Different Predictors of Neurological Worsening in Different Causes of Stroke

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**Objectives:** To investigate clinical determinants of neurological worsening and to delineate its predictors.

**Design:** Retrospective analysis of the data from the Lausanne Stroke Registry.

**Patients:** A total of 3038 patients with first-ever stroke consecutively admitted to a primary-care stroke center.

**Main Outcome Measures:** Neurological worsening in the acute phase of stroke.

**Results:** Neurological worsening was observed in 38% of 300 patients with brain hemorrhage, 34% of 1968 patients with noncardioembolic infarction, and 15% of 770 patients with cardioembolic infarction (P<.001). Neurological worsening was significantly less frequent in patients with small-artery disease than in those with large-artery atherosclerosis or other causes. A logistic multiple regression model in patients with noncardioembolic infarction showed age less than 65 years, hypertension, lesion outside the superficial anterior circulation, absence of transient ischemic attack, and reduced level of consciousness as the independent factors in the patients with small-artery disease, while it showed involvement of the posterior circulation and reduced level of consciousness in the patients with large-artery atherosclerosis. Severe functional disability or death was more common in patients with neurological worsening, both in patients with large-artery atherosclerosis and in those with small-artery disease (18% vs 9%; P<.001).

**Conclusions:** Determinants of neurological worsening may include causative aspects rather than just the evolution of the ischemic or hemorrhagic process itself. For a better comprehension and treatment of neurological worsening, the causative and pathophysiological conditions underlying stroke should be differentiated as early as possible.

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Worsening of neurological symptoms after acute cerebrovascular disease has always interested clinicians and was formally reported by Millikan and Siekert more than 40 years ago. Although various terms, such as progressive stroke, stroke-in-progression, or stroke-in-evolution, as well as various concepts about temporal profile have been proposed since then, there has not been any generally accepted term or definition for this clinical setting. This might be related in part to the lack of an effective specific treatment. Indeed, although the use of heparin is commonly recommended in patients with neurological worsening associated with acute ischemic stroke, its effectiveness remains controversial.

Recently, neurological worsening has attracted attention again in relation to advances in the understanding of the mechanism of ischemic injury derived mainly from experimental studies. In a clinical setting, attempts to find predictors of neurological worsening showed controversial results, which suggest heterogeneous mechanisms of neurological worsening. The aim of this study was to investigate clinical determinants of neurological worsening and to delineate its predictors in unselected patients admitted with a first stroke.

**RESULTS**

We studied 3038 consecutive patients from the Lausanne Stroke Registry (1889 men and 1149 women; mean [±SD] age, 62.7±14.7 years; median, 65 years; range, 16-97 years), including 300 patients with brain hemorrhage, 770 patients with cardioembolic infarct, and 1968 patients with noncardioembolic brain infarct. Neurological worsening was observed in 892 pa-
PATIENTS AND METHODS

We studied 3038 consecutive patients with a first stroke (brain infarct or hemorrhage) who were admitted to our community-based, primary-care center and included prospectively in the Lausanne Stroke Registry.13 All patients were examined according to a standard protocol that included brain computed tomography (CT), carotid ultrasound, transcranial Doppler, 12-lead electrocardiography, 3-lead electrocardiographic monitoring (24-70 hours), and standard blood and urine tests, including venous hematocrit and fasting blood cholesterol level. Cerebral angiography, brain magnetic resonance imaging, 2-dimensional transthoracic and transesophageal echocardiography with and without a microbubble test, and 24-hour electrocardiography (Holter) monitoring were performed in selected patients.

Neurological worsening was determined to be present if worsening of the neurological condition, including consciousness level, was observed by investigators (trained stroke neurologists and nurses) at and after admission in our acute stroke care unit. In patients with reliable observations before admission, neurological worsening before admission was also considered. We tried to exclude from our study patients with possible early recurrent stroke and deterioration of the general condition by performing repeated clinical assessment and investigations including CT and magnetic resonance imaging. We decided not to use any established neurological scoring system to determine neurological worsening because many symptoms, such as sensory deficits or ataxia, are systematically omitted, and because this would have excluded patients with neurological worsening before admission. The time when neurological worsening was observed was also recorded. In general, intravenous continuous heparin was given for neurological worsening in patients with supposed thrombus propagation or with cardioembolism, if there was no contraindication. Oral aspirin (200 mg/d) was given systematically to patients with ischemic stroke but not under anticoagulation.

Stroke was classified into brain hemorrhage or infarction, on the basis of CT findings. The presumed causes of brain infarction included the following: (1) large-artery atherosclerosis (with ≥50% stenosis in the corresponding artery, or with <50% stenosis or plaques in the corresponding artery and in patients with 2 or more risk factors); (2) small-artery disease (infect with a lacunar syndrome [pure motor hemiparesis, pure sensory stroke, sensory motor stroke, and ataxic hemiparesis] and a normal CT scan or small [≤15 mm] infarct in deep or subcortical white matter on CT, with only hypertension or diabetes mellitus [or nothing] as risk factors); (3) cardioembolic sources (mitral or aortic valvular diseases including mitral valve prolapse, prosthetic valves, recent myocardial infarction, infective or noninfarctive endocarditis, nonischemic dilated cardiomyopathy, left ventricular ischemic dyskinesia, left ventricular thrombus, atrial myxoma, atrial fibrillation, sick sinus syndrome, and patent foramen ovale with or without atrial septal aneurysm, with presumed paradoxical embolism); and (4) other causes that were not compatible with large-artery atherosclerosis, small-artery disease, or cardioembolic sources, or that remained undetermined.13 Infarct topography was classified as follows: (1) superficial anterior circulation, (2) posterior circulation, and (3) deep white matter according to established template mapping.14-16

The following risk factors were considered: (1) hypertension (blood pressure of >160/90 mm Hg at least twice before the stroke); (2) diabetes mellitus (known fasting hyperglycemia before the stroke); (3) current or former cigarette smoking; (4) hypercholesterolemia (cholesterol concentration of >6.5 mmol/L [>251 mg/dL]); and (5) transient ischemic attacks (TIAs) that occurred in the same arterial territory before the index stroke.13

For evaluating functional disability after stroke, we used a 5-level classification: 1 for no disability; 2 for mild disability (return to all activities but with some difficulty); 3 for moderate disability (return to most main activities but with difficulty); 4 for severe disability (impossible to return to most activities); and 5 for death.17 Functional disability was evaluated at discharge.

The Wilcoxon rank sum test for continuous data and χ² for noncontinuous data were used as univariate analysis. Then, a logistic multiple regression model was used to test for independence of other factors. All of the factors, other than clinical prognosis, that were shown by univariate tests to be related to neurological worsening with a threshold significance of P<.05 were included in the logistic regression analysis. Statistical analysis was performed with the STATA 4.0 package.
ing. As for lesion topography, infarcts in the superficial anterior circulation were less frequent, while those in the posterior circulation were more frequent in the neurological worsening group \( (P < .001) \). Bilateral lesions were more frequently observed in the neurological worsening group \( (P < .001) \). Small-artery disease was significantly less frequent in the neurological worsening group. Patients in the neurological worsening group showed a significantly worse prognosis than those in the immediately stabilized group \( (P < .001) \).

Next, we compared the factors related to neurological worsening in the patients with large-artery atherosclerosis and those with small-artery disease, respectively. \textbf{Table 4} shows the results of the univariate analysis. Age greater than 64 years and TIA were significantly less frequent in the neurological worsening group than in the immediately stabilized group, but only in the patients with small-artery disease. Hypercholesterolemia was significantly more frequent in the neurological worsening group than in the immediately stabilized group in the patients with small-artery disease, but not in those with large-artery atherosclerosis. The significant difference of a more than 50% stenosis in the corresponding artery that was observed in the whole group was absent in both cause subgroups. In contrast, reduced level of consciousness and lesions in the posterior circulation and bilateral lesions were significantly more frequent in the neurological worsening group than in the immediately stabilized group. In those with small-artery disease, age greater than 64 years (as a negative factor), hypertension, lesion in the superficial anterior circulation showed the highest negative coefficient in the patients with small-artery disease. In the patients with large-artery atherosclerosis, age greater than 64 years (as a negative factor), bilateral lesion, hypertension, lesion in the superficial anterior circulation (as a negative factor), TIA (as a negative factor), and reduced level of consciousness were independent factors. In those with small-artery disease, age greater than 64 years (as a negative factor), hypercholesterolemia, lesion in the superficial anterior circulation showed a relatively high coefficient in the patients with large-artery atherosclerosis, while a lesion in the superficial anterior circulation showed the highest negative coefficient in the patients with small-artery disease. We tried to construct a score to predict progressive stroke, combining these independent factors. However, the predictive power of the score was limited (at most 63% for large-artery atherosclerosis and 58% for small-artery disease) (data not shown).

\textbf{COMMENT}

This is the first study, to our knowledge, that compares predictors of neurological worsening in the different cause subgroups of stroke. It showed heterogeneous contributors to neurological worsening in the patients with different causes of stroke. First, patients with brain infarct and cardiac embolism experienced a lower rate of neu-

\begin{table}
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\begin{tabular}{|l|c|c|}
\hline
\multicolumn{3}{|c|}{Table 1. Patients With Neurological Worsening} \\
\hline
& No. of Patients & No. (%) With Neurological Worsening \\
\hline
Brain hemorrhage & 300 & 114 (38.0) \\
Cardioembolic brain infarct & 770 & 116 (15.1) \\
Noncardioembolic brain infarct & 1968 & 662 (33.6) \\
\hline
\end{tabular}
\end{table}

\begin{table}
\centering
\begin{tabular}{|l|c|c|}
\hline
\multicolumn{3}{|c|}{Table 3. Clinical Findings, Topography, Cause, and Prognosis in Noncardioembolic Infarct*} \\
\hline
& NW (n = 662) & IS (n = 1306) \\
\hline
Reduced level of consciousness & 151 (22.8) & 171 (13.1) \( P < .001 \) \\
Motor disturbance & 486 (73.4) & 976 (74.7) \\
Hemianopia & 120 (18.1) & 220 (16.8) \\
Ischemic heart disease & 83 (12.5) & 164 (12.6) \( P < .001 \) \\
50% Ipsilateral stenosis & 239 (36.1) & 364 (27.9) \( P < .001 \) \\
>50% Stenosis in other arteries & 44 (6.6) & 94 (7.1) \\
\hline
\end{tabular}
\end{table}

*NW indicates patients with neurological worsening; IS, patients with immediately stabilized stroke; and TIA, transient ischemic attacks that occurred in the same arterial territory before the index attack.
neurological worsening among different causes of ischemic stroke may be related to heterogeneous mechanisms of neurological worsening, in which causative aspects rather than just the evolution of the ischemic process itself\(^9\) may play a role.

In the patients with noncardioembolic infarcts, we found fewer patients with TIAs and more patients with greater than 50% stenosis in the corresponding artery in the neurological worsening group than in the immediately stabilized group. In the literature, a strong relationship between TIAs and severe stenosis in the corresponding artery has been reported.\(^22\) Therefore, the dissociation observed in the present study may underscore other mechanisms than sequential emboli, although previous studies have never demonstrated a correlation between TIA and neurological worsening.\(^9,12\)

The arterial changes associated with neurological worsening are poorly known, although “thrombus propagation” is commonly assumed to play a role. Toni et al\(^12\) suggested that carotid siphon occlusion may be an independent factor of neurological worsening. Inino et al\(^13\) investigated sequential changes of angiographic findings in patients with neurological worsening, emphasizing progression of arterial stenosis or thrombus displacement. Recently, it was suggested that thrombus propagation might not be a common mechanism of neurological worsening, while insufficient blood supply caused by poor collateral circulation development might commonly contribute.\(^8,12\)

It is surprising that younger rather than older patients tended to show neurological worsening. Patients with neurological worsening were usually older in previous studies, although this was not statistically significant.\(^8,12\) Possible reasons for our findings may include the following: (1) older patients tended to be in a more severe state on admission, so that it was not possible to recognize neurological worsening (however, this cannot explain why a higher rate was found in the patients with small-artery disease, while they had the least severe deficits); (2) neurological symptoms in the older patients tended to progress with the deterioration of their general condition, so that it was not taken as real neurological worsening than did patients with noncardioembolic brain infarct. Second, in the patients with noncardioembolic brain infarct, neurological worsening was related to different risk factors in the different subtypes of stroke.

It is difficult to compare directly our findings to other studies, because the definition of neurological worsening is variable.\(^11,18\) We chose a clinical definition mainly based on repeated clinical observation by neurologists and trained nurses in our stroke emergency unit. Moreover, we also took into account reliable observations made before admission, because we think neurological worsening should be treated as one of the early clinical symptoms of stroke.\(^8,18\)

In this study, neurological worsening was observed at about the same rate in the patients with brain hemorrhage and those with noncardioembolic infarction, but much less in the patients with cardioembolic infarction. This result is in agreement with other observations in the literature.\(^19,21\) In the Harvard Cooperative Stroke Registry, for example, nonsudden onset was observed in 60% of 233 patients with large-artery thrombosis, 62% of 131 patients with lacunar stroke, and 21% of 215 patients with embolism,\(^8\) although “nonsudden onset” includes stepwise and smooth onsets as well as onsets with fluctuations, and the criteria for each type are not clear. This difference in the prevalence of neurological worsening among different causes of ischemic stroke may be related to heterogeneous mechanisms of neurological worsening, in which causative aspects rather than just the evolution of the ischemic process itself\(^9\) may play a role.

Table 4. Neurological Worsening in Large-Artery Atherosclerosis and Small-Artery Disease\(^*\)

<table>
<thead>
<tr>
<th></th>
<th>Large-Artery Atherosclerosis, No. (%)</th>
<th>Small-Artery Disease, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NW (n = 196)</td>
<td>IS (n = 195)</td>
<td>NW (n = 250)</td>
</tr>
<tr>
<td>Age &gt;64 y</td>
<td>100 (51.0)</td>
<td>147 (58.8)(\uparrow) 91 (65.1)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>116 (59.2)</td>
<td>209 (83.8)(\uparrow) 426 (70.9)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>36 (18.4)</td>
<td>75 (30.0)(\uparrow) 139 (23.1)</td>
</tr>
<tr>
<td>Smoking</td>
<td>112 (57.1)</td>
<td>106 (42.4)(\uparrow) 266 (44.3)</td>
</tr>
<tr>
<td>TIA</td>
<td>44 (22.4)</td>
<td>22 (8.8)(\uparrow) 91 (15.1)</td>
</tr>
<tr>
<td>&gt;50% Ipsilateral stenosis</td>
<td>169 (86.2)</td>
<td>4 (1.6)(\uparrow) 5 (0.8)</td>
</tr>
<tr>
<td>Reduced level of consciousness</td>
<td>54 (27.6)§</td>
<td>37 (14.8)(\uparrow) 51 (8.5)</td>
</tr>
<tr>
<td>Superficial anterior circulation</td>
<td>96 (49.0)§</td>
<td>28 (11.2)(\uparrow) 142 (23.6)</td>
</tr>
<tr>
<td>Posterior circulation</td>
<td>57 (29.1)§</td>
<td>77 (30.8)(\uparrow) 137 (22.8)</td>
</tr>
<tr>
<td>Bilateral lesion</td>
<td>31 (15.8)</td>
<td>42 (16.8)(\uparrow) 73 (12.1)</td>
</tr>
<tr>
<td>Functional disability &gt;3</td>
<td>53 (27.0)§</td>
<td>26 (10.4)(\uparrow) 28 (4.7)</td>
</tr>
<tr>
<td>Functional disability ≤3</td>
<td>77 (39.3)§</td>
<td>129 (51.6)(\uparrow) 410 (68.2)</td>
</tr>
</tbody>
</table>

* NW indicates patients with neurological worsening; IS, patients with immediately stabilized stroke; TIA, transient ischemic attacks that occurred in the same arterial territory before the index attack; and >50% ipsilateral stenosis, more than 50% stenosis in the corresponding intracranial or extracranial artery.

† Significantly different compared with IS in small-artery disease (\(P<.05\)).

‡ Significantly different compared with IS in small-artery disease (\(P<.01\)).

§ Significantly different compared with IS in large-artery atherosclerosis (\(P<.01\)).

# Significantly different compared with IS in large-artery atherosclerosis (\(P<.001\)).

Table 5. Logistic Regression Model in Large-Artery Atherosclerosis and in Small-Artery Disease\(^*\)

<table>
<thead>
<tr>
<th></th>
<th>Coefficient</th>
<th>SE</th>
<th>95% CI</th>
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</thead>
<tbody>
<tr>
<td>Large-artery atherosclerosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Posterior circulation</td>
<td>0.9167</td>
<td>0.2248</td>
<td>0.4761 to 1.357</td>
</tr>
<tr>
<td>Reduced level of consciousness</td>
<td>0.5303</td>
<td>0.2198</td>
<td>0.0996 to 0.9612</td>
</tr>
<tr>
<td>Small-artery disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age &gt;64 y</td>
<td>-0.3311</td>
<td>0.1593</td>
<td>-0.6433 to -0.01900</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.5820</td>
<td>0.2004</td>
<td>1.0920 to 0.9749</td>
</tr>
<tr>
<td>Superficial anterior circulation</td>
<td>-0.8927</td>
<td>0.2347</td>
<td>-1.3530 to -0.4327</td>
</tr>
<tr>
<td>TIA</td>
<td>-0.6226</td>
<td>0.2556</td>
<td>-1.1240 to -0.01216</td>
</tr>
<tr>
<td>Reduced level of consciousness</td>
<td>0.8286</td>
<td>0.2434</td>
<td>0.3515 to 1.306</td>
</tr>
</tbody>
</table>

\(^*\) CI indicates confidence interval; TIA, transient ischemic attacks that occurred in the same arterial territory before the index attack.
cal worsening (however, we tried to exclude the patients who showed neurological worsening with deterioration of general condition, such as fever or cardiac failure); and (3) older patients tended to live alone and may have come to the hospital later after onset, so that the information gathered before admission was often insufficient, although we have no precise data supporting this hypothesis.

In this study, lesions in the anterior circulation were significantly less frequent and lesions in the posterior circulation were significantly more frequent in the patients with neurological worsening than in those without neurological worsening. Jones et al. reported that a progressive or unstable clinical course was observed twice as often in patients with posterior circulation infarction as compared with those with anterior circulation infarction. However, they included patients with potential cardiac sources of embolism that were less common in the patients with posterior circulation infarction. In another study, there was no difference in lesion topography between the patients with and without neurological worsening, while other authors found that cortical involvement was more frequent in the patients with neurological worsening than in those without neurological worsening. However, this may be caused by a lower frequency of lacunar infarction in the patients with neurological worsening. We found that bilateral lesions were observed more frequently in the patients with neurological worsening, and infarct volume was reported to be larger in the patients with neurological worsening than in those without neurological worsening; however, there is not enough information in the literature on lesion topography associated with neurological worsening to compare with our findings.

When the patients with large-artery atherosclerosis and those with small-artery disease were considered separately, we found a remarkable difference in the factors associated with neurological worsening. The logistic regression analysis chose only lesions in the posterior circulation and reduced level of consciousness as independent predictors in patients with large-artery atherosclerosis, while it selected age less than 65 years, hypertension, lesion in the superficial anterior circulation (as a negative factor), TIA (also as a negative factor), and reduced level of consciousness in the patients with small-artery disease. It is interesting that completely different factors were associated with neurological worsening in the different cause subgroups of stroke. This may be a reason for the controversial results of many studies trying to delineate predictive factors for neurological worsening.

The high incidence of reduced level of consciousness in patients with small-artery disease may be rather surprising. In the first 1000 patients in the Lausanne Stroke Registry, only 3% of the patients with hypertensive arteriopathy, which is the main cause of small-artery disease, showed decreased consciousness level at admission. However, only 13% of the patients with atherosclerosis showed decreased consciousness in the same series, while the incidence of reduced level of consciousness was 21% in the patients with large-artery disease. Because the basic system of the Lausanne Stroke Registry has not been changed from the beginning, a reason for the higher rate of reduced level of consciousness may be that stroke patients in the local area may be carried into our stroke unit more rapidly than before.

Lesions of small-artery disease in superficial artery circulation may include lacunar infarcts in the centrum ovale, ie, subcortical infarction in the superficial territory of the middle cerebral artery, as well as some previous cortical stroke, which should be asymptomatic. The results in the present study dissociate the finding we previously reported that small infarcts in the centrum ovale were frequently associated with nonsudden onset.

In the patients with small-artery disease, TIA was negatively related to neurological worsening. According to prospective studies of lacunar infarction, TIA is reported in about 20% of patients with lacunar infarction. However, its pathogenesis has not been fully discussed. Donnan et al. drew attention to a specific feature of lacunar syndrome with clustered TIAs called the “capsular warning syndrome,” which might correspond to a different situation than in progressing lacunar stroke.

Anticoagulation with heparin has often been recommended as treatment of neurological worsening, however, its effectiveness remains controversial. Haley et al. observed that further neurological worsening under anticoagulation was greater in patients with anterior circulation vs those with posterior circulation or lacunar infarction. This may suggest a differential benefit of heparin among patients with various causes of stroke. In any case, clinical trials are needed to find a better treatment for neurological worsening in the different subgroups of stroke.

Although we tried to predict neurological worsening by means of clinical factors chosen by a logistic regression model, the predictive power was limited even in selected subgroups of stroke, suggesting that clinical findings alone may be insufficient to predict neurological worsening. The combination of clinical analysis and differentiation of the underlying stroke cause, together with advanced investigations of brain function such as diffusion/perfusion magnetic resonance imaging in the acute phase, may allow further understanding of the various pathophysiological mechanisms underlying neurological worsening, which in turn would allow specific clinical trials in patients with neurological worsening to be developed.

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REFERENCES


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