Association of stroke severity, leukocytosis, and infarction size with early neurological deterioration in acute ischemic stroke

Jehan Saeed[a], Ghada M. Samir[a], Ahmed F. El-Said[b]

Departments of [a]Internal Medicine, [b]Department of Public Health and Community Medicine, Zagazig University, Zagazig, Egypt

Correspondence to Jehan Saeed, MD, Department of Internal Medicine, Zagazig University, Zagazig, 44519, Egypt. Tel: 02-01124199921; fax: +20 55 345 452; e-mail: aymanjehan@yahoo.com

Received: 1 February 2019
Accepted: 17 February 2019
Published: 18 August 2020

The Egyptian Journal of Internal Medicine
2019, 31:774–778

Background
About one-third of patients with acute ischemic stroke will endure early neurological deterioration (END), which leads to increased mortality and functional disability. A better understanding of risk factors for END is still required.
Objective
The aim of this study was to determine the risk factors of END in ischemic stroke patients.
Patients and methods
One hundred and twenty patients with first ever ischemic stroke were included in this study. All patients were clinically evaluated to determine the risk factors. END was assessed using the National Institute of Health Stroke Scale (NIHSS) after acute ischemic stroke. Laboratory and radiological investigations were done for all patients.
Results
In all, 35% patients showed clinical END after stroke onset and 65% patients were stable or improved. END patients had statistically significant high body temperature, increased leukocyte count, serum blood glucose, triglycerides, NIHSS at admission, high-sensitivity C-reactive protein, and infarction size. Multivariable logistic regression analysis for different variables showed that leukocyte count, stroke severity using NIHSS, and lesion size were independent factors associated with neurological deterioration.
Conclusion
Stroke severity, white blood cell, and lesion size of infarction were the only independent factors associated with END.

Keywords:
early neurological deterioration, ischemic stroke, National Institute of Health Stroke Scale, white blood cell

Egypt J Intern Med 31:774–778

1110-7782

Introduction

Approximately one-third of ischemic stroke patients will clinically deteriorate following hospital admission. This is called early neurological deterioration (END) [1].

END commonly occurs as a result of microglia activation and inflammation in the brain [2]. Inflammatory response is due to the activation of resident cells, production of cytokines, and inflammatory cellular infiltrate in the infarcted area [3].

Studies tried to recognize the predictive factors for END to clarify its occurrence. Demographic variables, risk factors, clinical examination, laboratory tests, and imaging studies affect the outcome [4,5].

Acute inflammatory response was associated with ischemic stroke including elevation of C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), total peripheral white blood cell count, and body temperature [6]. An increase in leukocyte count as well as hyperthermia in the acute phase of cerebral ischemia was significant independent predictors of poor initial stroke severity and clinical outcome [6,7]. Leukocytic infiltration of the penumbra that leads to excitotoxic neuronal death is thought to contribute to END [8].

CRP is a prognostic factor and an independent predictor of death and recurrent vascular events in acute ischemic stroke. Moreover, higher CRP levels were associated with larger infarct volumes and these results may serve as a marker for severity of acute ischemic stroke [9,10].

Patients and methods

This study was conducted on 120 ischemic stroke patients who were admitted in the Intensive Care Unit of Internal Medicine Department, Zagazig University Hospitals during the period from January 2018 to November 2018. Informed consent was obtained from the patients or their relatives regarding the study.

Patients were selected according to the following criteria; patients with first ever ischemic stroke and admitted within 24 h of symptom onset.

We excluded patients with hemorrhagic stroke and patients with hemorrhagic transformation on follow computed tomography (CT), pre-existing and poststroke infectious disease, trauma, burns, surgery, chronic inflammatory disease and patients with anti-inflammatory treatment, neoplasm, hepatic or renal impairment, hematological disorders, and recent myocardial infarction.

All patients were subjected to the following: detailed medical history taking plus complete general and neurological examination with particular stress on National Institute of Health Stroke Scale (NIHSS). stroke severity was classified into mild, moderate, and severe stroke [11]. END was defined as an increase by at least two points in the NIHSS between admission and day 5 [12]. Patients were categorized into two groups, with END and without END.

CT scan of the brain was performed to all patients to confirm the diagnosis of ischemic stroke and to evaluate the early signs of infarction. To assess the size of the infracted area, follow-up CT was done after 72 h. Stroke lesions were classified according to their size of infarction into small (<1.5 cm), moderate (1.5–3 cm), and large (>3 cm) [13]. Laboratory investigations were done for all patients including complete blood count, random blood sugars, lipid profile (cholesterol, low-density lipoprotein, high-density lipoprotein, and triglycerides), liver and renal function tests and high-sensitivity C-reactive protein (HS-CRP).

Statistical analysis

Data were analyzed using SPSS version statistics 20.0 (IBM corporation, Armonk, New York, USA) software package. Data were expressed as percentage for discrete variables and mean±SD for continuous variables. Student's *t*-tests, χ^2, correlation, and multivariable logistic regression analysis were done when appropriate. *P* value of up to 0.05 was considered significant and a *P* value less than 0.001 was considered highly significant.

Table 1 Demographic data of early neurological deterioration and nonearly neurological deterioration patients

Variables	END (*N*=42)	Without END (*N*=78)	*P* value
Age (mean±SD) (years)	64.08+12.34	63.99+10.48	>0.05
Sex [*n* (%)]			
Male	14 (33.3)	27 (34.6)	>0.05
Female	28 (66.7)	51 (65.4)	
Hypertension [*n* (%)]	23 (54.8)	38 (48.7)	>0.05
Diabetes mellitus [*n* (%)]	28 (66.7)	18 (23.1)	<0.01**
Cardiac [*n* (%)]	17 (40.5)	26 (33.3)	>0.05
Hyperlipidemia [*n* (%)]	24 (57.1)	18 (23.1)	<0.01**
Smoking [*n* (%)]	6 (14.3)	11 (14.1)	>0.05
Transient ischemic attacks [*n* (%)]	7 (16.7)	6 (7.7)	>0.05
Dysphagia [*n* (%)]	16 (38.1)	27 (34.6)	>0.05
Systolic blood pressure	158.00±27.30	150.52±24.62	>0.05
Diastolic blood pressure	88.90±15.27	86.36±14.10	>0.05
Body temperature	37.78±0.26	37.04±0.20	<0.05*
Glasgow coma scale	12.30±3.96	11.48±4.04	>0.05
National Institute of Health Stroke Scale			
At presentation	22.46±6.42	12.64±6.30	<0.001**
On the fifth day	21.73±7.58	11.32±5.70	<0.001**
Lesion size in CT [*n* (%)]			
Large	23 (54.8)	5 (6.4)	<0.001**
Medium	14 (33.3)	38 (48.7)	
Small	0	35 (44.9)	

CT, computed tomography; END, early neurological deterioration. *Statistically significant; **Statistically highly significant.

Table 2 Comparison between early neurological deterioration group and nonearly neurological deterioration regarding laboratory data at admission

Laboratory data	END (*n*=42)	Without END (*n*=78)	*P* value
Serum glucose level (mg/dl)	182.42 ±37.08	158.25±49.07	<0.05*
Triglycerides (mg/dl)	168.45 ±82.68	131.82±56.43	<0.05*
Cholesterol (mg/dl)	206.58 ±47.56	198.87±45.62	>0.05
HDL (mg/dl)	34.62 ±14.23	36.85±15.08	>0.05
LDL (mg/dl)	142.84 ±39.18	137.08±48.06	>0.05
Leukocyte count ($\times 10^3$/cm)	11.52 ±4.06	8.64±3.00	<0.001**
C-reactive protein (mg/l)	42.09 ±32.46	16.47±34.26	<0.05*

END, early neurological deterioration; HDL, high-density lipoprotein; LDL, low-density lipoprotein. *Statistically significant; **Statistically highly significant

Table 3 Correlation of parameters with neurological deterioration

Clinical and laboratory data	Neurological deterioration	
	R	*P* value
Age	0.066	0.55
Body temperature	0.226	0.04*
National Institute of Health Stroke Scale	0.925	0.000**
Leukocyte count (white blood cells)	0.332	0.002**
Systolic blood pressure	0.153	0.17
Diastolic blood pressure	0.094	0.40
Serum blood glucose	0.373	0.001**
Cholesterol	0.052	0.65
High-density lipoprotein	0.049	0.66
Low-density lipoprotein	0.029	0.80
Triglycerides	0.040	0.72
High-sensitivity C-reactive protein	0.233	0.03*
Size of infarction	0.616	0.000**

*Statistically significant; **Statistically highly significant

Results

This study included 120 ischemic stroke patients. They were divided into two main groups: with END [42 (35%) patients] and without END [78 (65%) patients]. Characteristics of the patients are shown in Table 1. There was no statistically significant difference between the END group and without END as regards sex and age. According to the history of risk factors, patients with END had a statistically significant history of diabetes mellitus and hyperlipidemia more than patients without END.

Concerning severity of stroke using NIHSS (mean ±SD), the END group has statistically significant higher level than without the END group at admission and on the fifth day. Also, temperature was significantly higher in the END group. Patients with END have significantly larger infarct size than the without END group. The laboratory results of both groups are shown in Table 2. END patients had significant elevation in leukocytes, HS-CRP, serum blood glucose, and triglyceride levels than without END patients.

Table 4 Multivariate logistic regression analysis of risk factors associated with neurological deterioration

Variables	Odds ratio	95% confidence interval	*P* value
White blood cell	1.369	1.007–1.866	0.04*
Serum blood glucose	1.010	0.998–1.032	0.10
Body temperature	0.819	0.066–10.216	0.87
National Institute of Health Stroke Scale	1.225	1.046–1.438	0.01*
C-reactive protein	1.009	0.990–1.029	0.35
Size of infarction	2.355	1.206–4.529	0.01*

*Statistically significant

Univariate analysis showed significant correlations between END and leukocyte count, serum blood glucose, body temperature, NIHSS at admission, HS-CRP, and infarction size as shown in Table 3. Multivariable logistic regression analysis (Table 4) for different variables showed that leukocyte count, stroke severity using NIHSS and lesion size were independent predictors of neurological deterioration.

Discussion

Stroke patients are at high risk of END which is often happened early after cerebral infarction [14]. It was reported that the frequency of END ranged from 15 to 40% [15–17]. This study included 120 ischemic stroke patients, 35% patients showed clinical END after stroke onset, and 65% patients were stable or improved. This result was in accordance with Siegler *et al.* [5], who reported a deterioration of 36.9% in their study.

There was no age difference between END and without END which was similar to other studies that found no association between age and the occurrence of neurological deterioration [14,18]; however, other studies established old age as a risk factor for END [5,16,19].

Our result found significant association between diabetes and hyperlipidemia with the END group compared with without END. This was similar to that observed by Hansson [20] and Tanaka *et al.*

[21]. Regarding history of hypertension, cardiac diseases, smoking, and transient ischemic attack, there was no significant difference between both groups. This results were in accordance with other studies [5,14].

The role of hyperthermia in neurological deterioration was supported by its association with higher plasma levels of proinflammatory markers in acute ischemic stroke [22]. Our results found a significant association between temperature and END which was supported by other studies [6,23]. Moreover, there was significant correlation between temperature and size of infarction. Our finding was in accordance with the results of Karaszewski *et al*. [24]. Saini *et al.* [6] realized that increased temperature might have a possible suggested cascade of events through opening the blood–brain barrier that leads to increased extracellular edema, more infarct enlargement, more limited capillary flow in the ischemic tissue with decreases reperfusion which leads to more ischemic damage and larger infarction size.

Elevated leukocyte count in this study was associated with END. Excitotoxic neuronal death which could be due to leukocytic infiltration of the penumbra gives an explanation for END [25]. This was in agreement with Nardi *et al*. [7], Miyoamoto *et al*. [14], and Kumar *et al*. [18]. Moreover, this elevated leukocyte count was significantly correlated with stroke severity which was supported by the results of Buck *et al.* [2] and Nardi *et al.* [7] studies.

The correlation of CRP with ischemic stroke is tortuous, while most studies have found that increased levels of CRP were associated with END and poor outcome in patients after ischemic stroke [9,10]. Di Napoli [26] and Toyoda *et al.* [27] studies could not realize that CRP can predict the outcome after stroke. In this study, a significant higher level of CRP was detected in patients with END. In addition, our study found significant correlation between CRP neurological deterioration and these results were supported by the results of Seo *et al*. [10], Abubakar *et al*. [28] and, Luo *et al*. [29].

Another significant factor of END in our study is the lesion size. We found that patients with large-sized infarctions on follow-up CT were more likely to deteriorate than patients with medium or small infarctions. This was supported by the result of Dohmen *et al*. [30], who found that the most common etiology of ND was the extension of the initial infarction.

Multivariable logistic regression analysis for different variables showed that leukocyte count, stroke severity using NIHSS, and lesion size were independent factors associated with neurological deterioration. Our result was in agreement with the studies of Siegler *et al*. [5], Siegler *et al*. [31], and Schonewille *et al*. [32]. This findings showed that increased susceptibility of stroke patients for END can be attributed to patients' characteristics, stroke-induced inflammation, and imaging data. Careful attention should be paid to patients with elevated total leukocyte count with severe stroke and large volume size. Finally, it can be concluded that stroke severity, white blood cell, and lesion size of infarctions were the only independent factors associated with END. Further large, randomized studies are needed to stratify risk factors for END.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

References

1 Siegler JE, Martin-Schild S. Early neurological deterioration (END) after stroke: the END depends on the definition. Int J Stroke 2011; 6:211–212.

2 Buck BH, Liebeskind DS, Saver JL, Bang OY, Yun SW, Starkman S, *et al.* Early neutrophilia is associated with volume of ischemic tissue in acute stroke. Stroke J Cerebral Circ 2008; 39:355–360.

3 Jin R, Yang G, Li G. Inflammatory mechanisms in ischemic stroke: role of inflammatory cells. J Leukoc Biol 2010; 87:779–789.

4 Smith CJ, Emsley HC, Gavin CM, Georgiou RF, Vail A, Barberan EM, *et al.* Peak plasma interleukin-6 and other peripheral markers of inflammation in the first week of ischaemic stroke correlate with brain infarct volume, stroke severity and long-term outcome. BMC Neurol 2004; 4:2–5.

5 Siegler JE, Boehme AK, Kumar AD, Gillette MA, Albright KC, Beasley M, Martin-Schild S. Identification of modifiable and nonmodifiable risk factors for neurologic deterioration after acute ischemic stroke. J Stroke Cerebrovasc Dis 2013; 5:1–7.

6 Saini M, Saqqur M, Kamruzzaman A, Lees KR, Shuaib A. Effect of hyperthermia on prognosis after acute ischemic stroke. Stroke 2009; 40:3051–3059.

7 Nardi K, Milia P, Eusebi P, Paciaroni M, Caso V, Agnelli G. Admission leukocytosis in acute cerebral ischemia: influenceon early outcome. J Stroke Cerebrovasc Dis 2012; 21:819–824.

8 Mu S, Ouyang L, Liu B. Relationship between inflammatory reaction and ischemic injury of caudate putamen in rats: inflammatory reaction and brain ischemia. Anat Sci Int 2011; 86:86–97.

9 Youn CS, Choi SP, Kim SH, Oh SH, Jeong WJ, Kim HJ, *et al.* Serum highly selective C-reactive protein concentration is associated with the volume of ischemic tissue in acute ischemic stroke. Am J Emerg Med 2012; 30:124–128.

10 Seo WK, Seok HY, Kim JH, Yu SW, Oh K, Koh SB, Park KW. C-reactive protein is a predictor of early neurologic deterioration in acute ischemic stroke. J Stroke Cerebrovasc Dis 2012; 21:181–186.

11 Kvistad CE, Thomassen L, Waje-Andreassen U, Naess H. Low body temperature associated with severe ischemic stroke within 6 h of onset: The Bergen NORSTROKE Study Vascular Health and Risk Management. Stroke 2012; 8:333–338.

12 Kwan J, Hand P. Early neurological deterioration in acute stroke: clinical characteristics and impact on outcome. QJM 2006; 99:625–633.

13 Kiers L, Davis SM, Larkins R, Hopper J, Tress B, Rossiter SC. Stroke topography and outcome in relation to hyperglycaemia and diabetes. J Neurol Neurosurg Psychiatry 1992; 55:263–270.

14 Miyamoto N, Tanaka Y, Ueno Y, Kawamura M, Shimada Y, Tanaka R, *et al.* Demographic, clinical, and radiologic predictors of neurologic deterioration in patients with acute ischemic stroke. J Stroke Cerebrovasc Dis 2013; 22:205–210.

15 Röden-Jüllig Å, Britton M, Malmkvist K. Aspirin in the prevention of progressing of stroke: a randomized controlled study. J Intern Med 2003; 254:584–590.

16 AboEl-Naga Y. Predictors of early progression in ischemic stroke. Eur J Neurol 2007; 44:207–223.

17 Ong CT, Wu CS. Neurological deterioration in patients with first-ever ischemic stroke. Acta Neurol Taiwan 2007; 16:143–149.

18 Kumar AD, Boehme AK, Siegler JE, Gillette M, Albright KC, Martin-Schild S. Leukocytosis in patients with neurologic deterioration after acute ischemic stroke is associated with poor outcomes. J Stroke Cerebrovasc Dis 2012; 22:1–7.

19 Lin LC, Hsiao KY, Tsai YH, Lai SL, Lei CC, Hsiao CT. Predictors of clinical deterioration during hospitalization following acute ischemic stroke. Eur Neurol 2012; 67:186–192.

20 Hansson GK. Inflammation, atherosclerosis, and coronary artery disease. N Engl J Med 2005; 352:1685–1695.

21 Tanaka R, Ueno Y, Miyamoto N, Yamashiro K, Tanaka Y, Shimura H, *et al.* Impact of diabetes and prediabetes on the short-term prognosis in patients with acute ischemic stroke. J Neurol Sci 2013; 332:45–50.

22 Leira R, Rodríguez-Yáñez M, Castellanos M, Blanco M, Nombela F, Sobrino T, *et al.* Hyperthermia is a surrogate marker of inflammation-mediated cause of brain damage in acute ischaemic stroke. J Intern Med 2006; 260:343–349.

23 Boysen G, Christensen H. Stroke severity determines body temperature in acute stroke. Stroke 2001; 32:413–417.

24 Karaszewski B, Wardlaw JM, Marshall I, Cvoro V, Wartolowska K, Haga K, *et al.* Measurement of brain temperature with magnetic resonance spectroscopy in acute ischemic stroke. Ann Neurol 2006; 60:438–446.

25 Akopov SE, Simonian NA, Grigorian GS. Dynamics of polymorphonuclear leukocyte accumulation in acute cerebral infarction and their correlation with brain tissue damage. Stroke 1996; 27:1739–1743.

26 Di Napoli M. Early inflammatory response in ischemic stroke. Thromb Res 2001; 103:261–264.

27 Toyoda K, Fujimoto S, Kamouchi M, Iida M, Okada Y. Acute blood pressure levels and neurological deterioration in different subtypes of ischemic stroke. Stroke 2009; 40:2585–2588.

28 Abubakar SA, Okubadejo NU, Ojo OO, Oladipo O, Ojini FI, Danesi MA. Relationship between admission serum C-reactive protein and short term outcome following acute ischaemic stroke at a tertiary health institution in Nigeria. Niger J Clin Pract 2013; 16:320–324.

29 Luo Y, Wang Z, Li J, Xu Y. Serum CRP concentrations and severity of ischemic stroke subtypes. Can J Neurol Sci 2012; 39:69–73.

30 Dohmen C, Galldiks N, Bosche B, Kracht L, Graf R. The severity of ischemia determines and predicts malignant brain edema in patients with large middle cerebral artery infarction. Cerebrovasc Dis 2012; 33:1–7.

31 Siegler JE, Boehme AK, Kumar AD, Gillette MA, Albright KC, Martin-Schild S. What change in the national institutes of health stroke scale should define neurologic deterioration in acute ischemic stroke? J Stroke Cerebrovasc Dis 2012; 22:675–682.

32 Schonewille WJ, Wijman CA, Michel P, Rueckert CM, Weimar C, Mattle HP, *et al.* Treatment and outcomes of acute basilar artery occlusion in the Basilar Artery International Cooperation Study (BASICS): a prospective registry study. Lancet Neurol 2009; 8:724–730.