Neurological Deterioration in Patients with First-Ever Ischemic Stroke

Cheung-Ter Ong and Chi-Shun Wu

Abstract- A study was conducted for 121 patients (55 female, 66 male; age 68.7 ± 10.4 years) with first-ever ischemic stroke to investigate the frequency and risk factors of early neurological deterioration (ND). The initial evaluation was carried out within 24 hours of stroke onset. National Institutes of Health Stroke Scale score and Barthel index were used to evaluate patients for a period of 2 months. Thirty-eight patients (31.4%) showed early ND and 83 patients (68.6%) were stable or improved. Among the 38 patients with ND, 25 (65.8%) patients occurred within 48 hours after initial evaluation.

In most patients, ND began on the first day and ceased on the third day after stroke onset. Neurological function started to improve after ND reaching the nadir. The mortality rate was 13.2% (5/38) for patients with ND and 1.2% (1/83) for patients without deterioration. At the end of the study, the functional ability and motility of patients were lower in the progressive group than in the non-progressive/stable group.

Results of this study seem to indicate that an elevated C-reactive protein level and total anterior circulation infarction are risk factors for ND. The results also suggest that more aggressive and early treatments are needed for stroke patients to prevent disease progression.

Key Words: Ischemic stroke, Neurological deterioration, Stroke progression, First-ever stroke, C-reactive protein

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INTRODUCTION

Neurological deterioration (ND) is a common event in the first hours or days of cerebral infarction. Stroke patients with ND stay longer in hospital, become more disabled and need more institutional care than patients without progression. The frequency of ND in cerebral infarction ranges from 15% to 40%[1-5].

ND is observed in stroke patients with mild neurological deficits as well as in severe stroke patients. In the patients with lacunar infarction and mild neurological deficits, the incidence of ND is between 13% and

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34%[6-8]. According to the ECASS (European Cooperative Acute Stroke Study) I data, the incidence of early and late progression in patients with moderate to severe stroke is 37.5% and 20.3%[9] respectively.

Over the past decades, many researchers have devoted their research to the cause of ND in acute stroke patients. Although several variables have been found to be associated with ND, little is known about the cause of stroke progression. Theories regarding the etiology of stroke progression include extension of brain edema, absence of recanalization, thrombus propagation, recurrent embolism and various system diseases[7,10].

Risk factors for ND in acute ischemic stroke patients that have been reported include neuroimaging, ultrasonographic and biochemical parameters[8,10]. The presence of mass effect on brain CT has been suggested to be a predicator of ND[11]. Transcranial Doppler has been reported as a useful technique in the identification of patients with risk of stroke progression[12]. The frequency of stroke progression occurs more often in cortical infarct than in deep infarcts. High plasma concentration of glucose, fibrinogen and glutamate on admission is associated with stroke deterioration[7].

The frequency of ND in patients with first-ever ischemic stroke has been shown to be related to the type of stroke. Tei and coworkers reported that the frequency of ND in ischemic stroke was very high in total anterior circulation infarcts (41.9%) but was very low in posterior circulation infarcts (6.3%)[13]. Since the incidence of ND was different in previous studies[1-5], it is important to know whether the incidence and risk factors of ND in the ischemic stroke patients in Taiwan are different from other ethnic groups.

The purposes of this study were to investigate the frequency and clinical course of progression in ischemic stroke and to identify the risk factors for ND in patients with first-ever ischemic acute cerebral infarction.

MATERIAL AND METHODS

Between July 2003, and June 2005, a prospective study was conducted to determine the incidence of ND in patients with first-ever stroke. Of 446 consecutive admissions to our neurological ward for stroke, 121 patients were identified for inclusion in the study. The inclusion criteria were patients who had: (1) Initial evaluation within 24 hours of symptoms onset, (2) Neurological symptoms that persists at time of initial evaluation, (3) No ongoing anticoagulant treatment, (4) No clinical indication of thrombolytic therapy, (5) No history of transient ischemic attack or stroke, and lastly, (6) Normal brain CT or CT showing ischemic infarction consistent with present neurological finding. The exclusion criteria were: (1) Symptoms disappeared within 24 hours, (2) Brain CT or MRI showed cerebral lesion, which did not correlate to the neurological finding and, (3) Patient in a state of coma or National Institutes of Health Stroke Scale over 25 points.

All patients were admitted to the neurological ward through the emergency unit. Blood pressure, blood sugar, biochemistries, cell count, C-reactive protein, chest X-ray, ECG, non-contrast brain CT were analyzed in the emergency unit before IV injection. Following an evaluation by a neurologist, 121 patients with first-ever cerebral infarction were included the study. The main reasons for the exclusion of 325 patients were: old stroke (220), initial evaluation was performed after 24 hours (37), symptoms disappeared before initial neurological evaluation (20) and brain CT showed silent infarct (44). Written informed consent was obtained from the 121 patients. National Institutes of Health Stroke Scale (NIHSS) and European Stroke Scale (ESS) were used for evaluation immediately after patients were selected for the study. Patients were re-evaluated daily during the first week, then weekly during the second to fourth weeks and finally on the day of discharge. After discharge, NIHSS, ESS and Barthel index were monitored for each patient at neurology clinic every two weeks for 60 days.

The first morning after patients were admitted to the neurological ward, levels of cholesterol, triglyceride, fasting sugar, fibrinogen, D-dimer were measured. Carotid sonography and intracranial Doppler were performed on the second day of hospitalization. While in the hospital, patients were treated with aspirin 100 mg/day, pentoxifylline 400mg twice a day and 0.9% nor-

mal saline 40 cc/hr. Aspirin was changed to ticlopidine 250 mg/day or clopidogrel 75 mg/day if patient showed signs of gastric ulcer or duodenal ulcer. Normal saline was not given to patients with congestive heart failure or with end stage renal disease. Initially, the same dosages of antihypertensive agents and/or hypoglycemic agents were prescribed for patients who used those drugs before the event, and then dosages were adjusted based on the condition of patients. ND was defined as an increase of ≥2 points in the NIHSS or a decrease of ≥6 points in the ESS[4,10,14]. All patients were evaluated and risk factors were assessed by the same neurologist. Hypertension in the study was defined as past use of antihypertensive drugs or systolic pressure ≥140 mmHg, or diastolic pressure ≥90 mmHg at the time of admission. Diabetes mellitus was defined as past use of oral hypoglycemic agents or insulin, or fasting blood sugar ≥126 mg/dl. Hypercholesterolemia was defined as past use of antilipidemic drugs or serum cholesterol level ≥200 mg/dl. History of smoking, alcohol intake, myocardial infarction and coronary artery disease were also recorded.

At the end of study, patients were divided into two groups: Progressive group, patients with ND; Stable group, patients without ND. Age, sex, risk factors and the time of first evaluation were compared between the two groups. Statistical analysis was performed to identify factors that were associated with ND. T-test was performed for continuous data and Chi square was used for the analysis of the non-continuous data.

RESULTS

The ages of the 121 patients (55 female, 66 male) that were included in the study were between 38 and 90 (mean 68.7±10.4). Thirty-eight patients (31.4%) showed clinical ND in the first week after stroke onset and 83 patients (68.6%) were stable or improved. In all the 38 patients with stroke progression, ND occurred in either motor function or facial palsy associated with dysarthria, dysphagia or sensory impairment. Among the 38 ND patients, 25 (65.8%) showed deterioration in the first 48 hours, 8 deteriorated between 48 and 72 hours and 4 patients had ND onset between 73 and 144 hours.

Four patients in the progressive group who showed one or more new neurological signs that were different from primary lesion were classified as recurrent stroke. One of the recurrent stroke patients occurred on the second day after stroke onset, two patients experienced recurrent stroke onset on the third day of stroke. One patient suffered from ND after 72 hours, then completely recovered but experienced recurrent stroke 15 days later.

The interval from symptom onset to hospital admission showed no significant difference between progressive and non-progressive stroke patients, (9.6±6.4 vs. 7.6±6.5 hours p=0.247). Almost one half of patients (47.7%) with progressive stroke and 56.6% of patients with non-progressive stroke were admitted within 6 hours after stroke onset. (p=0.346). About one third (28.9%) and 25.3% of progressive stroke and non-progressive stroke patients, respectively, were admitted within 3 hours after stroke onset (p=0.673). Initial NIHSS findings showed no significant difference between progressive groups and non-progressive group, (5.9±6.9 vs. 4.4±5.3, p=0.14).

There were no significant differences between the progressive and stable groups in regards to sex, age, current smoking habit (>10 cigarettes per day), alcohol consumption (>25gm/day); and the status of diabetes mellitus, hypertriglyceridemia, hypercholesterolemia, D-dimer and fibrinogen except congestive heart failure ($p<0.035$) (Table 1). The C-reactive protein level was significantly higher in patients with ND than in patients without ND (p=0.0003). Five out of 7 (74.1%) patients with total anterior circulation system infarction showed ND while only 28.8% (23/80) of patients with lacunar circulation system infarction showed ND (Table 2). Most of the ND reached their peak within 48 hours of stroke onset, then the neurological symptom(s) improved gradually or became stable (Fig. 1). On the third day of stroke progression, 19 patients maintained their NIHSS after initial deterioration, 6 patients recovered to the level of first evaluation. Eleven patients showed improvement but remained at a level higher than that of the first evaluation, 2 patients had NIHSS lower than that of the initial deterioration.

Table 1. *Characteristics of patient with and without neurological deterioration*

	Progressive group N=38	Stable group N=83	χ^2-test, *T-test P value
Age (year)	69.8±8.2	67.8±11.6	0.189*
Sex M/F	21/17	45/38	0.762
MI	1	1	0.567
Arrhythmia	5	11	0.989
Hypertension	24	52	0.957
Diabetes mellitus	18	29	0.192
Smoking	8	25	0.293
Hypercholesterolemia	15	32	0.923
CHF	2	17	0.035
Alcohol	4	5	0.382
Hypertriglyceridemia	8	24	0.362
Time of arrival (min)	549	455	0.340*
D-dimer >324ng/ml	9	13	0.286
CRP >0.8 mg/dl	19	15	0.0003
Fibrinogen >400 mg/dl	11	15	0.182

MI: Myocardial infarction; CHF: Congestive heart failure; CRP: C-reactive protein.

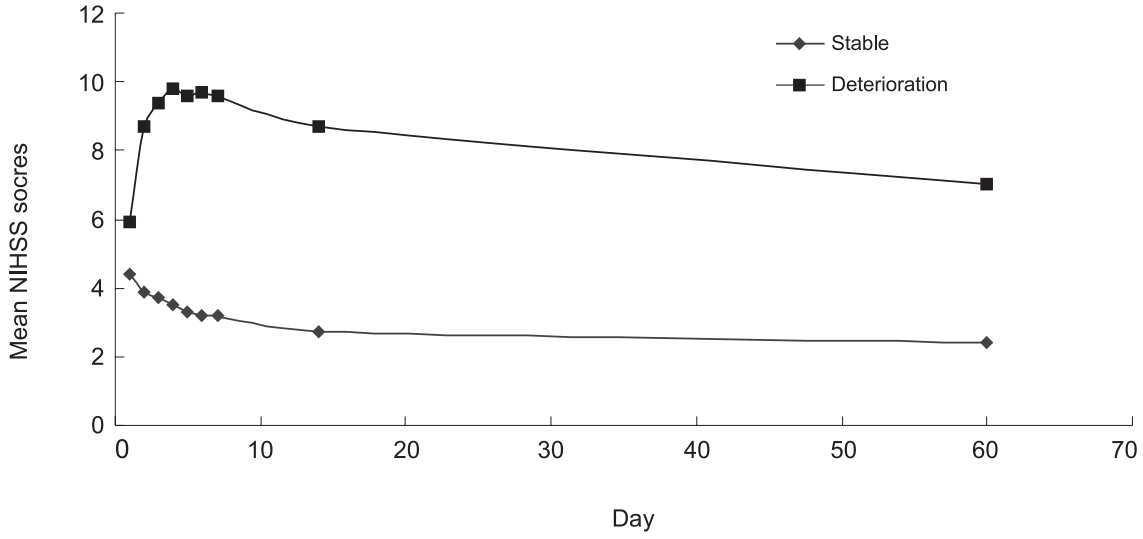

Figure. Mean National Institutes of Health Stroke Scale scores at fixed intervals of progressive and non-progressive stroke patients.

Sixty days after stroke onset, the mortality rate was 1.2% (1/83) in stable group and 13.2% (5/38) in progressive group. Mortality rate while hospitalized was 0% in the stable group and 5.3% (2/38) in the progressive group. The cause of mortality while hospitalized was complete basilar artery occlusion in one patient and encephalic herniation in the other. The causes of mortality after discharged were renal failure in one patient and pneumonia with sepsis in 3 patients. At 60 days, the NIHSS in the 33 survivals in the deterioration group was

Table 2. *Neurological deterioration and stroke type according to Oxfordshire stroke classification and TOAST classification*

Stroke subtype	Progressive group	Stable group	*P* value
Oxfordshire stroke classification	N (%)	N (%)	
Total anterior circulation system	5 (13.2)	2 (2.41)	0.02
Partial anterior circulation system	7 (18.4)	18 (21.7)	0.66
Lacunar circulation system	23 (60.5)	57 (68.7)	0.38
Posterior circulation system	3 (7.89)	6 (7.22)	0.88
TOAST stroke classification			
Cardioembolic	4 (10.5)	13 (15.7)	0.46
Small-artery disease	23 (60.5)	42 (50.6)	0.31
Large-artery atherosclerosis	10 (26.3)	7 (8.43)	0.008
Unknown etiology	1 (2.63)	21 (25.3)	0.003

15 points higher, 2 remained the same and 17 were lower then that of initial evaluation. The ability of self-care and motility were higher in the stable group than in the progressive group. The mean Barthel index was 38.4 in the progressive group and 79.2 in stable group 60 days after the stroke.

DISCUSSION

The frequency of stroke progression in ischemic stroke has been reported to be somewhere from 15% to 40%[1-5]. The frequency variations of stroke deterioration depend on the diagnostic criteria and the length of time from stroke onset to the time of first evaluation. Since ND may occur during the first few hours after stroke onset, patients that are evaluated earlier may have a higher frequency of deterioration. In this study, we examined patients within 24 hours of stroke onset. The time of first-evaluation was not significantly different between progressive and stable group.

There are two reasons to include patients admitted within 24 hours of symptom onset and exclude patients who had prior history of stroke. Firstly, if patients were first evaluated more than 24 hours after stroke, the frequency of stroke progression may be underestimated. Secondly, the frequency of stroke progression in patients with first-ever stroke can be determined.

In this study, the frequency of stroke progression (31.4%) was within the range of previous reports[1-5]. Based on our results and results reported by others[1-5], it appears that previous history of stroke or TIA is not related to stroke progression.

Age had been reported as a risk factor for progressive lacunar infarction. Kitanaka et al have shown that the risk of progressive lacunar infarction sharply increased in patients over 70 years old[2]. No significant age difference between stable group (67.8 ± 11.6) and progressive group (69.8 ± 8.2, P=0.189) was found in this study. Stroke progression was also found to occur on the first and second day after stroke onset in most patients with ND.

As mentioned before, stroke deterioration was defined as increase of ≥ 2 in NIHSS and decrease of ≥ 6 in ESS. These two markers appear to be consistent in the diagnosis of stroke deterioration except for one patient who showed a one point increase in NIHSS and a 6 point decrease in ESS. Due to inconsistency in NIHSS and ESS, this patient was excluded from the progressive group.

The mechanism of stroke progression is not really known. Systemic disease such as fever, higher leukocyte counts, metabolic change, hypotension and heart failure have been reported to be related to stroke progression[7,10]. Results of this study seem to indicate that congestive heart failure was reversely correlated with stroke progression (p=0.035).

Risk factors for vascular disease such as hypertension, diabetes mellitus, cardiovascular disease, hypercholesterolemia, hypertriglyceridemia, D-dimer, fibrinogen and cigarette smoking were not significantly differ-

ent between the two groups. Elevated C-reactive protein (CRP) level at admission, however, appears to be a risk factor for stroke progression. (P=0.0003).

Progressive hemiparesis in patients with lacunar infarct has been reported. In the study of Steinke and Ley, 23.9% of 92 patients with lacunar infarction had motor performance deterioration and they concluded that lacunar stroke is the major cause of progressive stroke[4]. However, strict inclusion criteria in patients with lacunar infarction may have a bias. In this study, we included patients with first-ever ischemic stroke and did not limit selection to the patients with lacunar infarct. In our study, the ND was observed in 28.8% of 80 patients with lacunar infarct. This number is close to that reported by Steinke and Ley[4]. Since 71.4% (5/7) of patients with total anterior circulation infarction showed ND, it seems that total anterior circulation infarction is also a risk factor for ND.

At present, neither effective treatment nor reliable clinical predicators of stroke progression are known. In the study by Röden-Jűlling et al, aspirin 325mg was given once daily for five consecutive days, however no positive effect from the aspirin was shown[3]. Continuous intravenous heparin treatment for patients with stroke progression appears to have limited effectiveness in the prevention of stroke progression[4,15]. In this study, aspirin 100mg daily and pentoxifylline 400mg twice daily were given to most of the patients. The frequency of stroke progression was found to be similar to that of the previous reports[1-5] but new stroke was found in 4 of the progressive stroke patients. Whether treatment of patients with heparin infusion or with a higher dose of aspirin could prevent acute recurrent stroke needs to be determined by further clinical studies.

In summary, ND was found to be common in patients with first-ever stroke and the functional capacity was lower in patients with progressive stroke. From this study, it appears that an elevated CRP and total anterior circulation infarction are risk factors for stroke progression. Measurement of CRP in patients with ischemic stroke, therefore, may be useful for identification of patients who are at risk for ND.

In the future, efforts must be made to identify patients who are at high risk for ND and to search for new therapies to prevent stroke progression. Furthermore, more aggressive treatments are needed for stroke patients who come to hospital during the first hours of stroke onset.

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