Lacunar Stroke Is the Major Cause of Progressive Motor Deficits

Wolfgang Steinke, MD; Stephan C. Ley

Background and Purpose—Severe motor deficits are the predominant cause of long-term disability in stroke patients. In particular, progressive hemiparesis in the initial stage after stroke onset is frequently devastating. Therefore, we attempted to define the population at risk with respect to the presumed pathogenesis.

Methods—Among 941 stroke patients hospitalized during a 3-year period, 92 patients (41 men, 51 women; mean age, 68 years) had a severe motor deficit (<25 of 42 points on the 7 motor items of the European Stroke Scale) resulting from brain infarcts. Risk factors, neurological examinations, comprehensive diagnostic tests, and therapy were documented. The study population was separated into patients with (group A) and without (group B) progressive motor deficits. Progression was defined as a further decrease of at least 5 points on the initial European Stroke Scale motor score during the first 5 days after stroke onset.

Results—Of the 92 patients, 23.9% had significant worsening of motor function with a decrease in the mean European Stroke Scale motor score from 20.3 to 12.9 points (P<0.01). Infarcts in group A patients were subcortical in 59.1%, whereas most infarcts were cortical in group B (61.4%, P<0.05). Progressive hemiparesis was also significantly associated with lacunar stroke (group A: 59.1%; group B, 24.3%; P<0.01). With regard to risk factors, diagnostic studies, and neuroimaging, small-vessel disease was the predominant presumed cause of stroke in group A (63.6%, P<0.01), whereas infarcts in group B patients were frequently caused by embolism from cardiac or undetermined sources (61.4%, P<0.01). Prevalence of high-grade carotid stenosis was not significantly different between groups A and B; however, subtotal stenoses and complete internal carotid artery occlusions were found only among patients without progressive motor deficits.

Conclusions—Lacunar stroke caused by small-vessel disease is the major cause of progressive motor deficits, probably because of stepwise occlusion of the branches of small penetrating arteries. (Stroke. 2002;33:1510-1516.)

Key Words: lacunar infarction • motor activity • prognosis • stroke

Factors associated with neurological deterioration in acute stroke have been investigated in some recent studies.1–4 In a review of 10 selected studies including 3022 patients, Röden-Jüllig5 reported frequencies of deteriorating stroke of between 12% and 42% when all signs were considered, whereas strictly focal progressing deficits occurred in 12% to 36% of the patients.6–8 However, interpretation and comparison of the results of available studies remain difficult because of different definitions of progression that commonly include decreasing consciousness and nonneurological causes such as decompensating cardiac insufficiency or infectious diseases.

While stroke subtypes were not differentiated in these studies, Tei et al9 used the clinical stroke categories of the Oxfordshire Community Stroke Project to investigate early deterioration, which was defined as a decrease of at least 1 point on the Canadian Stroke Scale or the Rankin Scale. Deterioration was found in 25.7% of 350 patients with the highest rate (41.9%) of total anterior infarcts, followed by lacunar infarcts (26.2%); however, mechanisms of progression in the latter group could not be determined from the available data. In a study from the Lausanne Stroke Registry,10 neurological worsening was analyzed for different pathogenetic types of stroke, including small-artery disease, but data for motor hemiparesis were not reported. This topic was addressed in a study of progressive motor deficits in lacunar stroke11 that demonstrated that diabetes mellitus and severity of the initial motor deficits were related to progression. Because persisting severe motor dysfunction is a predominant cause of long-term disability in stroke victims12 and because data on progressive hemiparesis during the initial stage after stroke are scarce, we attempted to further define this population at risk with respect to the presumed underlying pathogenesis.

Patients and Methods
Among 941 stroke patients hospitalized during a 3-year period (1997 to 1999), patients were consecutively included in the study if they had a severe deficit of motor function on admission resulting from ischemic stroke with an onset of symptoms in the preceding 24 hours. Ninety-two patients (41 men, 51 women; mean age, 68 years;
range, 28 to 95 years) fulfilled the inclusion criterion of <25 of 42 possible points assessed by use of the 7 motor items in the European Stroke Scale (ESS). The pure motor items of the ESS consist of (1) maintenance of outstretched arm position, (2) raising of the arm, (3) extension of the wrist, (4) grip strength, (5) maintenance of outstretched leg position, (6) leg flexion, and (7) dorsiflexion of the foot.

Patients with primarily hemorrhagic stroke (n=208), initial hemiplegia (n=49; ESS motor score <8 points), or coma (n=44) or patients with minor motor or predominantly other deficits (n=582) were not included in the study. Patients with ipsilateral residual hemiparesis from prior stroke (n=65) were also excluded. For the study population, epidemiological data, neurological examinations, comprehensive diagnostic studies, and therapeutic measures were systematically documented in a data bank consisting of a total of 381 items. According to the course of stroke, the study population was divided into 2 groups: group A, patients with progressive motor deficits, and group B, those without progressive motor deficits. Progression was defined as further decrease of at least 5 points on the initial ESS motor score at any point during the first 5 days after stroke onset. In addition, functional impairment was assessed with the Barthel score on admission and at discharge from hospital.

To investigate potential predictors of progressive motor deficits, the prevalence of vascular risk factors was compared between groups A and B. CT was performed on admission in all patients. CT scans were repeated 3 to 5 days after onset, and additional MRI studies (n=32) were performed according to clinical decision in the individual case or if mandatory to identify the acute stroke lesion. Neuroimaging studies were reviewed by an experienced neuroradiologist and an author (W.S.) to determine by consensus the anatomic location and topographic extension of the infarct considered to be responsible for the acute neurological deficit. In addition, results of neuroimaging studies were used, among other criteria, to separate stroke subtypes according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification. Furthermore, areas of infarction in patients with progressive strokes were transferred to the anatomic-vascular maps of Tatu et al. For the pathogenetic categorization of stroke subtype, results of neurovascular tests using extracranial (n=92) and transcranial (n=88) Doppler sonography, extracranial color-coded Duplex sonography (n=92), and magnetic resonance or intraarterial angiography (n=20), as well as the findings of cardiac studies such as a 12-lead ECG in all patients, 24-hour Holter monitoring (n=67), and echocardiography (n=62), were compared between groups A and B. Classification of abnormal sonographic and angiographic findings was performed according to previously described methods. Treatment in the acute stage consisted of activated partial thromboplastin time–adjusted full-dose intravenous heparin in 72.7% of group A and 47.1% of group B patients. Two patients in group B received intravenous thrombolysis with recombinant tissue-type plasminogen activator. Ten patients in group A (54.5%) and 38 in group B (54.3%) were treated with platelet inhibitors (aspirin 100 mg, clopidogrel 75 mg).

Statistical analysis was performed to identify risk factors associated with progressive motor deficits and pathogenetic differences between groups A and B. Student’s t test was used for continuous data, and the χ² or Fisher’s exact test was used for noncontinuous data.

Results

Comparison of epidemiological data and vascular risk factors did not reveal significant differences between groups A and B (Table 1), although there was a tendency for a higher prevalence of peripheral arterial disease and atrial fibrillation in group B patients. Laboratory parameters on admission demonstrated abnormal average values for blood glucose, cholesterol, triglycerides, high-density lipoprotein, and C-reactive protein; however, differences were not present between groups (Table 2). On admission, all patients in group A were fully alert, whereas in group B, a third of the patients (37.1%) had a reduced level of consciousness. The initial average modified ESS motor score in group A (20.3±2.9) was higher than in group B (15.9±7.3, P<0.01), whereas the deficits in motor function increased in group A (12.9±5.4) and were worse than in group B (23.5±6.9, P<0.01) at hospital discharge. Conversely, motor hemiparesis of group B patients improved (Figure 1). Similarly, the total average ESS scores on admission were 71.2±15.3 and 54.2±26.5 (groups A and B, respectively; P<0.01), whereas at discharge, group A patients had a worse score (59.7±23.4) than patients in group B (71.3±18.3); however, this difference was not significant. Functional disability as assessed by Barthel score increased in group A from an average of 15.0±4.6 to 10.5±5.4 (P<0.01), whereas in group B, the initial Barthel score (10.2±6.9) slightly improved at discharge (11.3±6.7; Figure 2). In-hospital mortality was 0% in group A and 5.7% in group B, resulting from brainstem infarction (n=2), brainstem herniation (n=1), and pneumonia (n=1).

Comprehensive neurovascular studies by means of extracranial and transcranial Doppler duplex sonography and angiography in selected cases demonstrated a high prevalence of atherosclerotic disease of the large brain-supplying arteries in both groups (Table 3). Less severe nonstenotic extracranial atherosclerosis and low-grade internal carotid artery (ICA) stenosis were found more frequently in group A (54.5%) than in group B (18.6%, P<0.05), whereas the frequency of high-grade stenosis (81% to 90%) was not different. Subtotal ICA stenosis and complete occlusion were diagnosed in group B but were absent in group A. In 77% of the 22 patients with high-grade ICA stenosis or subtotal or total occlusion, infarctions occurred on the side of the severe stenosis or occlusion. Most (68.2%) had large cortical territorial infarctions. Abnormal findings in the extracranial posterior circulation in a few patients in both groups consisted of vertebral artery stenosis and the subclavian- steals phenomenon (Table 3). Cardiac evaluation revealed permanent or intermittent atrial fibrillation less frequently among group A patients (9.1%) than group B patients (25.7%, P=0.064). The preva-
lence of echocardiographic abnormalities, which may indicate potential sources of embolism, was not significantly different between groups A and B (Table 4).

The anatomic topography of the acute brain infarction as displayed by CT and MRI and classified according to the predominant cortical versus subcortical (white matter, basal ganglia, thalamus, internal capsule) location and extension revealed subcortical stroke in 59.1% of group A and 32.9% of group B patients ($P < 0.016$). With the use of the arterial territory map by Tatu et al, $^{15}$ further classification of the type of infarction was performed, which demonstrated lacunar strokes in 59.1% in group A compared with 24.3% in group B ($P < 0.01$). Conversely, cortical territorial infarcts occurred more frequently in group B (61.4%) than in group A (36.4%, $P < 0.01$; Figure 3).

With regard to the findings of the neuroimaging studies, presence of vascular risk factors, and results of vascular and cardiac investigations, stroke pathogenesis was determined for the individual patients. According to this pathogenetic classification, 63.6% of group A patients but only 21.4% of group B patients presumably suffered strokes from small-vessel disease ($P < 0.01$). Embolic brain infarction from arterial, cardiac, or undetermined source occurred in 27.3% of group A and 61.4% of group B patients ($P < 0.01$), whereas low-flow infarcts in the cortical or subcortical junctional zone were found only in group B (2.9%). If the areas of brain infarction in group A patients are superimposed, it becomes obvious that the pyramidal tract is predominantly affected at different sites in its course; in particular, the paraventricular medial corona radiata, the posterior part of the internal capsule, and the ventral pontomesencephalic brainstem are involved (Figure 4).

**Discussion**

Strokes with progressive severe motor deficits during the first days after symptom onset were significantly associated with lacunar infarcts in the present study; conversely, deteriorating hemiparesis was relatively infrequent in cortical infarctions. To provide an adequate interpretation of these results, our definition of progression has to be considered. We did not regard as progression a decreasing level of consciousness or deterioration of the patient’s general condition that is frequently due to infection or the development of significant cardiac or respiratory insufficiency; we restricted the definition to further worsening of a relevant initial hemiparesis, one of the most important causes of persisting disability in stroke patients, also in the absence of other neurological deficits. $^{11,12}$ However, because patients with minimal weakness were not included in the study, a few of these patients who later deteriorated may have been missed for analysis.

**Table 2. Laboratory Parameters on Admission in Groups A and B**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group A (n=22)</th>
<th>Group B (n=70)</th>
<th>$P$</th>
<th>Normal range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin, g/dL</td>
<td>14.5±1.8</td>
<td>14.3±1.2</td>
<td>0.196</td>
<td>14–16</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>42.5±5.5</td>
<td>42.0±2.9</td>
<td>0.053</td>
<td>40–52</td>
</tr>
<tr>
<td>Leukocytes, $\mu$L</td>
<td>9.991±3.585</td>
<td>8.742±3.159</td>
<td>0.455</td>
<td>4.000–9.000</td>
</tr>
<tr>
<td>Thrombocytes, $\mu$L</td>
<td>247.217±83.550</td>
<td>210.619±59.068</td>
<td>0.155</td>
<td>177–406.000</td>
</tr>
<tr>
<td>Serum glucose, mg/dL</td>
<td>149.1±65.2</td>
<td>155.2±80.4</td>
<td>0.350</td>
<td>70–110</td>
</tr>
<tr>
<td>Cholesterol, mg/dL</td>
<td>232.7±55.3</td>
<td>242.0±53.9</td>
<td>0.906</td>
<td>&lt;200</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>151.1±119.0</td>
<td>159.1±88.3</td>
<td>0.772</td>
<td>&lt;150</td>
</tr>
<tr>
<td>HDL, mg/dL</td>
<td>49.8±16.1</td>
<td>48.8±18.2</td>
<td>0.588</td>
<td>&gt;40</td>
</tr>
<tr>
<td>LDL, mg/dL</td>
<td>150.1±50.4</td>
<td>164.6±45.4</td>
<td>0.644</td>
<td>&lt;190</td>
</tr>
<tr>
<td>Fibrinogen, mg/dL</td>
<td>335.5±159.5</td>
<td>164.6±128.2</td>
<td>0.324</td>
<td>150–350</td>
</tr>
<tr>
<td>Thromboplastin time, %</td>
<td>102±5.15</td>
<td>108.3±11.9</td>
<td>0.516</td>
<td>75–100</td>
</tr>
<tr>
<td>CRP, mg/L</td>
<td>31.8±52.9</td>
<td>50.7±164.8</td>
<td>0.107</td>
<td>&lt;5</td>
</tr>
</tbody>
</table>

Values are average±SD. HDL indicates high-density lipoprotein; LDL, low-density lipoprotein; and CRP, C-reactive protein.
capsule or corona radiata, Nakamura et al.\textsuperscript{11} found that patients with acute supratentorial lacunes in the internal motor deficits in lacunes was not specifically addressed. In 92 had a fluctuating or progressing onset; however, worsening of extracranial and intracranial anterior and posterior circulation

In the Harvard Cooperative Stroke Registry,\textsuperscript{18} 62% of 131 patients with lacunar infarction infrequently been investigated. In the Harvard Cooperative Acute Stroke Study (ECASS I),\textsuperscript{3} of the early clinical course of 83 patients with small, deep infarctions, whereas the prevalence of risk factors such as hypertension or the frequency of a probable cardiac source of embolism were not different in patients with infarcts with and without progressive deficits. However, another small series examining the clinical and epidemiological features of progressive lacunar infarction demonstrated that older age was significantly associated with progression.\textsuperscript{19} In addition, those researchers observed worsening of the neurological deficit only in patients with pure motor hemiparesis. In contrast, neurological deterioration, including a decreased level of consciousness, in lacunar strokes of the Lausanne Stroke Registry\textsuperscript{10} was independently related to age $<64$ years and hypertension in a multiple regression model. Surprisingly, a reduced level of consciousness was also an independent factor for progression in this study, but motor deficits were not analyzed separately.

The frequency of vascular diseases and prevalence of risk factors such as diabetes mellitus, arterial hypertension, cigarette smoking, hypercholesterolemia, previous myocardial, or cerebral infarction indicate the high risk of cerebrovascular events in our study population; however, epidemiological characteristics did not significantly differ between patients with (group A) and without (group B) progressing motor deficits. Probably because of the relatively small number of patients in each group, the more frequent occurrence of atrial fibrillation and peripheral artery disease in group B did not reach significance. Nevertheless, among other pathological results of cardiac studies, the presence of atrial fibrillation in 25.7% of group B patients supports the assumption of more frequent embolic strokes in these patients without progressive motor deficits. Among laboratory results, increased mean values of C-reactive protein were remarkable in both groups. This may be regarded as an indicator of the significance of previous infections and elevated C-reactive protein for stroke occurrence,\textsuperscript{2,11} whereas an association with further worsen-

TABLE 3. Results of Sonographic and Angiographic Studies in the Extracranial and Intracranial Anterior and Posterior Circulation

<table>
<thead>
<tr>
<th></th>
<th>Group A (n=22)</th>
<th>Group B (n=70)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extracranial</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonstenotic carotid</td>
<td>31.8</td>
<td>12.9</td>
</tr>
<tr>
<td>atherosclerosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low-grade (40%-60%) ICA stenosis</td>
<td>22.7</td>
<td>5.7</td>
</tr>
<tr>
<td>Moderate (61%-80%) ICA stenosis</td>
<td>4.5</td>
<td>0</td>
</tr>
<tr>
<td>High-grade (81%-90%) ICA stenosis</td>
<td>9.1</td>
<td>8.6</td>
</tr>
<tr>
<td>Subtotal ICA stenosis</td>
<td>0</td>
<td>5.7</td>
</tr>
<tr>
<td>Complete ICA occlusion</td>
<td>0</td>
<td>14.3</td>
</tr>
<tr>
<td>Vertebral artery stenosis</td>
<td>4.5</td>
<td>1.4</td>
</tr>
<tr>
<td>Subclavian-steal phenomenon</td>
<td>9.1</td>
<td>7.1</td>
</tr>
<tr>
<td>Intracranial</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICA siphon stenosis</td>
<td>0</td>
<td>2.9</td>
</tr>
<tr>
<td>ICA occlusion</td>
<td>13.6</td>
<td>11.4</td>
</tr>
<tr>
<td>Middle cerebral artery stenosis</td>
<td>9.1</td>
<td>7.1</td>
</tr>
<tr>
<td>Middle cerebral artery occlusion</td>
<td>0</td>
<td>5.7</td>
</tr>
<tr>
<td>Vertebral artery stenosis (V4)</td>
<td>4.4</td>
<td>2.9</td>
</tr>
<tr>
<td>Basilar artery stenosis</td>
<td>9.1</td>
<td>0</td>
</tr>
<tr>
<td>Ectatic basilar artery</td>
<td>0</td>
<td>2.9</td>
</tr>
</tbody>
</table>

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure2}
\caption{Comparison of mean Barthel scores of patients with (group A) and without (group B) progressive motor deficits at admission ($P<0.01$) and discharge ($P=\text{NS}$).}
\end{figure}
ing of the hemiparesis was not evident in our study population or in previous studies.

Extracranial and intracranial vascular disease was present in both patient groups; however, there were some differences in the degree of atherosclerosis in the carotid system. Nonstenotic plaques and low-grade stenoses were more frequent in group A patients who had lacunar strokes (59%). This corresponds with a recent analysis of data from the North American Symptomatic Carotid Endarterectomy Trial (NASCET),22 examining the relationship between carotid stenosis and lacunar infarction. Among 493 patients with probable or possible lacunar stroke, mild (<50%) ICA stenoses were more frequent, suggesting that less significant carotid atherosclerosis commonly is an indicator of cerebrovascular disease rather than a cause of lacunar infarction. Although the prevalence of high-grade (81% to 90%) ICA stenosis was the same in both groups, subtotal ICA stenosis and complete occlusion were found only in group B patients who presented with cortical infarctions (61%). In addition, more than two thirds of the patients in both groups with severe carotid obstructions had cortical infarctions. Using diffusion-weighted MRI to study different patterns of cerebral infarction in relation to ipsilateral carotid disease, Szabo et al23 found a significant association between territorial infarcts and ICA occlusion; however, diffusion-weighted MRI demonstrated small ischemic lesions in the internal hemodynamic risk zone in 51.6% of patients with high-grade stenosis and in 50% of patients with subtotal stenosis.

With regard to the patterns of infarction and the results of comprehensive diagnostic examinations, progression of a motor hemiparesis was significantly related to lacunar infarction and small-vessel disease, respectively, in the present study, whereas stable or improving motor deficits were more frequently found in cortical infarctions from embolic cause. Correspondingly, patients with cardioembolic infarcts had a stabilized course of stroke more frequently than patients with noncardioembolic infarcts in a recent large study.10 However, in the present study, worsening of the paresis was also seen in some patients with large lenticulostriate and cortical infarctions, whereas a number of patients with lacunar stroke presented with a mild hemiparesis and good recovery. Therefore, the pathogenetic mechanisms of progressive motor deficits in lacunar and nonlacunar infarcts have to be considered in greater detail.

Among the arteriopathies of small penetrating vessels that may lead to lacunar infarction, microatheroma is probably the most common and was found in 6 of 11 capsular infarcts in a pathological study, whereas lipohyalinosis and fibrinoid necrosis are less frequent, and embolism from large-vessel disease may also occur rarely.24–27 Lacunar infarctions may produce different patterns of motor hemiparesis if the pyramidal tract of the corona radiata, posterior limb of the internal capsule, or brainstem is involved28,29; however, mechanisms of progressive motor deficits are less clear. Terai et al30 reported a patient in whom worsening of a motor hemiparesis was associated with enlargement of the lacunar corona radiata infarction on diffusion-weighted MRI. Because of the absence of collateral vessels, the infarct usually extends from the site of occlusion through the territory of the affected penetrating artery29; however, the size of the ischemic area is variable, depending on the vessel caliber and extent of ramifications.31,32 Progression of motor hemiparesis may thus be caused by either stepwise occlusion of the proximal segment of a perforating artery or distal-to-proximal clot propagation with subsequent occlusion of small branches, leading to enlargement of the lacunar infarct and progressive destruction of axons of the pyramidal tract.

In a recent article, Castillo33 reviewed different biochemical and hemodynamic pathophysiological mechanisms of deteriorating stroke. Reduction in blood flow below a particular threshold for a sufficient period of time leads to cerebral ischemia, initiating a cascade of chemical reactions, such as release of glutamate and glycine. Intracellular edema may result, followed by vasogenic brain edema and progressive deterioration in many patients with large cortical infarcts. However, there are scarce clinical data on the pathogenesis of
worsening of the motor deficit developed. Unfortunately, in no patient was further progression was prevented or motor deficits improved with the initiation of full-dose heparin. However, because this was an observational study, conclusions concerning the use of heparin in the management of progressive hemiparesis are of limited value. Because most experimental models focus on the pathophysiology of cortical ischemic lesions, identification of the mechanisms of progressive motor deficits in lacunar infarction is mandatory as the basis for the development of an effective therapy. However, the use of modern neuroimaging techniques in future clinical studies will probably at least enhance our understanding of the dynamic nature of this distinct type of stroke.

References


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Stroke. 2002;33:1510-1516
doi: 10.1161/01.STR.000016326.78014.FE
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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