



Risk factor profile by etiological subtype of ischemic stroke in the young

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ABSTRACT

Background and purpose: Studies of risk factors for ischemic stroke in the young have generally considered ischemic stroke as a whole. The purpose of the present study was to evaluate the association of traditional cardiovascular risk factors with etiological subtypes of ischemic stroke in young adults.

Methods: Retrospective review of data from patients aged 16–54 years consecutively treated for first-ever ischemic stroke in an academic stroke unit. Definite causes of stroke were classified using the ASCO (A for atherothrombosis, S for small vessel disease, C for cardiac source, O for other cause) classification system. We used multinomial logistic regression analysis to evaluate associations of age, gender, smoking, hypertension, diabetes and blood lipids with each etiological subtype.

Results: A total of 400 patients were included: 244 men (61.1%), 156 women (38.9%); mean age (SD) 44.5 (8.5) years. A definite cause of stroke could be identified in 202 (50.5%) patients. Definite causes of stroke included: atherothrombosis, 72 (18.0%) patients; cardioembolism, 37 (9.25%) patients; small vessel disease, 28 (7.0%) patients; other definite cause, 65 (16.25%) patients including 44 patients with carotid or vertebral artery dissection. Atherothrombosis was associated with age, smoking, diabetes, hypertension and low HDL-cholesterol. Small vessel disease was associated with age and hypertension. Cardioembolism was associated with age.

Conclusion: The risk factor profile differs between etiological subtypes of ischemic stroke in young adults. Our findings emphasize the impact of smoking, diabetes, hypertension and low HDL-cholesterol as risk factors for atherothrombosis, and of hypertension as a risk factor for small vessel disease in young adults.

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1. Introduction

The incidence of ischemic stroke is strongly correlated with age. Stroke in young subjects is, therefore, relatively infrequent. However, recent epidemiological data suggest that the incidence of stroke in the young is growing [1–3]. Knowledge of risk factors for ischemic stroke in the young is of the utmost importance to prevent this potentially devastating disease. Case-control studies have shown that smoking, hypertension and low HDL-cholesterol are the traditional cardiovascular risk factors most commonly associated with ischemic stroke in the young [4–11]. It is important to note that ischemic stroke was considered as a whole in these

studies. Yet, ischemic stroke in the young can be caused by a great variety of diseases [12–14]. It is thus possible that specific associations of risk factors with some etiological subtypes could have been diluted and underestimated in an analysis combining all etiological subtypes in one stroke category [15]. Uncontrolled cohort studies including large numbers of patients have confirmed the high frequency of smoking and hypertension among young patients with ischemic stroke, but, again, these studies did not report an analysis of risk factors by etiological subtype [12,16]. The purpose of the present study was to evaluate the associations of traditional cardiovascular risk factors with etiological subtypes of ischemic stroke in young adults.

2. Materials and methods

Patients aged 16–54 years consecutively treated for first-ever ischemic stroke in an academic stroke unit from June 2006 to June

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2012 were included in this retrospective analysis. Patients with cerebral venous thrombosis, ischemic stroke secondary to subarachnoid hemorrhage, or transient ischemic attack (defined as transient neurological deficit without evidence of cerebral infarction on brain imaging) were excluded.

The diagnosis of stroke was made using a predefined algorithm [14]. Initial evaluation included brain MRI or CT, EKG, routine blood studies (complete blood cell count, prothrombin time, activated partial thromboplastin time, and C-reactive protein, fibrinogen, D-dimer, serum creatinine, and glucose concentrations) and non-invasive angiography of cerebral and cervical vessels using magnetic resonance or CT angiography. We used axial T1-weighted MRI scans with fat saturation for the diagnosis of arterial dissection. Transesophageal echocardiography (TEE) was performed in patients with no definite cause of stroke after initial evaluation. Transthoracic echocardiography (TTE) was also performed in patients with a suspicion of intraventricular thrombus. Patent foramen ovale (PFO) was assessed at rest and during provocative maneuvers using IV injection of agitated saline. PFO and atrial septal aneurysm were diagnosed using criteria published previously [17]. Complementary investigations were done in selected patients with abnormal findings on initial evaluation, e.g., CSF analysis and syphilis serology in a patient with HIV infection and basilar artery stenosis, blood cultures in patients with fever or elevated C-reactive protein, a search for active malignancy in patients with otherwise unexplained elevated D-dimer levels, and testing for cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy and Fabry disease in patients with small vessel disease. Continuous EKG monitoring using inpatient telemetry or Holter monitoring and testing for inherited thrombophilia (antithrombin, protein C, and protein S deficiencies and factor V Leiden and prothrombin G20210A mutations), hyperhomocysteinemia, and antiphospholipid antibodies (lupus anticoagulant, anticardiolipin, and anti- β_2 glycoprotein 1 antibodies) were performed on an optional basis in selected patients with suggestive findings on initial evaluation or with no apparent cardiac source of embolism after completion of echocardiography.

Clinical, biological and radiological data were collected using the electronic database of our institution. A senior vascular neurologist reviewed individual data and classified the causes of stroke using the ASCO classification system into atherosclerosis, small vessel disease, cardioembolism, other determined cause, and undetermined cause [18]. For the purpose of this study, we only considered definite (ASCO grade 1) causes of stroke. Patients with complete evaluation and no definite cause of stroke were classified as undetermined cause. We considered that evaluation was incomplete when brain and neck vessels angiography or TEE was not performed.

Hypertension was defined as persistent elevation of systolic blood pressure >140 mm Hg or diastolic blood pressure >90 mm Hg documented before stroke or treatment with antihypertensive drugs before stroke. Diabetes was defined as a previous diagnosis of type 1 or type 2 diabetes. Smoking was recorded in patients currently smoking or with a past history of smoking.

A detailed lipid profile including cholesterol, triglycerides, HDL-cholesterol, LDL-cholesterol, and lipoprotein (a) concentrations was performed in selected patients at the discretion of physician for each patient. Lipid assessment was performed on the working day after admission to hospital.

Since all data had been obtained as part of routine clinical care, the ethical review board of our institution did not require patient informed consent.

2.1. Statistical analysis

Data are presented as mean and standard deviation for quantitative variables and percentages for categorical ones. The Chi-squared

test was used to compare the distribution of qualitative variables between groups of ASCO classification. Comparisons of age and blood lipids among the five groups of ASCO classification were analyzed by one-way ANOVA test. When basic assumptions were not satisfied, data were logarithmically transformed or subjected to a Kruskal–Wallis one-way analysis of variance. Multivariable multinomial logistic regression analyses were performed to explore the association between the ASCO categories as the dependent variable with other confounding variables included in the model. All the variables were entered into the model a priori without any specific selection, by introducing first age, sex, hypertension, smoking and diabetes, and second by adding blood lipids. Multivariate models were tested with and without adjustment for statin treatment. The adjusted odds ratios with *P*-values are presented in the text, with confidence intervals and also are presented in the tables. Model assumptions were verified before analyses. All tests were two-tailed at the level of significance of 0.05. The statistical software SAS 9.2 (SAS Institute, Cary, NC, USA) and STATA 11.2 (StataCorp, TX, USA) were used for the analyses.

3. Results

Of 436 patients treated during the study period, diagnostic assessment was complete in 400 patients including 244 (61.1%) men and 156 (38.9%) women, with a mean age (SD): 44.5 (8.5) years. A total of 157 (39.2%) patients were aged 44 years or less.

A flow chart detailing stroke diagnosis is shown in Fig. 1. A definite cause of stroke could be identified in 202 (50.5%) patients. Definite causes of stroke comprised: atherothrombosis, 72 (18.0%) patients; cardioembolism, 37 (9.3%) patients including 14 patients with atrial fibrillation; small vessel disease, 28 (7.0%) patients; other definite cause, 65 (16.3%) patients. Other definite causes of stroke included carotid or vertebral artery dissection (44 patients), thrombosis of unruptured cerebral artery aneurysm (4), intravascular coagulation associated with active cancer (4), lupus anticoagulant (3), aortic dissection (1), reversible cerebral vasoconstriction syndrome (1), cerebral syphilitic arteritis (1), moyamoya disease (1), Buerger disease (1), paradoxical embolism (1), heparin-induced thrombocytopenia (1), basilar dolichoectasia (1), intra-arterial insertion of a portacath (1), radiation cerebral arteritis (1). All dissections were spontaneous or occurred after trivial trauma.

Data on smoking, hypertension and diabetes were available in 390 patients. A full data set for blood lipids was available in 291/390 patients. Missing values for blood lipids were significantly more common in patients with other definite cause of stroke and, to a lesser extent, in patients with cardioembolism (data not shown), suggesting that the main reason for not performing lipid studies was the early documentation of a definite cause of stroke presumably unrelated to dyslipidemia. The overall frequency of smoking, hypertension and diabetes in the 390 patients with available data were 54.1%, 25.3% and 8.7%, respectively. The demographics of etiological subtypes and distribution of smoking, hypertension and diabetes between groups are shown in Table 1. The results from multinomial logistic regression analysis evaluating the adjusted associations of smoking, hypertension and diabetes with each etiological subtype of stroke are presented in Table 2. Atherothrombotic stroke was associated with age, diabetes, smoking and hypertension. Small vessel disease was associated with age and hypertension. Cardioembolism was associated with age. The subtype “Other definite cause of stroke” was negatively associated with smoking.

Table 3 shows the mean values (SD) of blood lipids in each etiological subtype. Triglycerides and LDL levels were higher and HDL levels were lower in patients with atherothrombotic stroke. Table 4 shows the results from multinomial regression analysis

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