ORIGINAL CONTRIBUTION

# Neurologic Worsening During the Acute Phase of Ischemic Stroke

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**Background:** Although capacities for intensive monitoring of patients with stroke are still limited, patients at risk for early neurologic worsening are poorly defined.

**Objective:** To identify patients at risk for neurologic worsening.

**Design:** An inception cohort was assessed using the National Institutes of Health Stroke Scale (NIH-SS) at hospital admission and again 48 to 72 hours later.

**Setting:** Eleven neurologic departments with acute stroke units.

**Patients:** A total of 1964 consecutive patients admitted within 4 hours of the onset of acute cerebral ischemic symptoms.

**Main Outcome Measures:** Underlying reasons for and possible predictors of neurologic worsening.

**Results:** A total of 256 patients (13.0%) had an increased score of 1 point or more on the NIH-SS after 48 to 72 hours. Neurologic worsening was attributed to progressive stroke in 33.6% of patients, increased intracranial pressure in 27.3%, recurrent cerebral ischemia in 11.3%, and secondary parenchymal hemorrhage in 10.5%. A multivariate logistic regression analysis identified internal carotid artery occlusion, medial cerebral artery (M1) occlusion, territorial infarction, brainstem infarction, and diabetes mellitus as independent predictors of neurologic worsening on the NIH-SS. Worsening of key neurologic functions (consciousness, gaze, arm or leg motor function, and speech) occurred in 223 patients (11.4%), and worsening of 4 points or more on the NIH-SS total score occurred in 148 patients (7.5%).

**Conclusion:** Besides initial stroke severity and comorbid conditions, ultrasound and imaging can provide valuable information about the risk of worsening of stroke symptoms in the acute phase and thus can identify patients who could benefit most from intensive monitoring.

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NEUROLOGIC WORSENING after acute ischemic stroke is a frequent observation in clinical routine and in a variety of previous studies.[1-13] Because little can be done to alter the course of stroke before hospital admission, most studies have focused on neurologic worsening occurring after hospital admission. The later a patient is admitted after the onset of ischemic symptoms, the more likely it is that secondary worsening occurs before baseline assessment and is thus being missed. Few studies, however, have based their definition of neurologic worsening on a very short delay from the start of ischemic symptoms to hospital admission. These studies are based on either small or highly selected patient cohorts.[7,13] We, therefore, focused our study on neurologic worsening that was assessed 48 to 72 hours after admission in patients admitted within 4 hours of symptom onset, thus including patients with ischemic stroke and transient ischemic attacks.

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**Group Information:** A list of members of the German Stroke Study Collaboration appears on page 397.

## METHODS

Eleven neurologic departments (German Stroke Study Collaboration) participated in this study. Enrollment of patients started July 1, 2000, and ended March 15, 2002. Details of data collection and management have been described in previous publications.[14,15] All patients were treated according to best current knowledge in clinical routine. Imaging studies were performed to exclude patients with primary hemorrhage and causes other than cerebral ischemia. Patients or their next of kin were informed about study participation, and informed writ-

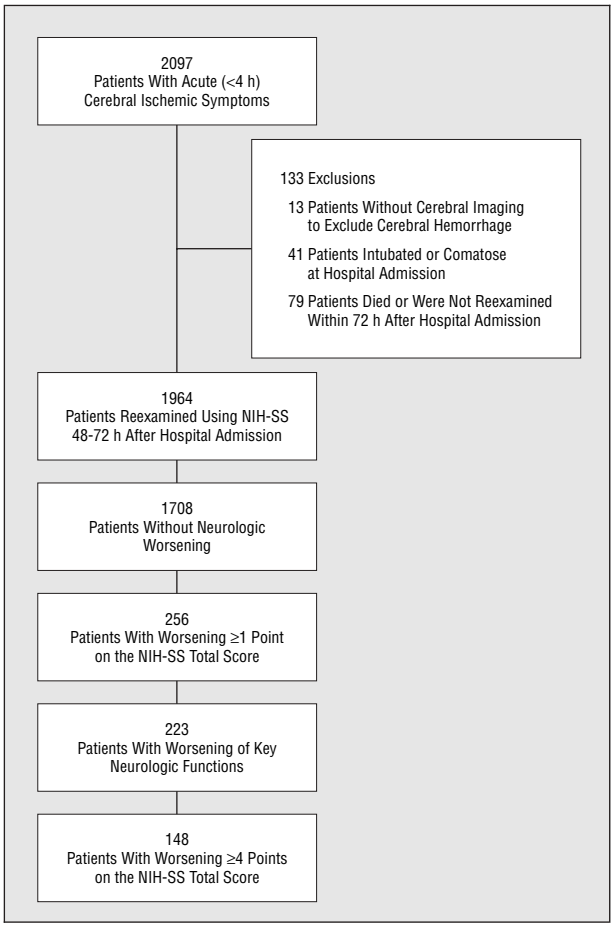


**Figure.** Patient inclusion flowchart. NIH-SS indicates National Institutes of Health Stroke Scale.

ten consent was obtained to forward personal data to the coordinating center. The study was approved by the ethics committee of the University of Essen, and aspects of data safety were approved by the responsible data protection state representative. Severity of stroke was assessed using the National Institutes of Health Stroke Scale (NIH-SS) at hospital admission and 48 to 72 hours later.[16] Investigators were trained in the application of the NIH-SS by using videotapes and other clinical studies. Worsening of stroke was defined as an increase of 1 point or more on the NIH-SS total score from hospital admission until 48 to 72 hours later. As suggested by an internationally recognized definition, we also investigated worsening until 48 to 72 hours after admission in 1 of the following NIH-SS items: level of consciousness, gaze, arm and leg motor function, and speech.[1] Finally, we also investigated worsening of 4 points or more on the NIH-SS until 48 to 72 hours after hospital admission. Underlying causes of neurologic worsening have been defined in previous publications.[17] In addition, we defined progressive stroke as progressive worsening of neurologic deficits without evidence of increased intracranial pressure, recurrent cerebral ischemia, or secondary parenchymal bleeding. A central follow-up was performed by telephone interview by the coordinating center or by the treating hospital itself if the patient did not consent to having personal data forwarded. Patient outcome was assessed using the Barthel Index within 85 to 120 days after the event or by confirmation of death within 120 days of the initial stroke. Otherwise, follow-up data on functional status were considered as missing for analysis. Only patients with acute cerebral ischemic symptoms who were admitted to the hospital within 4 hours of onset and who were not intubated or comatose at admission were included in this study. The flowchart of patient inclusion is depicted in the **Figure**.

Statistical analysis was performed using a software program (SPSS version 10.0; SPSS Inc, Chicago, Ill). If a single variable was not available for all patients, only valid cases were reported. If more than 1% of cases were missing for any variable, the number of valid cases was also provided. For a better identification of patients at risk for neurologic worsening, we developed 3 logistic regression models and included all statistically significant variables from the descriptive analysis that could be assessed in the first hours after hospital admission. The number of events per variable was greater than 20. Nevertheless, we included only those variables with a resulting $P<.01$. Any variable with $P>.05$ was excluded stepwise. In the final model, regression coefficients with standard errors, odds ratios, and 95% confidence intervals are reported.

## RESULTS

Of 1964 patients included in this study, 846 (43.1%) were women. The mean patient age was 67.6 years (median age, 70 years; age quartiles, 61 and 77 years). According to the modified TOAST (Trial of ORG 10172 in Acute Stroke Treatment) classification,[18] the cause of cerebral ischemia was classified as atherosclerotic or large vessel disease in 335 patients (17.1%), cardioembolic in 599 patients (30.5%), lacunar or small vessel disease in 291 patients (14.8%), "other" in 106 patients (5.4%), and undetermined in 633 patients (32.2%). A total of 354 patients (18.0%) were classified as having a transient ischemic attack with complete restitution of symptoms within 24 hours. Seventy-three patients (3.7%) also participated in clinical studies, none of which was found to cause neurologic worsening. Neurologic worsening on the NIH-SS total score after 48 to 72 hours was observed in 256 patients (13.0%). Worsening of consciousness after 48 to 72 hours was observed in 127 patients (6.5%), and 43 patients (2.2%) were intubated. A confirmation of death or a follow-up interview up to 120 days after hospital admission was obtained for 1522 patients (77.5%). Of these patients, 167 (11.0%) had died, 563 (37.0%) were not functionally recovered, and 792 (52.0%) were completely recovered, with a Barthel Index score of 95 or greater.

Patients with neurologic worsening had a worse neurologic status on the NIH-SS at hospital admission, more often a diagnosis of diabetes mellitus, and more territorial and brainstem infarctions (all statistically significant) (**Table 1**). Occlusions of the internal carotid artery (ICA) and middle cerebral artery (MCA) (M1) were also found statistically significantly more often in patients with neurologic worsening, whereas a classification of microangiopathy according to the TOAST criteria was less frequent. Additional characteristics of these patients are given in Table 1. Reasons for neurologic worsening were classified as progressive stroke in 33.6% of patients, intracranial pressure in 27.3%, recurrent cerebral ischemia in 11.3%, and secondary parenchymal bleeding in 10.5%. A multivariate logistic regression analysis identified ICA occlusion, brainstem infarction, MCA (M1) occlusion, territorial infarction, and diabetes mellitus as independent predictors of neurologic worsening after 48 to 72 hours using the NIH-SS (**Table 2**). On use of the

**Table 1. Characteristics of Patients With Different Forms of Neurologic Worsening***

| | No Neurologic Worsening (n = 1708) | Worsening of the NIH-SS Total Score (n = 256) | Worsening of Key Neurologic Functions (n = 223) | Worsening of ≥4 Points on the NIH-SS (n = 148) |
|---|---|---|---|---|
| Age, mean (SD), y | 67.6 (13) | 69.1 (13) | 69.7 (13)† | 68.2 (13) |
| Women | 43.1 | 42.6 | 44.4 | 38.5 |
| Rankin Scale score before the event >2 | 6.2 | 6.3 | 6.7 | 6.8 |
| Delay from event to hospital admission, mean (SD), min | 119 (70) | 117 (59) | 117 (59) | 115 (57) |
| NIH-SS score at hospital admission, mean (median) | 7.3 (5) | 10.0 (9)‡ | 9.4 (8)‡ | 10.5 (9)‡ |
| NIH-SS after 48-72 h, mean (median) | 4.7 (2) | 13.8 (13)‡ | 13.6 (12)‡ | 16.6 (14)‡ |
| Previous stroke | 24.5 | 23.0 | 23.8 | 25.7 |
| Previous myocardial infarction | 23.8 | 27.0 | 27.4 | 27.0 |
| Acute infection before stroke | 3.0 | 3.9 | 3.1 | 4.1 |
| Arterial hypertension | 67.9 | 73.4 | 73.1 | 72.3 |
| Diabetes mellitus | 20.7 | 28.9‡ | 28.7† | 26.4 |
| Hypercholesterolemia | 32.1 | 29.7 | 31.4 | 28.4 |
| Smoking | 22.7 | 24.0 | 27.1 | 24.7 |
| Territorial infarction | 41.6 | 66.4‡ | 63.7‡ | 75‡ |
| Infarction <15 mm in diameter | 11.4 | 9.4 | 9.4 | 7.4 |
| Brainstem infarction | 5.2 | 10.5 | 7.2 | 8.1 |
| Internal carotid artery occlusion | 9.3 | 24.3‡ | 23.8‡ | 25.7‡ |
| Middle cerebral artery (M1) occlusion | 4.0 | 16.0‡ | 13.9‡ | 20.3‡ |
| Cardiac embolism | 30.2 | 32.4 | 30.0 | 35.1 |
| Large vessel disease | 16.5 | 21.5 | 22.9† | 20.9 |
| Small vessel disease | 15.9 | 7.8‡ | 6.7‡ | 4.7‡ |
| Recurrent cerebral ischemia | 2.1 | 11.3‡ | 11.2‡ | 15.5‡ |
| Progressive infarction | 2.2 | 33.6‡ | 31.8‡ | 39.9‡ |
| Secondary parenchymal bleeding | 2.5 | 10.5‡ | 9.4‡ | 13.5‡ |
| Intracranial pressure | 2.0 | 27.3‡ | 18.8‡ | 37.2‡ |
| Temperature >38.0°C | 5.7 | 25.4‡ | 20.2‡ | 31.1‡ |
| Hyperglycemia >200 mg% | 6.0 | 15.6‡ | 11.2† | 16.2‡ |
| Recurrent hypertension >200/110 mm Hg | 5.4 | 12.5‡ | 9.9† | 14.2‡ |
| Systemic thrombolysis | 12.5 | 17.6† | 14.8 | 22.3%‡ |
| Barthel Index score ≥95 at follow-up, % (No. evaluated) | 57.7 (1313) | 16.7 (209)‡ | 19.4 (197)‡ | 8.6 (128)‡ |
| Died before follow-up, % (No.) | 7.6 (1313) | 32.1 (209)‡ | 25.9 (197)‡ | 35.9 (128)‡ |

Abbreviation: NIH-SS, National Institutes of Health Stroke Scale.
*Data are given as percentage of patients, except where indicated otherwise.
†$P<.05$.
‡$P<.01$.

**Table 2. Regression Model for Worsening of ≥1 Point on the NIH-SS Total Score**

| Variable | β | SE | Odds Ratio (95% CI) | *P* Value |
|---|---|---|---|---|
| Intercept | –2.881 | 0.161 | 0.056 | NA |
| ÍCA occlusion | 1.199 | 0.245 | 3.316 (2.052-5.357) | <.001 |
| Brainstem infarction | 1.198 | 0.243 | 3.314 (2.057-5.339) | <.001 |
| MCA (M1) occlusion | 0.845 | 0.184 | 2.329 (1.622-3.344) | <.001 |
| Territorial infarction | 0.799 | 0.160 | 2.223 (1.625-3.041) | <.001 |
| Diabetes mellitus | 0.483 | 0.159 | 1.621 (1.187-2.213) | .002 |

Abbreviations: CI, confidence interval; ICA, internal carotid artery; MCA, middle cerebral artery; NA, not applicable; NIH-SS, National Institutes of Health Stroke Scale.

threshold 0.120, the resulting model had a sensitivity of 68.0% and a specificity of 66.6%.

Of 256 patients with neurologic worsening, 43 were intubated 48 to 72 hours after hospital admission. The other patients most often had deterioration of arm paresis (37.6%), leg paresis (35.1%), level of consciousness (28.6%), sensory deficits (27.2%), and dysarthria (25.4%). Forty-four patients (17.2%) with neurologic worsening died before hospital discharge. At the first follow-up, 85 to 120 days after hospital admission, another 23 patients were found to have died, and 24 patients could not be reached for follow-up.

Patients with worsening of any key neurologic function (level of consciousness, gaze, arm and leg motor function, and speech) 48 to 72 hours after hospital admission are included in Table 1. Progressive infarction (31.8%) and increased intracranial pressure (18.8%) were the most frequent neurologic causes of worsening in these

**Table 3. Regression Model for Worsening of Any Key Neurologic Function (Level of Consciousness, Gaze, Arm and Leg Motor Function, or Speech)**

| Variable | β | SE | Odds Ratio (95% CI) | *P* Value |
|---|---|---|---|---|
| Intercept | –2.647 | 0.159 | 0.071 | NA |
| ICA occlusion | 0.869 | 0.246 | 2.385 (1.472-3.864) | <.001 |
| MCA (M1) occlusion | 0.750 | 0.197 | 2.117 (1.439-3.116) | <.001 |
| Territorial infarction | 0.592 | 0.163 | 1.808 (1.313-2.491) | <.001 |
| Diabetes mellitus | 0.478 | 0.165 | 1.613 (1.167-2.227) | .004 |

Abbreviations: CI, confidence interval; ICA, internal carotid artery; MCA, middle cerebral artery; NA, not applicable.

**Table 4. Regression Model for Worsening of ≥4 Points on the NIH-SS Total Score**

| Variable | β | SE | Odds Ratio (95% CI) | *P* Value |
|---|---|---|---|---|
| Intercept | –3.464 | 0.208 | 0.031 | NA |
| ICA occlusion | 1.201 | 0.257 | 3.323 (2.008-5.501) | <.001 |
| Territorial infarction | 1.105 | 0.215 | 3.019 (1.979-4.604) | <.001 |
| MCA (M1) occlusion | 0.651 | 0.220 | 1.917 (1.246-2.948) | .003 |

Abbreviations: CI, confidence interval; ICA, internal carotid artery; MCA, middle cerebral artery; NA, not applicable; NIH-SS, National Institutes of Health Stroke Scale.

patients. Occlusion of the ICA and MCA (M1), territorial infarction, and diabetes mellitus were identified as independent predictors using multivariate logistic regression analysis (**Table 3**). On use of the threshold 0.115, the resulting model had a sensitivity of 55.9% and a specificity of 72.6%.

Patient characteristics for worsening of 4 points or more on the NIH-SS until 48 to 72 hours after hospital admission are displayed in Table 1. Multivariate logistic regression analysis identified ICA occlusion, territorial infarction, and MCA (M1) occlusion as independent predictors of worsening of 4 points or more on the NIH-SS until 48 to 72 hours after admission (**Table 4**). On use of the threshold 0.09, the resulting model had a sensitivity of 68.9% and a specificity of 68.4%.

## COMMENT

The 13.0% overall incidence of neurologic worsening after acute cerebral ischemia in this study seems lower than that reported in previous studies.[1-12] One explanation is our definition of neurologic worsening, which included all patients with persisting deficits at hospital admission to allow for prospective identification of patients at risk and thus included 18% patients with transient ischemic attack. We consecutively included patients admitted within 4 hours after the start of ischemic symptoms, which is a very tight inclusion criterion compared with previous studies. A standardized reassessment 48 to 72 hours after hospital admission covered the acute phase of stroke and thus included the 2 most frequent causes of neurologic worsening: progressive stroke and increased intracranial pressure. However, we did not assess the interrater reliability between different investigators. In addition, deterioration of certain deficits, such as ataxia or distal motor functions that are not included in the NIH-SS, or more transient deficits could have gone undetected by our definition of neurologic worsening. For more severe strokes, on the other hand, key neurologic functions or a higher threshold for worsening of the NIH-SS total score might be more specific indicators of neurologic worsening.

Although different causes were identified for specific aspects of neurologic worsening, there was a consistent set of independent predictors identified in multivariate regression analysis. Occlusion of the ICA or MCA (M1) and territorial infarction were shown to be independent predictors for all definitions of neurologic worsening, whereas diabetes mellitus and brainstem infarction could be shown to be independent predictors for particular definitions of worsening only. Other studies[8-10] with different definitions of worsening likewise have identified occlusion of ipsilateral cerebral arteries and extent of infarction as predictors of neurologic deterioration. In agreement with previous studies, diabetes mellitus[2,7,10,18] and recurrent arterial hypertension[2,10,18] are associated with further secondary neurologic deterioration. The TOAST categories were not included in the logistic regression analysis because they are rarely known during the first hours after acute stroke. In contrast to a recent publication by Steinke and Ley,[3] microangiopathy (small vessel disease), however, was less frequent in patients with all types of neurologic worsening. Another hospital-based study[8] from the Lausanne Stroke Registry likewise found a reduced incidence of small vessel disease in patients with neurologic worsening at or after hospital admission. The reasons for this discrepancy could be the definition of neurologic worsening and, in particular, the delay from the start of ischemic symptoms to baseline neurologic assessment. Patients with small vessel disease often have less severe symptoms and are more often admitted to the hospital with a greater delay from

the start of their symptoms, by which time they may have already experienced partial restitution. At this point, however, they could be more susceptible to neurologic worsening from recurrent events or stuttering courses. A recent study[19] found a greater risk of adverse long-term outcome in patients with the greatest improvement the first day after the event.

Different therapies are warranted to prevent or treat different causes of neurologic worsening. Platelet aggregation inhibitors are now universally acknowledged to provide moderate protection against recurrent cerebral ischemia. No effective therapy is available yet to prevent or treat secondary parenchymal hemorrhage. Craniotomy and hypothermia, the only seemingly effective symptomatic therapies for large cerebral infarctions at risk for intracranial pressure, remain restricted to selected patients and stroke centers.[20,21] Neither systemic thrombolysis[7] nor any of the more than 50 neuroprotective drugs tested in clinical trials during the past 10 years have been shown to reduce the risk of early neurologic worsening in patients. Whether correction of hyperglycemia, hyperthermia, or excessive blood pressure in the acute phase can reduce the risk of neurologic worsening remains uncertain. Nevertheless, patients at risk for neurologic worsening should be closely monitored in intensive care or acute stroke units. Prospective identification of these patients could be useful for the allocation of limited monitoring or intensive care resources.

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