Infarction Size, Interleukin-6, and Their Interaction Are Predictors of Short-Term Stroke Outcome in Young Egyptian Adults

Rasha M. Fahmi, MD, PhD,* and Ahmed F. Elsaid, MD, PhD†

Background: A trend of increasing incidence of first-ever cerebral ischemic stroke in young adults has been recently reported. The current study was conducted with the objective of identifying independent predictors of short-term outcome of first-ever cerebral ischemic stroke affecting young Egyptian adults. *Methods:* The present hospital-based study included 50 patients, 23 males and 27 females, aged 18-45 years, with first-ever ischemic stroke confirmed by computed tomography (CT) and magnetic resonance imaging. Twenty healthy age- and sex-matched random control subjects were included to set the reference laboratory values. Detailed medical, neurological, and laboratory data were collected. Stroke severity and short-term stroke outcome were assessed using the Canadian Neurological Scale and the National Institutes of Health Stroke Scale (NIHSS), respectively. *Results:* High prevalence of modifiable risk factors was observed in young Egyptian adults affected with first-ever ischemic cerebral stroke. Although all studied risk factors were significantly correlated with NIHSS score, multiple regression analysis revealed that only infarction size (CT size), interleukin-6 (IL-6), and their synergistic interaction were the most important predictors of NIHSS stroke outcome. *Conclusions:* IL-6 and infarction size were independent predictors of short-term stroke outcome in young Egyptian adults. Synergistic interaction of IL-6 with infarction size suggests an investigative value for assessing serum IL-6 level and a therapeutic benefit for its reduction during the course of early ischemic stroke treatment. **Key Words:** Stroke—IL-6—CT size—CRP—NIHSS—short-term stroke outcome—young adults—Egypt.

Introduction

Stroke is the third leading cause of death and the most frequent cause of permanent disability worldwide.[1] Increasing trend in the incidence of stroke in young adults under the age of 45 years has been reported in recent studies.[2,3] The greatest burden of this increasing trend has been observed in developing countries where stroke in young adults represent 19%-30% of all stroke patients compared to only 5% in well-developed countries.[4-6] The reason for this difference is not clear. Understanding the pathophysiological mechanisms of stroke in young adults is crucial to explain and hopefully prevent stroke in this important age group.

Several risk factors, including both modifiable and novel, have been reported to be associated with the incidence and prognosis of ischemic stroke. Modifiable stroke risk factors include hypertension, dyslipidemia, diabetes, atrial fibrillation, cigarette smoking, and contraceptive pills. Epidemiological studies revealed the important role of genetic component in determining the pattern of prevailing risk

From the *Department of Neurology, Faculty of Medicine, Zagazig University, Zagazig, Egypt; and †Department of Community Medicine and Public Health, Faculty of Medicine, Zagazig University, Zagazig, Egypt.

Received September 24, 2015; revision received April 25, 2016; accepted June 13, 2016.

Address correspondence to Ahmed F. Elsaid, MD, PhD, Department of Community Medicine and Public Health, Faculty of Medicine, Zagazig University, Zagazig, Egypt. E-mail: elsaid_af@hotmail.com.

1052-3057/$ - see front matter

http://dx.doi.org/10.1016/j.jstrokecerebrovasdis.2016.06.021

factors and its association with stroke incidence and outcome.[7] A large cohort study conducted in the U.S. counties reported an incidence risk of stroke that was 2.9 more likely in whites than in blacks at the age of 45 years.[7] The prevailing modifiable risk factors observed in one study conducted in young Chinese adults affected with stroke were hyperlipidemia (53%), smoking (50%), and hypertension (46%).[8] In Australian patients aged 15-55 years, the odds of developing stroke were highest among patients with diabetes followed by hypertension, heart disease, cigarette smoking, and long-term heavy alcohol consumption.[9] Thus, it is important to identify the predominant stroke risk factors for each population of interest.

Chronic inflammation is an important novel stroke risk factor. Inflammation has been reported both as a cause and effect of ischemic cerebral stroke.[10,11] On one hand, the incidence of ischemic cerebral stroke was reported to trigger acute and prolonged cerebral and systemic inflammatory process. On the other hand, inflammation was suggested as a common pathological pathway by which modifiable risk factors such as hypertension, dyslipidemia, diabetes mellitus, and cigarette smoking could predispose to ischemic cerebral stroke.[12] Local vascular inflammation, which occurs in pathological lesions such as atheromatous plaques, was also suggested as a predisposing risk factor of ischemic stroke. Vascular inflammation induces endothelial injuries that result in the expression of several endothelial adhesion molecules, which lead to the recruitment and subendothelial deposition of macrophages and T cells.[10,13] Aggregated subendothelial macrophages and T cells release proinflammatory cytokines that favor procoagulant conditions, which could culminate in the initiation of thrombotic ischemic stroke.[10,14] Cytokines are major mediators of inflammatory-induced pathological lesions. C-reactive protein (CRP) and interleukin-6 (IL-6) were among the inflammatory cytokines that had been extensively studied in stroke.[15] Importantly, elevated levels of CRP and IL-6 were shown in multiple prospective cohort studies to be significant predictors of future incidence of stroke.[16-18]

The current hospital-based study was conducted with the objective of identifying significant independent risk factors that could predict short-term stroke outcome in young adults.

Subjects and Methods

Fifty patients, 23 males and 27 females, were recruited consecutively from the intensive care units of Departments of Cardiology, Internal Medicine, and Neurology, Zagazig University Hospital, during the period from March 2012 to June 2014. Only patients aged 18-45 years with first-ever stroke, neurological deficit lasting more than 24 hours with no other cause other than vascular, and with computed tomography (CT) and/or magnetic resonance imaging brain for radiological confirmation were included. Patients were excluded if presented with transient ischemic attack, nonischemic stroke, recent clinical infection, malignancy, recent surgery or major trauma, renal or hepatic failure, and inflammatory diseases. Twenty healthy age-matched control subjects (8 males and 12 females) were recruited to assess the reference levels of IL-6 and CRP. Informed consent was obtained from all participants and/or their relatives. The study was conducted according to the recommended guidelines for clinical studies provided by Zagazig Faculty of Medicine and was approved by the institutional review board.

All participants were subjected to detailed medical history, comprehensive general and neurological examination, and laboratory investigations. Blood samples were drawn within 24 hours of admission. Forty-five samples were collected at 6 hours after admission, 3 samples at 7 hours, and 2 samples at 12 hours. The average time between onset of symptoms and hospital admission was 5.5 ± 1.5 hours. Thus, the majority (>90%) of our samples were collected between 12 and 15 hours after the onset of symptoms. Laboratory investigations included complete blood count, erythrocyte sedimentation rate, fasting blood sugar, and lipid profile analysis. IL-6 and CRP levels were estimated by IL-6 IMMULITE 1000 System (Siemen, Munich, Germany) using the the Immulite 1000 IL-6 kit (Siemen) Kit and CRP-Turbilatex (SPINREACT, S. A. U. Spain), respectively. The evaluation of stroke severity was assessed using the Canadian Neurological Scale (CANS) within the first 24 hours of stroke onset.[19] The CANS is a simple, well-recognized scoring system of stroke severity that has well-established validity and reliability characteristics.[20,21] Short-term stroke outcome was assessed after 15 days of onset of stroke using the National Institutes of Health Stroke Scale (NIHSS).[22] The NIHSS has been used in clinical trials to assess neurological outcome after therapy of acute stroke.[23] Importantly, the NIHSS has been shown to be sensitive to detect clinical changes assessed within short time intervals, 7-10 days, after stroke.[23,24] Compared with other outcome measuring scales such as the Barthel Index and the modified Rankin Scale, the NIHSS was shown to be the most sensitive outcome measure, requiring potentially smaller sample sizes to detect relevant therapeutic effects.[25] Brain lesions were assessed using cranial CT and/or magnetic resonance imaging.

Statistical Analysis

The sample size was calculated based on the previously reported mean difference of 17 pg/mL in the levels of IL-6 and 7 mg/L in the levels of CRP between control subjects and stroke patients, respectively.[26,27] With 50 patients and 20 controls, the study had more than 80% power to detect a modest increase of 4 mg/L in stroke patients when using 2-sided *t*-test with 95% confidence interval. Data from stroke patients were collected, checked, and