and to the retrospective nature of our analysis. It suggests, however, that intravenous rtPA is worthwhile in patients with the HMCAS.

In conclusion, in the setting of a multicenter trial, the HMCAS was an infrequent finding. It was associated with severe brain ischemia and poor functional outcome. It had, however, no independent prognostic value when accounting for the effect of initial neurological severity and early parenchymal ischemic changes on CT. Patients with the HMCAS who where given rtPA had better neurological recovery than those who received placebo.

Acknowledgments
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References
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