Hyperdense Internal Carotid Artery Sign
A CT Sign of Acute Ischemia

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Background and Purpose—The hyperdense middle cerebral artery sign (HMCAS) is a well-established marker of early ischemia on noncontrast computed tomography of the brain (NCCT). Recently the MCA dot sign has been described and proposed to indicate thrombosis of the M2 or M3 middle cerebral artery branches. The purpose of this study was to define the hyperdense ICA sign (HICAS) and determine its prevalence, diagnostic and prognostic value, and its reliability as a marker for ischemia.

Methods—Noncontrast computed tomography scans of 71 patients with acute ischemic stroke were analyzed for the presence of a HICAS, HMCAS, or MCA dot sign. For the validation of HICA and HMCA signs on NCCT, 32 of 71 patients who underwent gold standard CT angiography (CTA) before thrombolytic therapy were included in the analysis. The presence of a HICAS was correlated with initial neurological severity and the short and long-term outcomes.

Results—A HICAS was found in 24% of patients on NCCT. In patients with a HICAS, mean age was 63±17.4 and mean time from symptom onset to CT was 103 minutes. Interobserver agreement was excellent for the HICAS. The HICAS has high specificity (100%) and positive predictive value (100%) in predicting the presence of distal internal carotid artery thrombus on CTA. Patients with a HICAS had a more severe initial neurological deficit and worse prognosis than patients without a HICAS.

Conclusion—The HICAS is a reliable and a highly specific marker of thromboembolic occlusion of the distal ICA and is associated with severe initial neurological deficit and worse outcome despite thrombolytic therapy. (Stroke. 2008;39:2011-2016.)

Key Words: internal carotid artery ■ acute ischemic stroke ■ computed tomography

Noncontrast computed tomography (NCCT) is the most frequently used diagnostic modality used in the evaluation of acute stroke in many hospitals, despite the widespread availability of MRI. With the approval of intravenous (IV) tissue plasminogen activator (rt-PA) therapy for ischemic stroke within 3 hours of symptom onset,1 recognition of early ischemic changes on NCCT has become increasingly important for physicians administering thrombolytic therapy. Observation of these early ischemic changes on NCCT in the territory of the middle cerebral artery (MCA) has diagnostic and prognostic value,2-5 however these changes are subtle and, hence, of variable reliability.6,7

Hyperdensity of a cerebral artery on NCCT is a marker of intraluminal thrombus and was one of the first CT signs described in ischemic stroke patients.8 Before the infarct becomes visible, NCCT may display a hyperdense MCA sign (HMCAS), which appears as increased density of the MCA along the imaging plane of axial CT slices, following the course of the M1 segment from its origin to the Sylvian fissure.9,10 The HMCAS has been associated with severe neurological deficits and poor clinical outcome.11,12 More recently, the MCA “dot” sign was described, representing a hyperdensity of the MCA branches (M2 or M3 segment) within the Sylvian fissure.13 The MCA dot sign is a marker of thromboembolic occlusion of distal MCA branches and is associated with better outcome than the HMCAS sign.13 In the posterior circulation the hyperdense posterior cerebral artery (PCA) sign was defined as hyperdensity within the ambient cistern, medial to the tentorium cerebelli.14

In the present study, we described the “hyperdense ICA” sign (HICAS) on NCCT that appears as hyperdensity in the distal segment of the internal carotid artery (ICA) indicating intraluminal thrombus within the supraclinoid segment of the distal ICA. The purpose of the study is to validate the HICAS against the gold standard of CT angiography (CTA) and to determine its frequency and reliability. We also report the
association of the HICAS with initial neurological severity, its relevance to clinical outcome after treatment with intraarterial (IA) IV or combined IV and IA rt-PA.

Subjects and Methods
Between December 2004 and December 2006, 125 consecutive patients with acute ischemic stroke presenting <6 hours from symptom onset treated with IV or IA rt-PA at the London Health Science Centre were identified. Demographic information, stroke risk factors, stroke type, and neurological and functional outcome were documented. For the present study, we analyzed 71 patients who underwent CT before thrombolytic therapy.

Radiological Data Analysis
Patients had pretreatment NCCT brain scans and a second scan at 24 hours. NCCT scans were performed on a fourth-generation General Electric scanner. The section thickness was 2.5 mm through the posterior fossa and 5 mm for the cerebral hemispheres.

All 71 NCCT scans were reviewed retroactively and independently by a neuroradiologist (A.L.) and a stroke fellow (O.O). The two clinicians, who were blinded to all clinical information, inspected initial NCCT scans for the presence of the following signs: (1) The HMCAS defined as “an MCA denser than its contralateral counterpart.”15 (2) The MCA dot sign, defined as “hyperdensity of the MCA in the Sylvian fissure relative to the contralateral side or other vessels within the Sylvian fissure.”13 (3) HICAS, defined as hyperdensity of the supraclinoid part of the ICA observed in the prepontine or premesencephalic cistern where the vessels form the Cir of Willis. A HICAS is present if the distal ICA was denser than its contralateral counterpart (Figures 1 and 2). Both the HMCA, MCA dot, and the HICA signs were rated as absent or present. Disagreements were settled by a third rater who is an experienced neuroradiologist for the validation of study (D.P.).

The extent of hypodensity on baseline CT was quantified as described in the Alberta Stroke Program Early CT Score Study (ASPECTS).6 Using this method, the MCA territory was divided into 10 standardized regions, and 1 point was subtracted for each area of early ischemic change and swelling in defined regions. A normal scan received ASPECTS of 10 points. A score of 0 indicated diffuse ischemic involvement throughout the MCA territory. ASPECTS was presented as dichotomized into ≤7 and >7.6

Validation of HICA and the HMCA Signs
For the validation of HICA and the HMCA signs, 32 of 71 patients who underwent CTA were included in the analysis. To validate these signs, the gold standard CTA was reviewed independently and retrospectively by a neuroradiologist (A.L.). CTA was performed directly after baseline NCCT and before thrombolytic therapy.

Clinical Assessment
Clinical severity at baseline and 24 hours after symptom onset were assessed prospectively by using the National Institutes of Health Stroke Scale (NIHSS) conducted by stroke fellows certified in NIHSS scoring. The modified Rankin Scale (mRS) was used to assess neurological and functional outcome at 24 hours and 90 days after stroke onset. The patients with NIHSS ≥10 at 24 hours were considered to have severe neurological deficits. Poor outcome at 90 days was defined as a mRS score ≥3. Intracranial hemorrhage was considered as symptomatic if the patient had a ≥4 points decrease in
NIHSS and if the hemorrhage was likely to be the cause of neurological deterioration. Stroke type was determined using the Trial of Org 10172 in Acute Stroke Treatment (TOAST) trial criteria after the diagnostic work-up was completed. Echocardiogram, EKG, and 24-Holter monitoring were used to determine the cardiac source. A potential large-artery atherosclerotic source of thrombosis or embolism was assessed by carotid ultrasound, CT/ MR angiography, or DSA.

Statistical Analyses
The interobserver agreement for the HICAS, HMCAS, and the MCA dot sign was assessed between the 2 readers using Cohen Kappa statistics. The presence of a HMCA or HICA sign on NCCT was compared with the gold standard of an ipsilateral M1 and distal ICA occlusion at CTA. The specificity, sensitivity, positive predictive value, negative predictive value, overall accuracy, positive likelihood ratio, and the negative likelihood ratio were calculated. Demographic and clinical predictors of the presence or absence of the HICAS were analyzed with \( t \) tests and Mann–Whitney U test for continuous variables and \( \chi^2 \) tests for categorical variables.

Results
Seventy-one consecutive patients were assessed. Symptom onset to time of NCCT did not differ between patients with the HICAS (104±47.6) versus those without the HICAS (113±41.6; \( P=0.486 \)). In patients with the HICAS, the mean age was 63±17.4 years and 12 (70.5%) were men. The baseline demographic and clinical characteristics are presented according to presence or absence of the HICAS in Table 1. Patients with the HICAS were significantly less likely to have hyperlipidemia than patients without this sign (\( P=0.004 \)). No significant difference was found in sex, history of diabetes, hypertension, atrial fibrillation, coronary artery disease, and smoking status between patients with or without the HICAS (Table 1). The baseline glucose and hematocrit levels were not significantly different between the two groups (Table 1). According to the TOAST criteria cardioembolic strokes were more common in patients with the HICAS (47%) compared to patients without the HICAS (33%; \( P=0.05 \)). Patients without the HICAS had significantly more large artery atherosclerotic disease than patients with the HICAS (35% versus 23%; \( P=0.002 \)). Seventeen of 71 patients (24%) showed a HICAS on the NCCT scan. The HICAS was ipsilateral to the clinically and radiologically involved hemisphere in all patients. A HMCAS was noted in 25 of 71 patients (35%). Seventeen of 71 patients (24%) had a MCA dot sign. Nine of 71 patients (13%) had the combination of an HICA and HMCA signs, and 5 cases (7%) had both HICA and MCA dot signs. Among the 17 patients with a HICAS, 8 patients had an isolated HICAS.

Baseline Neurological Deficit, Hemorrhagic Transformation, Early Ischemic Changes, and the HICA Sign
Patients with a HICAS had a significantly higher baseline median NIHSS score (16; interquartile range 8) compared to those without this sign (12; interquartile range 8; \( P=0.016 \)). Early ischemic changes quantified by ASPECTS (dichotomized score \( \leq 7 \) versus \( >7 \)) were not statistically different between these 2 groups (\( P=0.597 \); Table 1). Symptomatic intracerebral hemorrhage was detected on the 24-hour NCCT scan in 1 of the 17 (5.8%) patients with the HICAS and in 3 of the 54 (5.5%) patients without the HICAS (\( P=0.675 \)). The presence of any visible hyperdense sign on NCCT was detected in 41 patients (58%).

The Interobserver Agreement for the HDICA, HMCA, and MCA Dot Sign
Table 2 provides the \( \kappa \) values expressing interrater agreement between the 2 pairs of observers for the HICA, HMCA, and the MCA dot signs.

Validation of HICAS and the HMCA and Sign
Thirty-two of 71 patients (45%) underwent CTA within 6 hours of symptom onset. Sensitivity, specificity, accuracy,
negative predictive value, positive predictive value, positive likelihood ratio, and negative likelihood ratio are presented in Table 3. All of these signs correlated with ipsilateral arterial occlusion and the M1 segment of MCA occlusion in 3 patients. Occlusions of both the A1 segment of the anterior cerebral artery and the M1 segment of MCA were noted in 3 patients with distal ICA occlusion on CTA.

**Short-Term and Long-Term Outcome, Mortality, and the HICA Sign**

At 24 hours, severe neurological deficits (NIHSS score ≥10 points) were found in 9 of 17 patients (53%) with a HICAS compared to 13 of 54 patients (24%) without this sign (P=0.025). An HICAS on baseline NCCT scan was associated with poor clinical outcome at 3 months. Twelve of 17 patients with the HICAS (%70.6) and 20 of 54 patients (37%) without the HICAS were dependent or dead (mRS 3 to 6) at 3 months (P=0.015; Table 1). Of the patients with HICAS, the proportion of patients with long-term poor outcome was not affected by the treatment modalities (IV rt-PA versus IA or combined treatment; 75% versus 67%, respectively P=0.563). The presence of a HICAS was not statistically associated with a greater probability of death than when this sign was absent (P=0.694) (Table 1). The HICAS disappeared in 4 of 17 patients on control NCCT that was done at 24 hours after ischemic stroke. Furthermore, only 1 of these 4 patients with a favorable outcome after 3 months. The presence of either a MCA dot sign or a HMCA was not associated with poor long-term neurological outcome (P=0.688, P=0.297, respectively). Patients with any hyperdense sign on NCCT had poorer long-term neurological outcome compared to patients without any hyperdense sign (P=0.029).

**Discussion**

In the first few hours of acute ischemic stroke, NCCT may show parenchymal abnormalities as well as a hyperdense artery sign, which represents acute thrombus within a segment of a cerebral vessel. One study has described the appearance of distal ICA thrombus on thin-section NCCT, however the HICAS has not been described in detail previously in a large series of

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**Table 1. Baseline Characteristics and Outcome of Patients With HICA Sign or Without HICA Sign**

<table>
<thead>
<tr>
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<th>Patient With HICA Sign</th>
<th>Patient Without HICA Sign</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>63 (17.4)</td>
<td>62 (17.4)</td>
<td>0.867</td>
</tr>
<tr>
<td>Female</td>
<td>5 (71%)</td>
<td>19 (65%)</td>
<td>0.661</td>
</tr>
<tr>
<td>Baseline NIHSS</td>
<td>16 (12–20)</td>
<td>12 (8–16)</td>
<td>0.016</td>
</tr>
<tr>
<td>Hematocrit at baseline</td>
<td>0.37 (0.06)</td>
<td>0.40 (0.073)</td>
<td>0.350</td>
</tr>
<tr>
<td>Glucose at baseline, mmol/L</td>
<td>7.2 (2.4)</td>
<td>8 (2.3)</td>
<td>0.994</td>
</tr>
<tr>
<td>Time to rt-PA treatment, minutes</td>
<td>146 (53.8)</td>
<td>153 (60.8)</td>
<td>0.679</td>
</tr>
<tr>
<td>Route of rt-PA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>6 (35%)</td>
<td>35 (65%)</td>
<td></td>
</tr>
<tr>
<td>IA</td>
<td>6 (35%)</td>
<td>10 (18%)</td>
<td></td>
</tr>
<tr>
<td>IV plus IA</td>
<td>5 (30%)</td>
<td>9 (17%)</td>
<td></td>
</tr>
<tr>
<td>Time to CT, minutes</td>
<td>104 (47.6)</td>
<td>113 (41.6)</td>
<td>0.486</td>
</tr>
<tr>
<td>Symptomatic intracerebral hemorrhage</td>
<td>1 (5.8%)</td>
<td>3 (5.5%)</td>
<td>0.675</td>
</tr>
<tr>
<td>Cause of stroke</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atherothrombotic</td>
<td>4 (23%)</td>
<td>19 (35%)</td>
<td></td>
</tr>
<tr>
<td>Cardioembolic</td>
<td>8 (47%)</td>
<td>18 (33%)</td>
<td></td>
</tr>
<tr>
<td>Lacunar</td>
<td>0</td>
<td>2 (4%)</td>
<td></td>
</tr>
<tr>
<td>Undetermined and other causes</td>
<td>5 (30%)</td>
<td>14 (14%)</td>
<td></td>
</tr>
<tr>
<td>Risk factors (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>10 (59%)</td>
<td>31 (57%)</td>
<td>0.918</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1 (6%)</td>
<td>11 (20%)</td>
<td>0.165</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>4 (23.5%)</td>
<td>12 (22%)</td>
<td>0.910</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>5 (29%)</td>
<td>11 (20%)</td>
<td>0.437</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>4 (23.5%)</td>
<td>34 (63%)</td>
<td>0.004</td>
</tr>
<tr>
<td>Current smoking</td>
<td>7 (41%)</td>
<td>21 (39%)</td>
<td>0.866</td>
</tr>
<tr>
<td>Poor outcome at 90 days (mRS 3–6)</td>
<td>12 (71%)</td>
<td>20 (37%)</td>
<td>0.015</td>
</tr>
<tr>
<td>Mortality at 90 days</td>
<td>3 (18%)</td>
<td>7 (13%)</td>
<td>0.694</td>
</tr>
</tbody>
</table>

Values are mean (SD), median (Q1 to Q3), or n (%) as appropriate. NIHSS indicates National Institute of Health Stroke Scale, mRS; Modified Rankin Score, rt-PA; tissue plasminogen activator, ASPECT; Alberta Stroke Program Early CT Score IV, intravenous; IA, intraarterial; rt-PA, tissue plasminogen activation.

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**Table 2. Interobserver Agreement Between 2 Pairs Using Kappa Statistics**

<table>
<thead>
<tr>
<th></th>
<th>HMCA Sign (95% CI)</th>
<th>MCA Dot Sign (95% CI)</th>
<th>HICA Sign (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observer 1 vs observer 2</td>
<td>0.702 (0.53 to 0.87)</td>
<td>0.851 (0.71 to .99)</td>
<td>0.857 (0.72 to 0.99)</td>
</tr>
</tbody>
</table>

The balanced k statistic is a measure of agreement between the 2 observers (stroke neurologist and neuroradiologist). CI indicates confidence interval.
patients. We defined this sign as focal hyperdensity corresponding to the distal supraclinoid segment of ICA within the prepontine cistern that may extend to premesencephalic cistern where the basal cerebral vessels form the Willis polygon (Figures 1 and 2). The HICAS can also be visualized within the petrous bone and cavernous sinus. Nevertheless we did not use these locations because of the excessive bone artifact.

We detected the presence of the HICAS on baseline NCCT in 24% patients. The prevalence of distal carotid thrombus on 5-mm thickness NCCT was 5.8% in a previous study, which was lower than our finding (Fisher exact test; P=0.012). The higher proportion of the HICAS in our population may be explained by several reasons. All of our patients, who had presumed large vessel occlusions, underwent MRI, CT, or DSA, and 35% of these patients received either IA or combined IA and IV rt-PA. Therefore the patients that we studied may not be fully representative of the entire acute stroke population. Additionally, it is well known that shorter delay between onset of symptoms and CT scanning is a major factor that may increase the proportion of HMCAS on NCCT. The higher proportion of HICAS in our patients may be attributable to shorter interval between symptom onset and CT scanning. The prevalence of HMCAS was 35% on the initial CT scan in our population which is consistent with other studies reporting a prevalence within a range of 17.5% to 50%. The prevalence of the MCA dot sign was 25% in a previous study which is comparable to our prevalence of 24% (Fisher exact test; P=0.239).

In the present study the interobserver reliability for the HICAS and MCA dot sign was excellent, whereas there was good agreement for the HMCAS. Moulin et al reported a fair to moderate agreement regarding the early parenchymal changes on NCCT among all physician groups. Barber et al observed a moderate to good agreement for the HMCA and MCA dot signs. The HICAS was validated against CTA in our analysis. The HICAS is a reliable predictor of thromboembolic occlusion of the distal ICA, with specificity of 100%. Calcified atherosclerosis or a high hematocrit have also been reported in patients with a false-positive HMCAS, which may also account for HICAS. However, our patients did not have any calcification in the basal cerebral vessels and their hematocrit levels were within normal limits. It is important to emphasize that our population may be younger than the entire stroke population, thus it is still possible to visualize false-positive HICAS attributable to calcified atherosclerosis in the general stroke population. CTA was performed before thrombolytic therapy in all of our patients, therefore the possibility of recanalized distal ICA thrombus resulting in false-negative result highly unlikely. In the present study the sensitivity of HICAS was low. In 3 cases, the prepontine cistern and the cerebral basal vessels including the distal ICA could not be visualized well. A previous study has demonstrated that reduction of section thickness improves the detectability of a clot within cerebral vessels. Therefore optimal visualization of the basal cerebral vessels in the prepontine and premesencephalic cisterns by performing thin-section NCCT may contribute to higher sensitivity of HICAS.

A thrombus is considered to be the most likely explanation for the hyperdense artery sign given the fact that hyperdense can resolve over time or after thrombolysis. In a previous study, the CT attenuation of pure fibrin thrombi did not exceed 24 HU ±8, whereas red thrombi had CT attenuation of 65 HU ±9 or higher. However, in a case report, the radiological-pathological correlation of a HMCAS showed that the clot not only consisted of fibrin and erythrocytes but also contained neutrophils and cellular debris. In the same case report the adjacent arterial wall showed no abnormalities. Based on these studies, clots with low attenuation attributable to different components may not demonstrate the typical hyperdense vessel sign, thereby decreasing the sensitivity of the hyperdense vessel signs. In our study, CTA comparison showed that the HMCAS is a highly specific but only moderately sensitive indicator of thromboembolic occlusion of the M1 segment of MCA, which is comparable to a previous study.

Patients with the HICAS presented with more severe baseline neurological deficits compared to those patients without this sign. Furthermore, the HICAS is associated with poor neurological and functional status at 24 hours and 3 months after the ischemic stroke. Treating these patients with IV rt-PA route rather than IA or combined IA/IV routes did not influence the long-term outcome. Although the association of poor outcome with HICAS has not been studied before, evidence from the literature analyzing the outcome of patients with distal ICA occlusions may provide additional information. Previous studies are consistent with our results and demonstrated higher mortality and morbidity rates in patients with distal ICA occlusion despite thrombolytic therapy.

Study Limitations
Our study has several limitations. The population in the study may not be fully representative of the entire acute stroke population. Although the clinical risk factors, demographics, and functional and neurological outcome of patients were assessed prospectively, NCCT were studied retrospectively. Therefore optimal visualization of the basal cerebral vessels in the prepontine and premesencephalic cisterns by performing thin-section NCCT may contribute to higher sensitivity of HICAS.

The current study is not a randomized study, therefore our results regarding the choice of therapy in patients with HICAS cannot be generalized. A randomized trial is warranted to delineate the best therapeutic option for the treatment of distal ICA thrombus.

Conclusion
The HICAS is a reliable early NCCT scan finding in acute ischemic stroke with a high positive predictive value and
specificity for distal ICA occlusion. However, the absence of the sign does not exclude distal ICA occlusion. The HICAS is associated with severe neurological deficit and poor outcome. Early recognition of the sign may not only be helpful in the early diagnosis of distal ICA occlusion but also guide the choice of therapeutic options including chemical thrombolysis, mechanical embolectomy, and mechanical clot disruption to improve eventual outcome.

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Disclosures

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References
