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Stroke-in-Evolution: Infarct-Inherent Mechanisms versus Systemic Causes

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Key Words
First-ever ischemic stroke · Stroke deterioration, infarct-inherent mechanisms

Abstract
Background: It is uncertain whether deterioration after acute ischemic stroke is neurological and/or systemic (somatic) in origin. ***Methods:*** 442 consecutive patients admitted with first-ever ischemic stroke (FIS) were assessed by the Unified Neurological Stroke Scale (UNSS) at admission, on hospitalization days 1, 2 and 3 and before discharge. ***Results:*** Among 71/442 (16.1%) patients deteriorated during hospitalization, the worsening from stroke onset was early ($\leq$72 h) in 67 (94.4%) of them. The majority (57/71, 80.3%) had CT-confirmed cerebral causes and 14/71 (19.7%) had systemic causes. The causes of late deterioration were exclusively systemic. In the logistic regression analysis the initial mean UNSS score was the only significant independent predictor of stroke deterioration ($p < 0.0001$). ***Conclusions:*** Early clinical deterioration in FIS patients results from infarct-inherent mechanisms while late stroke deterioration is due primarily to systemic factors. An initially severe neurological deficit might predict further decline.

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

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Table 1. Variables recorded in the emergency room

Age
Creatine phosphokinase
Gender
Systolic blood pressure
Diastolic blood pressure
Body temperature
Hematocrit
Hemoglobin
White blood cell count
Platelet count
Blood glucose
Vascular risk factors[1]

[1] Arterial hypertension, diabetes mellitus, smoking, myocardial infarction, ischemic heart disease, atrial fibrillation, congestive heart failure, hyperlipidemia.

results [2–5, 7, 8, 12, 13]. The difficulty in establishing accepted predictors was explained by the heterogeneous nature of the mechanisms involved in neurological deterioration [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 infarct-inherent mechanisms and systemic causes of clinical worsening following first-ever ischemic stroke (FIS) and to delineate which factors cause early or late deterioration, thereby contributing more clinical data to help resolve these issues.

Patients and Methods

This prospective study included all consecutive patients admitted with acute FIS to Tel Aviv Sourasky Medical Center from October 1997 through October 1998. The patient's neurological condition 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 diagnosed in those patients who experienced worsening of their neurological 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 emergency 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 performed 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 defined 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 conditions 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 characteristics. 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), recurrent ischemic stroke (n = 66) and intracerebral hemorrhage (n = 46) were excluded. The remaining 442 consecutive patients who were admitted to the hospital with FIS were evaluated in the ER and they comprise the present 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 repeated 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 infarct 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 infection, deep vein thrombosis, sepsis, gastrointestinal bleeding) were found in 14 (19.7%) of the early deteriorated

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

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

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 nondeteriorating 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).

Table 3. Comparison of selected variables between deteriorating and nondeteriorating strokes: numerical data[1]

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

[1] Mann-Whitney U test.

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 the1st 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-

ing, hypercholesterolemia, and previous transient ischemic attacks as predictors of deteriorating stroke: they suggested that neurological worsening is related to different risk factors in the different subtypes of stroke and that this divergency could explain the disagreement among the studies.

Age is a recognized predictor of stroke deterioration [12]. Hachinski and Norris [10] suggested that advancing age is a critical factor for deterioration. According to the findings of Yamamoto et al. [8], patients older than 64 years were less numerous in the neurologically worsening group ($p < 0.001$) and they concluded that surprisingly younger rather than older patients tended to show neurological worsening. Age was not a significant differentiating factor between our patients with deteriorating and nondeteriorating strokes.

Diabetes mellitus was considered as being predictive of stoke deterioration in some studies but not in others [4, 17, 18]. High plasmatic concentrations of glucose on admission were associated with a higher risk of early stroke deterioration [1, 3, 5, 7, 19]. Hyperglycemia, both in diabetic and nondiabetic patients, was observed as an acute-phase response with no prognostic value after the first 24 h from the onset of symptoms [20]. We did not find either diabetes mellitus or hyperglycemia as predictive factors for stroke-in-evolution.

Arterial hypertension is another established predictor of deteriorating stroke [3, 4]. Yamamoto et al. [8], however, found that hypertension was significantly more frequent in the neurologically worsening group compared with the stabilized group in patients with small-artery disease, but not in those with large-artery atherosclerosis. In our study, arterial hypertension was not found to be a statistically significant factor for stroke-in-evolution.

Several studies have reported that an initial neurological deficit was 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.

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