Predictors of Fatal Brain Edema in Massive Hemispheric Ischemic Stroke

Scott E. Kasner, MD; Andrew M. Demchuk, MD, FRCPC; Jörg Berrouschot, MD; Erich Schmutzhard, MD; Lutz Harms, MD; Piero Verro, MD; Julio A. Chalela, MD; Rekha Abbur, MD; Harold McGrade, MD; Ioannis Christou, MD; Derk W. Krieger, MD

Background and Purpose—Early identification of stroke patients at risk for fatal brain edema may be useful in selecting patients for aggressive interventions. Prior studies suggested that early nausea/vomiting and major hypodensity on baseline computed tomography (CT) were predictive of herniation.

Methods—This study was a retrospective multicenter case-control study of patients with large middle cerebral artery (MCA) strokes admitted within 48 hours of symptom onset. Medical records, laboratory data, and CT scans were analyzed. Cases, defined as patients who died of massive brain swelling, were compared with all remaining patients as controls.

Results—Two hundred one patients with large MCA strokes were identified: 94 (47%) died of brain swelling, 12 (6%) died of non-neurological causes, and 95 (47%) survived at day 30. Multivariable analysis, adjusted for age and clustered by center, identified the following predictors of fatal brain edema: history of hypertension (OR 3.0, 95% CI 1.2 to 7.6, \( P=0.02 \)), history of heart failure (OR 2.1, 95% CI 1.5 to 3.0, \( P<0.001 \)), elevated white blood cell count (OR 1.08 per 1000 white blood cells/\( \mu \)L, 95% CI 1.01 to 1.14, \( P=0.02 \)), >50% MCA hypodensity (OR 6.3, 95% CI 3.5 to 11.6, \( P<0.001 \)), and involvement of additional vascular territories (anterior cerebral artery, posterior cerebral artery, or anterior choroidal artery; OR 3.3, 95% CI 1.2 to 9.4, \( P=0.02 \)). Initial level of consciousness, National Institutes of Health Stroke Scale score, early nausea/vomiting, and serum glucose were associated with neurological death in bivariable but not multivariable analyses.

Conclusions—Among patients with large MCA infarctions, an increased risk of fatal brain edema is associated with history of hypertension or heart failure, increased baseline white blood cell count, major early CT hypodensity involving >50% of the MCA territory, and involvement of additional vascular territories. These data confirm and expand on prior research with a broad-based patient population. The presence of these risk factors identifies those stroke patients who may require aggressive therapeutic approaches. (Stroke. 2001;32:2117-2123.)

Key Words: brain edema ■ stroke mortality ■ stroke, acute

Massive hemispheric infarctions constitute =5% of all ischemic strokes and have a mortality rate of 50% to 80%.1 The principal cause of death in patients with this “malignant middle cerebral artery syndrome” is focal brain edema, with resultant compartmental shift and cerebral herniation.2 Because of the high mortality rate and the poor functional outcome among survivors, aggressive therapeutic maneuvers have been considered for this catastrophe, including decompressive hemicraniectomy and induced hypothermia. Animal experiments and preliminary human studies suggest that both of these approaches may limit infarct size and improve mortality, particularly if instituted early after stroke onset.3–10 Hemicraniectomy and hypothermia remain contentious therapies, however, because they are both unproven and may pose considerable risk to the patient. Randomized clinical trials of both interventions are necessary and are currently in the planning stages. Careful selection of patients for these studies is critical to avoid unnecessarily aggressive procedures in patients who have little chance of benefit. Furthermore, an adequate assessment of the probability of death among the untreated control patients is required to appropriately determine the sample size for these studies. In a prospective cohort of patients with severe stroke derived from the placebo arm of the Lub-INT-9 clinical trial,11 only early nausea/vomiting and massive computed tomographic (CT)
hypodensity (exceeding 50% of the middle cerebral artery [MCA] territory) were identified at the time of initial presentation as independent predictors of fatal brain swelling. However, that study was limited by a relatively small number of neurological deaths and thus had limited statistical power to identify multiple predictors. Moreover, the results may not be widely applicable because they were obtained from a heterogeneous population of strokes that met the specific inclusion and exclusion criteria of the clinical trial. Other small studies have supported the prognostic role of major CT findings and other neuroimaging data but failed to identify any clinical or laboratory predictors of outcome. Therefore, we evaluated the early clinical, laboratory, and radiographic characteristics associated with fatal brain edema after stroke in a larger, broad-based patient population.

Subjects and Methods

Study Design and Patient Selection

This was a retrospective case-control study of patients with large hemispheric ischemic stroke drawn from 7 centers in 3 countries between January 1995 and December 1998. Patients were identified from review of all neurology admission logs and other health-record sources. Patients were eligible for the present study if all of the following inclusion criteria were fulfilled: (1) cerebral infarction involving at minimum both the anterior and posterior divisions of the MCA territory (with or without the deep MCA territory supplied by the lenticulostriate arteries) equivalent to “60” size or more MCA infarction according to the criteria of Wardlaw and Sellar on a late CT scan that revealed infarct size; (2) awake or drowsy but arousable with minor stimulus to obey, answer, or respond at some time during first 5 days of hospital course; (3) hospital presentation within 48 hours of symptom onset; (4) admitted to neurocritical or other intensive care units in participating hospital; and (5) at least 2 CT scans performed within first 5 days of hospital course. The study thus did not include persistently stuporous or comatose patients, because such patients may have already herniated, have a virtually uniformly poor prognosis, and are seldom considered as candidates for experimental therapies. Patients were not eligible if any of the following exclusion criteria were met: (1) incomplete hospital records or missing CT scans that would prevent complete data collection; (2) large parenchymal hematoma (>30% of infarct territory causing mass effect or edema); or (3) therapeutic hypothermia or hemicraniectomy during hospital course. The rationale for exclusion of patients treated with hemicraniectomy or hypothermia was based on the possibility that such therapies may alter the morbidity and mortality of large hemispheric strokes, and the purpose of the present study was to characterize the natural history of large hemispheric strokes.

All available patient data, including detailed clinical summaries, were reviewed to verify cause of death and to specifically determine which patients died as a result of massive brain edema. Only in-hospital mortality was addressed in the present study. Neurological death was defined as death caused by brain herniation with documented evidence of brain stem compression (enlarged pupil, coma, or loss of other brain stem reflexes) preceding death. Cardiac arrest at the time of neurological signs of herniation was considered neurological death. All other causes of death without signs of herniation, such as pulmonary embolus, pneumonia, or cardiac arrest, were considered non-neurological death. Deaths of patients with “do-not-resuscitate” orders implemented before neurological decline were not considered neurological death. For the present study, cases were defined as those patients who suffered neurological death (fatal brain edema), whereas controls were defined as all remaining patients with large strokes who survived the acute hospitalization or died of other causes.

Data Collection

Standardized case report forms were used for data collection, which was performed by experienced stroke neurologists at each site. Demographic characteristics and baseline clinical information regarding stroke risk factors, clinical stroke severity (estimated in 5-point increments of the National Institutes of Health Stroke Scale [NIHSS]), blood pressure, fever, and timing of initial clinical evaluation in relation to stroke onset were extrapolated from the medical record information. Specific clinical data regarding presence of early nausea or vomiting, headache, gaze deviation, and level of consciousness were obtained from the initial acute clinical history and/or admission notes. The timing and severity of any clinical deterioration during the hospitalization were extrapolated from the medical record. All laboratory measurements of serum glucose, sodium, potassium, magnesium, and white blood cell count (WBC) on admission were recorded. Information regarding interventions during the hospital course, including airway intubation, thrombolytic therapy, or osmotic diuresis, was recorded. Each CT scan performed during hospitalization was reexamined and interpreted by a stroke neurologist at each center. Information from the initial CT scan only is reported in this analysis of early predictors. The CT scan was evaluated allowing for technical factors, including window settings, movement artifacts, or head positioning in the gantry, all of which may influence interpretation. Particular attention was directed toward early signs of infarction, vascular distribution of the infarction, site of vessel occlusion, intracerebral hemorrhage, and measurement of mass effect.

Early signs of infarction were interpreted according to the methods of von Kummer and colleagues. Early CT signs evaluated included the following: (1) hyperdense MCA sign, defined as spontaneous high contrast in the MCA that is brighter than adjacent brain tissue and other intracranial arteries (particularly contralateral MCA) and not attributable to calcification; (2) Hyperdense internal carotid artery sign was defined on the same terms as spontaneous high contrast in the terminal internal carotid artery (ICA) distinguishable from opposite ICA and surrounding bony structures. (3) Lentiform obscuration was defined as a loss of the precise delineation of the lentiform nucleus due to a decrease in density compared with the contralateral nucleus; (4) Sylvian fissure obscuration was defined as effacement of the sylvian fissure compared with the contralateral side. Infarct size was classified as defined by Wardlaw and Sellar. Other vascular territory involvement was defined as hypodensity in the anterior cerebral, anterior choroidal, or posterior cerebral arteries. Determination of vascular distribution was based on the vascular territory templates provided by Tatu et al. (6) Mass effect was determined by grading hemispheric swelling. Greater than 2 on this scale corresponds to complete sylvian fissure obscuration and extensive effacement of the hemisphere, including lateral ventricle compression. (7) Mass effect was also graded by a quantitative measure with pineal gland shift and septum pellucidum (anterior-superior) shift.

Statistical Methods

Cases and controls were compared in terms of demographic features, preexisting conditions, clinical characteristics, laboratory results, and CT findings. In the initial bivariable analyses, dichotomous or categorical variables were compared with the χ² test, and continuous variables were compared with the unpaired t test or Wilcoxon rank sum test, as indicated. All tests were 2 sided. Variables were considered for multivariable analysis if they were associated with neurological death in the bivariable analysis at the P<0.10 level, to reduce the chance of type II error due to the modest sample size. Multivariable analysis was performed with logistic regression, with clustering by site. This method assumes that patients within a site may have been treated similarly but that there may have been important differences in management and outcome among the multiple sites. Age was retained in the final logistic model because it was deemed a highly probable confounder. Stepwise procedures were avoided, because these may lead to suboptimal final models; instead, the regression was performed to assess the importance of each potential variable as it affected the other parameter OR.
estimates in the model. In the final model, an association was considered significant if \( P < 0.05 \).

The study was powered to be able to identify as many as 10 important variables that were predictive of fatal brain edema. Therefore, the sample required \( \approx 100 \) patients with this outcome in the study. A risk stratification index was developed by assigning 1 point for each of the risk factors determined by the final multivariable logistic regression model. Continuous variables, if significant in the multivariable model, were dichotomized at their medians for this analysis. If data for a variable were missing, they were arbitrarily coded as not present for this analysis. The risk of fatal brain edema was calculated for each score on the index, as were the sensitivity and specificity, with 95% binomial CIs for each threshold score, and the overall area under the receiver operator characteristic curve. Likelihood ratios were also calculated for each threshold score. The association between risk score and neurological death was evaluated with the test for trend.

All statistical analyses were performed with STATA version 6.0 (Stata Corporation).

**Results**

**Patient Outcomes**

Review of hospital admission logs yielded \( \approx 12000 \) stroke patients from the 7 participating centers. A total of 201 patients with large strokes met all eligibility criteria and were included in the present study. Fatal brain swelling occurred in 94 patients (47%), who were designated as cases for this study. Another 12 patients (6%) died of other causes: pneumonia \((n=5)\), sepsis \((2)\), cardiac arrest \((1)\), cardiac tamponade \((1)\), recurrent stroke \((1)\), and withdrawal of care unrelated to brain swelling \((2)\). The remaining 95 patients \((47\%)\) survived until hospital discharge. These latter 2 groups served as the 107 controls. Outcomes were similar at all 7 participating sites \( (P=0.54) \).

Fifty additional patients met all inclusion and exclusion criteria except that they were treated with hemicraniectomy. This procedure was performed at 6 of the 7 participating centers. An additional 19 patients at 2 institutions were excluded because of treatment with hypothermia. Those patients were not included in the present study and will be reported in a separate analysis.

**Clinical Features**

Clinical characteristics of the cases and controls are summarized in Table 1. Age, race, and sex were similar in the 2 groups. Cases were more likely to have a history of hypertension \((OR 2.1, 95% CI 1.15 to 3.91)\) and history of congestive heart failure \((OR 2.15, 95% CI 1.14 to 4.03)\) but were similar with regard to other risk factors. Although all patients in the present study had large strokes, cases had higher NIHSS scores by one 5-point category \((OR 1.67 per 5-point category increase, 95% CI 1.29 to 2.16)\). Cases were also more likely to have depressed level of consciousness \((OR 8.21, 95% CI 2.83 to 23.7)\) and early nausea/vomiting \((OR 3.39, 95% CI 1.07 to 10.7)\). Early headache and fever were not associated with fatal brain edema. Initial blood pressure recordings were similar in the 2 groups.

**Laboratory Results**

Initial laboratory parameters for cases and controls are summarized in Table 2. Serum glucose and sodium levels were similar between the 2 groups. Serum magnesium levels were significantly lower in cases \((1.5 \pm 0.6 \text{ mEq/dL})\) than in controls \((1.8 \pm 0.4 \text{ mEq/dL}; P=0.03)\), but this measure was only available for 71 patients \((35\%)\) and therefore was not used in subsequent multivariable analyses. WBC count tended to be higher in cases \((10.873 \pm 422 \text{ WBC/μL})\) than in controls \((10.055 \pm 363 \text{ WBC/μL}; P=0.09)\).

**Radiographic Findings**

Initial CT scans were obtained a median 2.6 \((range 0.2 to 40)\) and mean 5.0 \(\pm 5.9 \) hours after onset of symptoms \(\) (timing uncertain in 47 patients). Baseline CT characteristics are outlined in Table 1. The frequencies of hyperdense vessel signs and of subtle early ischemic signs were similar between cases and controls. However, the 2 groups differed significantly with regard to major early CT findings. Early involvement of more than half of the MCA territory was significantly more common in cases than controls \((OR 3.76, 95\% CI 2.05 to 6.91)\), as was involvement of other vascular territories \((OR 6.25, 95\% CI 2.11 to 18.4)\) and early mass effect \((OR 2.51, 95\% CI 1.31 to 4.78)\). Early temporal lobe involvement also tended to be more common in cases than in controls \((OR 1.78, 95\% CI 0.97 to 3.31)\). Despite these differences on baseline CT, both groups ultimately developed large infarctions with Wardlaw scores \(\geq 60\) on the late CT scans.

**Multivariable Analysis**

Clinical, laboratory, and radiographic features tested in multivariable analysis included age, history of hypertension, history of congestive heart failure, NIHSS category, early nausea/vomiting, early stupor/coma, WBC count, CT involvement of \(>50\%\) of the MCA territory, involvement of other vascular territories, temporal lobe hypodensity, and early mass effect. The role of each individual site was not found to be a significant confounder \((P=0.54)\), and all results were clustered by site.

The significant predictors of fatal brain swelling were \((1)\) history of hypertension \((OR 3.03, 95\% CI 1.21 to 7.62, P=0.018)\), \((2)\) history of congestive heart failure \((OR 2.12, 95\% CI 1.49 to 3.02, P<0.001)\), \((3)\) WBC count \((OR 1.07 per 1000 \text{ WBC/μL}, 95\% CI 1.01 to 1.14, P=0.015)\), \((4)\) CT involvement of \(>50\%\) MCA territory \((OR 6.34, 95\% CI 3.48 to 11.6, P<0.001)\), and \((5)\) CT involvement of additional territories \((OR 3.34, 95\% CI 1.19 to 9.38, P=0.022)\). The role of WBC count was also evaluated as a dichotomous variable, scored as present if it exceeded its median value of 10 000/μL and absent if less than or equal to this value. In this case, elevated WBC count also was a significant variable in the model \((OR 3.93, 95\% CI 2.41 to 6.43, P<0.001)\), and its inclusion as a dichotomous rather than continuous variable had minimal effects on the ORs of the other variables in the model. Also, in the initial multivariable analysis, temporal lobe involvement appeared to be associated with a reduced risk of fatal brain edema \((OR 0.38, 95\% CI 0.18 to 0.79, P=0.010)\). However, this apparent reduction was due to an interaction between temporal lobe hypodensity and the other significant CT abnormalities. The majority \((70\%)\) of patients who had temporal lobe involvement also had \(>50\%\) MCA involvement and/or involvement of additional vascular terri-
When this interaction was included in the model, the role of temporal lobe hypodensity was no longer significant (OR 1.10, 95% CI 0.31 to 3.91, \( P = 0.89 \)).

Risk Index

A 5-point risk index was calculated for each patient based on the predictors of herniation identified in the multivariable analysis. The 2 clinical and the 2 radiographic predictor variables were each assigned 1 point. WBC count was dichotomized and scored as 1 point if it exceeded its median value of 10 000/\( \mu \)L and zero points if less than or equal to this value. The relationship between fatal brain edema and the risk score is depicted in the Figure. The overall association between risk index and neurological death and the test for trend were statistically significant ( \( P = 0.001 \)). Sensitivity, specificity, and likelihood ratios for each risk index score are

### TABLE 1. Patient Characteristics (Bivariable Analysis)

<table>
<thead>
<tr>
<th></th>
<th>Cases (n=94)</th>
<th>Controls (n=107)</th>
<th>( P )</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y, mean±SD</td>
<td>67±12</td>
<td>67±14</td>
<td>0.95</td>
<td></td>
</tr>
<tr>
<td>Female, %</td>
<td>51</td>
<td>55</td>
<td>0.56</td>
<td></td>
</tr>
<tr>
<td>White, %</td>
<td>81</td>
<td>82</td>
<td>0.80</td>
<td></td>
</tr>
<tr>
<td><strong>Risk factors, %</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>76</td>
<td>60</td>
<td>0.02</td>
<td>2.11</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>45</td>
<td>40</td>
<td>0.52</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>40</td>
<td>35</td>
<td>0.50</td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>25</td>
<td>21</td>
<td>0.47</td>
<td></td>
</tr>
<tr>
<td>CHF</td>
<td>36</td>
<td>21</td>
<td>0.02</td>
<td>2.15</td>
</tr>
<tr>
<td>Prior stroke</td>
<td>23</td>
<td>16</td>
<td>0.18</td>
<td></td>
</tr>
<tr>
<td><strong>Clinical features</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NIHSS, 5-point category</td>
<td>21–25</td>
<td>16–20</td>
<td>0.008</td>
<td>1.67/5-point category</td>
</tr>
<tr>
<td>Fever, %</td>
<td>38</td>
<td>33</td>
<td>0.49</td>
<td></td>
</tr>
<tr>
<td>Headache, %</td>
<td>9</td>
<td>11</td>
<td>0.70</td>
<td></td>
</tr>
<tr>
<td>Vomiting, %</td>
<td>13</td>
<td>4</td>
<td>0.04</td>
<td>3.39</td>
</tr>
<tr>
<td>Stupor/coma, %</td>
<td>25</td>
<td>4</td>
<td>0.0001</td>
<td>8.21</td>
</tr>
<tr>
<td>Peak SBP, mm Hg</td>
<td>171±30</td>
<td>172±30</td>
<td>0.78</td>
<td></td>
</tr>
<tr>
<td>Trough SBP, mm Hg</td>
<td>138±28</td>
<td>143±28</td>
<td>0.37</td>
<td></td>
</tr>
<tr>
<td>Thrombolysis, %</td>
<td>15</td>
<td>20</td>
<td>0.35</td>
<td></td>
</tr>
<tr>
<td><strong>Laboratory data</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose, mg/dL</td>
<td>175±88</td>
<td>161±75</td>
<td>0.25</td>
<td></td>
</tr>
<tr>
<td>Sodium, mEq/dL</td>
<td>140±4</td>
<td>140±4</td>
<td>0.29</td>
<td></td>
</tr>
<tr>
<td>Magnesium, mEq/dL</td>
<td>1.5±0.6</td>
<td>1.8±0.4</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>WBC/( \mu )L</td>
<td>10 873±422</td>
<td>10 055±363</td>
<td>0.09</td>
<td></td>
</tr>
<tr>
<td><strong>Initial CT data, %</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HICAS</td>
<td>10</td>
<td>13</td>
<td>0.54</td>
<td></td>
</tr>
<tr>
<td>HMCAS</td>
<td>39</td>
<td>32</td>
<td>0.34</td>
<td></td>
</tr>
<tr>
<td>Lentiform obscuration</td>
<td>65</td>
<td>70</td>
<td>0.47</td>
<td></td>
</tr>
<tr>
<td>Sylvian obscuration</td>
<td>56</td>
<td>46</td>
<td>0.16</td>
<td></td>
</tr>
<tr>
<td>&gt;50% MCA</td>
<td>61</td>
<td>29</td>
<td>0.0001</td>
<td>3.76</td>
</tr>
<tr>
<td>Temporal lobe</td>
<td>71</td>
<td>57</td>
<td>0.06</td>
<td>1.78</td>
</tr>
<tr>
<td>Other territory</td>
<td>21</td>
<td>4</td>
<td>0.0004</td>
<td>6.25</td>
</tr>
<tr>
<td>Mass effect</td>
<td>35</td>
<td>18</td>
<td>0.005</td>
<td>2.51</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>0</td>
<td>2</td>
<td>0.18</td>
<td></td>
</tr>
<tr>
<td>Atrophy</td>
<td>43</td>
<td>36</td>
<td>0.35</td>
<td></td>
</tr>
</tbody>
</table>

CHF indicates congestive heart failure; SBP, systolic blood pressure; HICAS, hyperdense internal carotid artery sign; and HMCAS, hyperdense MCA sign. Dichotomous and categorical variables were compared with the \( \chi^2 \) test, and continuous variables were compared with the unpaired \( t \) test or Wilcoxon rank sum test.

*Magnesium was not included in multivariable analyses because of large amounts of missing data.
summarized in Table 2. The area under the receiver operator characteristic curve was 0.70, which suggests that the model based on the risk index has good ability to discriminate between outcome states.25

**Discussion**

Patients with large hemispheric strokes are at high risk of fatal brain edema and may be considered potential candidates for aggressive treatments, such as hemicraniectomy or hypothermia. However, some patients with large strokes are more likely to die as a result of herniation than others, and improved methods are needed to stratify risk. A few prior studies have addressed this issue in relatively small groups of very carefully selected stroke patients, so the results may not apply to the majority of large strokes that are encountered in clinical practice.

The present study sought to identify clinical, laboratory, and radiographic factors that predicted fatal brain edema among a broad population of patients with large strokes. The patients were drawn from multiple centers in 4 countries and were demographically diverse. Compared with patients included in published acute stroke trials,11,26,27 the patients in the present study had a greater proportion of some vascular risk factors, such as atrial fibrillation and diabetes. The strokes in the present study were also more severe than in most prior studies, with median NIHSS scores in the 16-to-20 category. Furthermore, the neurological mortality rate of 47% in our population far exceeds that of other studies, even the category. Furthermore, the neurological mortality rate of 47%, most prior studies, with median NIHSS scores in the 16-to-20 range. The present study had a greater proportion of some vascular risk factors, such as atrial fibrillation and diabetes. The strokes in the present study were also more severe than in most prior studies, with median NIHSS scores in the 16-to-20 category. Furthermore, the neurological mortality rate of 47% in our population far exceeds that of other studies, even the category. Furthermore, the neurological mortality rate of 47%, most prior studies, with median NIHSS scores in the 16-to-20 range.

The radiographic findings in the present study are similar to and expand on those in prior studies. Hacke and colleagues1 evaluated 55 patients with complete MCA territory infarction and described the clinical and radiographic course of their neurological decline. They found that occlusion of the internal carotid artery or MCA and poor collateral blood flow were associated with fatal outcomes. However, no specific features, the other using only CT data. In the former, they in a subset of patients from the placebo arm of a randomized clinical trial and attempted to identify a composite of clinical, laboratory, and radiographic predictors of neurological death. In their sample of 23 cases who herniated and 112 controls, they performed 2 separate logistic regression analyses, one using only clinical factors and laboratory features, the other using only CT data. In the former, they identified nausea/vomiting as a possible baseline predictor of fatal brain edema. Although the present study initially found nausea/vomiting to be associated with fatal brain swelling in the bivariable analysis, this was not upheld by the multivariable analysis. This suggests that nausea/vomiting may be a confounding clinical indicator, or a proxy for 1 or more of the significant predictors, but is itself unlikely to be an independent predictor in clinical practice.

The radiographic findings in the present study are similar to and expand on those in prior studies. Hacke and colleagues1 evaluated 55 patients with complete MCA territory infarction and described the clinical and radiographic course of their neurological decline. They found that occlusion of the internal carotid artery or MCA and poor collateral blood flow were associated with fatal outcomes. However, no specific features, the other using only CT data. In the former, they identified nausea/vomiting as a possible baseline predictor of fatal brain edema. Although the present study initially found nausea/vomiting to be associated with fatal brain swelling in the bivariable analysis, this was not upheld by the multivariable analysis. This suggests that nausea/vomiting may be a confounding clinical indicator, or a proxy for 1 or more of the significant predictors, but is itself unlikely to be an independent predictor in clinical practice.

The radiographic findings in the present study are similar to and expand on those in prior studies. Hacke and colleagues1 evaluated 55 patients with complete MCA territory infarction and described the clinical and radiographic course of their neurological decline. They found that occlusion of the internal carotid artery or MCA and poor collateral blood flow were associated with fatal outcomes. However, no specific

**TABLE 2. Risk Index Score and Probability of Fatal Brain Swelling**

<table>
<thead>
<tr>
<th>Risk Index</th>
<th>Fatal Brain Edema</th>
<th>No Fatal Brain Edema</th>
<th>Sensitivity (95% CI)†</th>
<th>Specificity (95% CI)†</th>
<th>Likelihood Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>13</td>
<td>29</td>
<td>1.00</td>
<td>0.00</td>
<td>0.51</td>
</tr>
<tr>
<td>1</td>
<td>9</td>
<td>34</td>
<td>0.86 (0.72, 0.92)</td>
<td>0.27 (0.09, 0.37)</td>
<td>0.30</td>
</tr>
<tr>
<td>2</td>
<td>39</td>
<td>30</td>
<td>0.77 (0.67, 0.85)</td>
<td>0.59 (0.49, 0.68)</td>
<td>1.49</td>
</tr>
<tr>
<td>3</td>
<td>16</td>
<td>12</td>
<td>0.35 (0.26, 0.46)</td>
<td>0.87 (0.79, 0.93)</td>
<td>1.52</td>
</tr>
<tr>
<td>4</td>
<td>13</td>
<td>2</td>
<td>0.18 (0.11, 0.27)</td>
<td>0.98 (0.93, 1.00)</td>
<td>7.40</td>
</tr>
<tr>
<td>5</td>
<td>4</td>
<td>0</td>
<td>0.04 (0.01, 0.11)</td>
<td>1.00 (0.97, 1.00)</td>
<td>∞</td>
</tr>
</tbody>
</table>

†Sensitivity reflects the probability of having a risk index score equal to or greater than the score indicated for the stratum among the total number of patients who suffered a neurological death. Specificity reflects the probability of having a risk index score less than the score indicated among the total number of patients who did not suffer a neurological death.
clinical or laboratory factors were identified as predictors of herniation. Von Kummer and colleagues\textsuperscript{14} investigated the prognostic value of CT in 53 patients with MCA trunk occlusions. Of these, 18 patients died, and the only predictor of outcome was major early CT hypodensity. Haring and colleagues\textsuperscript{33} also demonstrated that major hypodensity in the MCA territory predicted herniation but found that attenuation of contrast between the gray and white matter was the single best predictor of this outcome in a study of 62 patients with hemispheric infarctions. In the analysis of radiographic factors by Krieger and colleagues,\textsuperscript{12} only CT involvement of $>$50\% of the MCA territory was found to predict fatal brain swelling. The present study supports this predictive role of major early CT changes in the MCA territory and demonstrates an additional effect when there is involvement of other vascular territories, such as the anterior cerebral artery or anterior choroidal artery. Concurrent acute infarction in these territories contributed to poor outcome and was likely indicative of poor hemispheric collateral flow, larger or more proximal vascular occlusion (such as the intracranial internal carotid artery), and greater volume of edematous brain tissue.\textsuperscript{34}–\textsuperscript{36}

In the present study, there were several factors notably absent from the final list of predictors. Among the initial clinical factors, neither level of consciousness nor stroke severity on presentation was associated with neurological death. Both of these appeared to be associated with outcome in preliminary bivariable analyses but did not contribute to the final multivariable analysis. The lack of association could be related to limited statistical power, although the study had an adequate sample size to detect up to 9 or 10 predictive variables.\textsuperscript{13} Alternatively, there may be no real predictive role of these clinical features. Impaired level of consciousness usually occurs relatively late after stroke onset and may not be a useful predictor of ultimate outcome. Similarly, because the present study only evaluated large strokes, most patients had severe deficits at baseline, and the severity of the deficit as measured by the NIHSS may simply not be useful for distinguishing which patients have the grimmer prognosis. The use of thrombolytic therapy for the stroke was not predictive of fatal brain edema in any analysis in the present study. Although this could be interpreted as implying that large strokes do not respond to thrombolysis, it is also likely that there was a selection bias in this study, because we systematically excluded patients with smaller strokes on late CT, including those who may have had favorable responses to thrombolytic therapy.

The probability of neurological death increased dramatically with increasing risk index score. This score could serve as a convenient summary marker for the risk of fatal brain edema and may be useful for the selection of patients for trials of aggressive interventions. For example, in a trial of hemicraniectomy, it would be ideal if the study only included patients who were at greatest risk of fatal brain edema. Therefore, a diagnostic method with high specificity is desirable, because it would ensure that very few patients at low risk would be potentially exposed to an invasive experimental procedure. Given our results, patients with 3 or more points on the risk index could be selected with 87\% specificity. The sensitivity at this threshold is relatively low, such that only 35\% of patients destined toward a neurological death would be identified by our criteria. This relatively low sensitivity would reduce the number of patients eligible for the proposed intervention but would maximize the safety of patients who are ultimately included.

Our study has potential limitations caused primarily by its retrospective design. The abstraction of medical records often results in some misclassified or missing data. However, it is unlikely that there was a differential bias as a result of misclassification, because baseline data were recorded well in advance of the outcome and therefore should not have led to false-positive associations (type I errors). Although larger than prior studies, our study was still relatively small. However, we had sufficient power to identify more variables than we did, which suggests that false-negative associations (type II errors) also were unlikely. Our data were collected from multiple centers and countries to reflect actual clinical practice rather than clinical trials. Although we did not find significant heterogeneity among the sites with regard to outcome, this study still has limited generalizability because these were all tertiary care centers with neurocritical care units staffed by trained subspecialists. Only a small fraction of all stroke patients at these institutions met the inclusion and exclusion criteria, so the results are only applicable to similar patients encountered in clinical practice. Furthermore, the exclusion of patients with persistent stupor or coma and patients treated with hemicraniectomy or hypothermia also precludes the use of our predictive model for such patients. All data were generated at each site without blinded central reading of the imaging data or adjudication of outcomes, so there is potential for additional bias that cannot be identified. Finally, we did not collect data on outcomes other than mortality, and severe dependency after stroke is also likely to affect future treatment decisions.\textsuperscript{37}

In conclusion, this study identified several readily available clinical, laboratory, and radiographic features that may be useful in predicting which patients with large hemispheric ischemic strokes are at highest risk for fatal brain swelling. Such patients may be reasonable candidates for aggressive intervention and could serve as the study population for trials of hemicraniectomy or hypothermia. The predictors identified in this study may be more generalizable than those in prior studies because they were derived from a broad-based population in real clinical practice. These predictors should be validated in a prospective study.

Acknowledgments
Dr Kasner was supported by NIH/NINDS K23 grant NS02147. Dr Demchuk was supported by the Medical Research Council of Canada and the Alberta Heritage Foundation for Medical Research and by NIH/NINDS training grant NS07412 to the University of Texas-Houston Medical School. Dr Christou was supported by the Hellenic Ministry of Defense Visiting Clinician Grant, Athens, Greece.

References


Predictors of Fatal Brain Edema in Massive Hemispheric Ischemic Stroke

Stroke. 2001;32:2117-2123
doi: 10.1161/hs0901.095719

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2001 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/32/9/2117

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/