Introduction

Clinical deterioration of patients with acute ischemic stroke is a serious complication and one frequently associated with increased rates of mortality and morbidity. The occurrence of deteriorating stroke varies from 10 to 50% among various published studies [1–8]. The potential reasons for such wide differences may be associated with differences in terminology and in the concept of what is progressive stroke. The terms ‘stroke-in-evolution’, ‘progressive stroke’, ‘worsening stroke’ and ‘deteriorating stroke’ are used interchangeably regardless of whether the deterioration is caused by extension of the infarction or various other reasons [9]. The terms ‘stroke-in-evolution’ or progressive stroke’ are used when the stroke progresses in a stepwise manner or smoothly over several hours. The term ‘deteriorating stroke’ was coined to include not only ‘stroke-in-evolution’ but also other strokes that deteriorate as a result of either cerebral or systemic (somatic) causes during the 1st week [10]. ‘Deteriorating stroke’ is also identified with any neurological worsening, whereas ‘progressive stroke’ is used in those conditions in which neurological worsening parallels the progression of ischemia [11].

Several studies have been performed to ascertain whether cerebral or systemic causes are the major determinants of stroke deterioration, but they have yielded controversial
results [2–5, 7, 8, 12, 13]. The difficulty in establishing ac-
cepted predictors was explained by the heterogeneous na-
ture of the mechanisms involved in neurological deteriora-
tion [8, 10]. Nevertheless, narrowing down the origins of
the decline in the patients’ condition following a stroke
would serve to enhance their management and possibly
provide some indication of their outcome.

The aim of our current study was to identify the in-
farct-inherent mechanisms and systemic causes of clini-
cal worsening following first-ever ischemic stroke (FIS)
and to delineate which factors cause early or late deterio-
ratio, thereby contributing more clinical data to help
resolve these issues.

Patients and Methods

This prospective study included all consecutive patients admit-
ted with acute FIS to Tel Aviv Sourasky Medical Center from Oc-
tober 1997 through October 1998. The patient’s neurological con-
dition was assessed by neurologists of the stroke team who used the
Unified Neurological Stroke Scale (UNSS) [14]. These evaluations
took place immediately after admission, at days 1, 2 and 3 during
hospitalization, and before discharge. Stroke-in-evolution was di-
agnosed in those patients who experienced worsening of their neu-
rological condition as indicated by a decrease of ≥ 4 points from
their previous UNSS score within the given time frame. Routine
clinical and laboratory characteristics were recorded in the emer-
gency room (ER) and are listed in table 1. Changes in the patients’
general condition were assessed daily throughout hospitalization
by repeated clinical evaluations, including the monitoring of blood
pressure. Computerized tomography (CT) of the brain was per-
formed in 97% of all FIS patients during hospitalization and in
100% of the patients who had deteriorating stroke. All CT scans
were evaluated by an independent team of neuroradiologists, who
were blinded to the aim of the study. Early deterioration was de-
finite as worsening of the patient’s condition occurring ≤ 72 h from
stroke onset and late deterioration as signs of decline appearing
≥ 72 h from stroke onset.

Statistics

All demographic, clinical and laboratory parameters and initial
median UNSS scores were compared between patients whose con-
ditions deteriorated and patients whose conditions did not. Statistical
analysis was performed in two stages. The first stage was a
univariate analysis comparing all of the above-mentioned charac-
teristics. The odds ratio (OR) with 95% confidence intervals (CI)
was used to compare qualitative factors, and the Mann-Whitney U
test compared quantitative factors between groups. The second
stage was a multivariate analysis with a backward logistic regression
procedure including only the significant variables of the univariate
analysis.

Results

During the study period, 667 patients with acute stroke
were hospitalized in Tel Aviv Sourasky Medical Center. Patients with transient ischemic attacks (n = 113), recur-
rent ischemic stroke (n = 66) and intracerebral hemorrhage (n = 46) were excluded. The remaining 442 con-
secutive patients who were admitted to the hospital with
FIS were evaluated in the ER and they comprise the pres-
ent study cohort. There were 372 patients with anterior
and 70 patients with posterior circulation stroke. Of these
442 patients, 71 (16.1%) were determined as having
stroke-in-evolution. There were 18 (13%) patients with
stroke in the posterior circulation in the group of patients
with deteriorating stroke. Most of patients with stroke-in-
evolution (67/71, 94.4%) had early deterioration. All the
patients who had stroke-in-evolution underwent a repeat-
ed CT scan. The causes were cerebral in most patients
with stroke-in-evolution (57/71, 80.3%). Enlargement of
a previous cortical lesion with new neurological signs was
found in 32 (56.1%) of these patients, new cortical strokes
in 5 (8.8%), new lacunar strokes in 4 (7.0%), symptomatic hemorrhagic transformation in 4 (7.0%), and new
hemorrhagic stroke in 3 (5.3%). Malignant edema was
found as a result of malignant middle cerebral artery in-
farct in 3 patients with deteriorating stroke. The cause of
neurological worsening could not be determined by the
repeated CT scans in 9 cases of deteriorating stroke
(15.8%). Systemic causes of stroke worsening (e.g., acute
myocardial infarction, pneumonia, urinary tract infec-
tion, deep vein thrombosis, sepsis, gastrointestinal bleed-
ing) were found in 14 (19.7%) of the early deteriorated

Table 1. Variables recorded in the emer-
gency room

<table>
<thead>
<tr>
<th>Variable</th>
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</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>Creatine phosphokinase</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td></td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td></td>
</tr>
<tr>
<td>Body temperature</td>
<td></td>
</tr>
<tr>
<td>Hematocrit</td>
<td></td>
</tr>
<tr>
<td>Hemoglobin</td>
<td></td>
</tr>
<tr>
<td>White blood cell count</td>
<td></td>
</tr>
<tr>
<td>Platelet count</td>
<td></td>
</tr>
<tr>
<td>Blood glucose</td>
<td></td>
</tr>
<tr>
<td>Vascular risk factors1</td>
<td></td>
</tr>
<tr>
<td>1 Arterial hypertension, diabetes mellitus, smoking, myocardial infarction, ischemic heart disease, atrial fibrillation, congestive heart failure, hyperlipidemia.</td>
<td></td>
</tr>
</tbody>
</table>

Neurological versus Systemic Decline in Evolving Stroke
patients. The causes of the worsening condition in the all FIS patients with late deterioration were identified as being systemic.

The first stage of statistical analysis (univariate analysis) demonstrated that most of the demographic, clinical and laboratory characteristics recorded in the ER were comparable among deteriorated and nondeteriorated FIS patients (tables 2, 3). The initial mean UNSS score that had been measured in the ER was 10 (range 3–22) for patients with stroke-in-evolution, while it was 23 (range 14–29) for nondeteriating stroke (p = 0.0001, univariate analysis, Mann-Whitney U test). A multivariate analysis with a backward logistic regression revealed that only the initial UNSS score remained a significant independent predictor of stroke deterioration (OR = 1.45, 95% CI = 1.27–1.74, p = 0.0001; beta coefficient = 0.6145).

**Discussion**

Our results demonstrated that early (i.e., <72 h within stroke onset) deterioration in patients after FIS is the main indication of neurological worsening. These findings support those of several other studies. In a retrospective review of 298 cases, Carter [15] reported that 38% of ischemic strokes were progressive during the first 2 h. Davalos and Castillo [13] found that neurological deterioration occurred in 23% of acute stroke patients treated or not treated by recombinant tissue plasminogen activator and increased up to 32% during the first 8 h from the initiation of drug or placebo administration. The frequency of late progression was 5.6% in our study, a figure similar to the data presented by Millikan et al. [16].

We demonstrated that early deterioration in FIS was strongly correlated with infarct-inherent mechanisms (80.3%), but not with systemic factors (19.7%). In contrast, late deteriorating stroke was related only to systemic factors. The ratio of neurological to somatic causes of deterioration during the 1st week of stroke onset in the current study was 5.7 (10/57). This is in contrast to Hachinski and Norris [10], who reported that this ratio was only 2.2 during the 1st week after stroke. They listed cardiac disorders, infections (including septicemia and pneumonia), pulmonary embolism, renal and hepatic failure as causes of deterioration in their study cohort. We also found cardiac factors and infections to be the main causes of deterioration among our patients with both early and late stroke deterioration.

We found no differences in the demographic, clinical and laboratory characteristics recorded in the ER of the deteriorated and nondeteriorated stroke patients. Previous studies had established advanced age, history of diabetes, coronary disease, atrial hypertension, and hyperthermia as clinical predictors of stroke deterioration [3, 4, 7, 12, 16]. Yamamoto et al. [8] ruled out gender, smok-

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**Table 2. Comparison of selected variables between deteriorating and nondeteriorating strokes (univariate analysis): categorical data**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Deterrating stroke (n = 71)</th>
<th>Improving or stable (n = 371)</th>
<th>OR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender</td>
<td>54</td>
<td>269</td>
<td>1.20 (0.39–1.44)</td>
<td>NS</td>
</tr>
<tr>
<td>Arterial hypertension</td>
<td>43</td>
<td>233</td>
<td>1.02 (0.49–1.018)</td>
<td>NS</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>40</td>
<td>214</td>
<td>0.95 (0.51–1.13)</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>16</td>
<td>74</td>
<td>1.17 (0.71–1.47)</td>
<td>NS</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>10</td>
<td>45</td>
<td>1.19 (0.62–1.39)</td>
<td>NS</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>10</td>
<td>47</td>
<td>1.13 (0.49–1.51)</td>
<td>NS</td>
</tr>
<tr>
<td>Smoking</td>
<td>19</td>
<td>104</td>
<td>0.84 (0.29–1.22)</td>
<td>NS</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>6</td>
<td>24</td>
<td>1.33 (0.71–1.80)</td>
<td>NS</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>7</td>
<td>33</td>
<td>1.12 (0.51–1.49)</td>
<td>NS</td>
</tr>
</tbody>
</table>

**Table 3. Comparison of selected variables between deteriorating and nondeteriorating strokes: numerical data**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Deterrating stroke (n = 71)</th>
<th>Improving or stable (n = 371)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, median (range)</td>
<td>74 (51–88)</td>
<td>75 (55–91)</td>
<td>0.49</td>
</tr>
<tr>
<td>Mean systolic blood pressure</td>
<td>146 (100–215)</td>
<td>144 (90–220)</td>
<td>0.26</td>
</tr>
<tr>
<td>Mean diastolic blood pressure</td>
<td>76 (60–130)</td>
<td>81 (60–125)</td>
<td>0.31</td>
</tr>
<tr>
<td>Body temperature, °C</td>
<td>37 (36–40)</td>
<td>37 (36–40)</td>
<td>0.82</td>
</tr>
<tr>
<td>Hematocrit, %</td>
<td>42 (31–50)</td>
<td>41 (32–53)</td>
<td>0.21</td>
</tr>
</tbody>
</table>

1 Mann-Whitney U test.
Progression of stroke: a strong predictor for stroke deterioration [4, 8, 12]. As a rule, neurological deficits are evaluated by means of different scoring scales. Deteriorating or progressing stroke is defined by a decrease in the patient’s score on the Canadian Stroke Scale, Scandinavian Stroke Scale and National Institute of Health Stroke Scale [3–6, 12]. We are aware that using the UNSS in the present study had some limitations, e.g., for the evaluation of ataxia, but our choice of this scale provided us with several advantages. Our stroke team is highly trained in using this scale with a high level of interrater agreement (week = 0.91) [21], and the UNSS provided a high level of standardization in the assessment of patients’ neurological state in our study. Indeed, the initial UNSS score was the only independent and significant predictor for stroke deterioration (OR = 1.45; CI = 1.27–1.74, p < 0.0001), in close correlation with several other studies [4, 8, 12]. Another limitation of our study is the use of cranial CT in contradistinction to magnetic resonance imaging (MRI) in the evaluation of infarct-inherent mechanisms for deteriorating stroke. We recommend that studies on this subject using MRI technology be conducted.

In conclusion, we demonstrated that early clinical deterioration in patients with acute stroke does not result from systemic, but from infarct-inherent mechanisms, including the consequences of enlargement of a previous cortical lesion, recurrent cortical or lacunar stroke, new hemorrhagic stroke, or hemorrhagic transformation of a previous ischemic lesion. Alternatively, systemic factors are dominant among the causes of late stroke deterioration. An initially severe neurological deficit might predict further deterioration in a patient with acute ischemic stroke.

Acknowledgment

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References


