Tobacco Use and Cryptogenic Stroke in Young Adults

Aude Jaffre, MD,* Jean Bernard Ruidavets, MD, PhD,† Nathalie Nasr, MD, PhD,* Brigitte Guidolin, MD,* Jean Ferrieres, MD, PhD,† and Vincent Larrue, MD*

Objective: Cryptogenic stroke is the leading subtype of ischemic stroke in the young. We sought to evaluate the association between traditional cardiovascular risk factors and cryptogenic stroke by using a case–control study. *Methods:* Patients aged 18-54 years, consecutively treated for first-ever cryptogenic ischemic stroke in an academic stroke unit, were compared with subjects from the general population living in the same geographic area. Control subjects were matched for age and sex with patients. We further evaluated the association between significant risk factors and nonobstructive (<50% stenosis) carotid plaque and thrombus among patients with cryptogenic stroke. Odds ratios [OR] were calculated using logistic regression analysis. *Results:* A total of 155 patients with cryptogenic stroke (66.4% men, mean age 43.5 years [SD 8.4]) were included in the study. Cryptogenic stroke was associated with current tobacco use (42.6% in patients versus 23.9% in control subjects; OR = 2.38, 95% confidence interval [CI] 1.40-4.05, $P = .002$). Current tobacco use was associated with nonobstructive carotid plaque (OR = 6.22; 95% CI, 2.43-15.9; $P = .001$) and nonobstructive carotid thrombus (OR = 13.7; 95% CI, 1.42-132.7; $P = .03$) among the patients. *Conclusion:* Our case–control study showed a strong link between current tobacco use and cryptogenic stroke in young adults. **Key Words:** Stroke—young—cryptogenic—tobacco use—ischemic stroke.

Ischemic stroke in the young is relatively uncommon, but recent epidemiological data suggest that the incidence of ischemic stroke is growing in young adults.[1-3] Ischemic stroke in young adults can be caused by a great variety of diseases, artery dissection being the most frequent one. However, the cause of ischemic stroke cannot be determined in a substantial number of young adults despite extensive workup (cryptogenic stroke). The frequency of cryptogenic stroke ranges from 25% to 50% between studies depending on the diagnostic criteria and the classification system used for subtyping.[4-7] Potential risk factors for cryptogenic stroke in the young are ill-defined. An association of cryptogenic stroke with patent foramen ovale (PFO) has been established by case–control studies in patients under the age of 55.[8] In contrast, the association of cryptogenic stroke with traditional cardiovascular risk factors has not been the subject of much analysis. Indeed, most previous case–control studies evaluating traditional cardiovascular risk factors in the young considered ischemic stroke as a whole and did not discriminate between cryptogenic stroke and stroke of known cause.[9-16] Recently, a large number of case series studies of stroke in young adults have shown a seemingly high prevalence of traditional cardiovascular risk factors among patients.[4,5,7] However, as these studies were uncontrolled, the strength of possible association between these factors and stroke could not be ascertained. In the present study, we aimed at investigating the association of traditional cardiovascular risk factors

From the *Department of Neurology, Toulouse University Hospital, 31059 Toulouse Cedex 9, France; and †Department of Epidemiology and INSERM U1027, Toulouse University Hospital, 31059 Toulouse Cedex 9, France.

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Address corresponding to Aude Jaffre, Service de Neurologie Vasculaire, Hôpital Pierre Paul Riquet, CHU Toulouse, 1 Place Baylac, 31059 Toulouse Cedex 9, France. E-mail: jaffre.a@chu-toulouse.fr.

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with cryptogenic stroke in young adults using a case–control design. We further analyzed the association between significant risk factors and nonobstructive carotid plaque and thrombus among patients.

Methods

Patients aged 18-54 years, consecutively treated for first-ever ischemic stroke in an academic stroke service between June 2006 and June 2012, and without potential cause of stroke despite extensive workup, were included in the present study.

The diagnosis of ischemic stroke was confirmed by brain magnetic resonance imaging or computed tomography (CT) scan. The initial etiologic workup included vascular imaging, electrocardiogram, and routine blood studies. Vascular imaging consisted of magnetic resonance (MR) or CT angiography of cerebral and cervical vessels, performed in all patients, and carotid duplex ultrasonography. A transesophageal echocardiography was performed in all patients without potential cause of stroke after initial workup. PFO was assessed at rest and during provocative maneuvers using intravenous injection of agitated saline.[17] Other diagnostic tests including 24-hour Holter, thrombophilia screening (antithrombin III, protein S and protein C deficiencies, Factor V Leiden and prothrombin G20210A mutations, hyperhomocysteinemia, lupus anticoagulant, anticardiolipin, and anti-β2 glycoprotein 1), and CSF analysis were performed in patients without potential cause of stroke after transesophageal echocardiography and depending on clinical findings.

The present study was approved by our local institutional review board. These data were collected by a retrospective review of our institutional electronic database. Because all data had been acquired as part of routine clinical care, consent to participate in the study was not required from the patients.

Causes of stroke were classified and graded using the ASCOD (A for atherosclerosis, S for small-vessel disease, C for cardiogenic embolism, O for other definite cause, and D for dissection) phenotyping system. Patients without ASCOD grade 1 (potentially causal) cause of stroke were classified as cryptogenic.[18] PFO is not considered a grade 1 cause of stroke in ASCOD, except in rare cases with evidence of paradoxical embolism. A stroke is ascribed to large vessel atherosclerosis in case of atherosclerotic stenosis (≥50%) or occlusion of the symptomatic artery. Large vessel atherosclerosis is also considered a potential cause of stroke when there is evidence of a thrombus attached to a nonobstructive plaque (<50% stenosis) of the symptomatic artery. However, nonobstructive carotid thrombus is a heterogeneous condition. In many cases, the underlying carotid wall is free from atherosclerotic lesions and the cause of thrombus formation is not clear.[19] For this reason, we decided to include patients with nonobstructive carotid thrombus in the cryptogenic subgroup.

Intracranial artery stenosis was visually graded by a senior neuroradiologist using MR or CT angiography. Extracranial carotid artery stenosis was graded using MR angiography or CT angiography and duplex ultrasonography.[20]

Extracranial carotid nonobstructive (<50% stenosis) plaque and thrombus were assessed with duplex ultrasonography (Philips IU22, Bothell, WA, USA) using B-mode unenhanced images in the longitudinal and horizontal planes with and without color flow. We used consensual criteria for plaque definition.[21] A thrombus was suspected in case of a intraluminal structure attached to the carotid wall and mobile with the cardiac cycle. Thrombus was confirmed by a complete disappearance or significant regression of the initial intraluminal structure on repeat duplex ultrasonography.

Control Subjects

Control subjects matched for age (±3 years) and sex, and living in the same geographic area, were randomly selected using a 1:1 ratio among the participants in the MONA LISA population-based study recruited between 2006 and 2007. The MONA LISA study protocol was approved by the appropriate independent ethics committee and written informed consent was obtained from all the participants.[22]

Definition of Risk Factors

History of hypertension was defined as a persistent elevation of systolic blood pressure (≥140 mmHg) or diastolic blood pressure (≥90 mmHg) documented before a stroke, or treatment with antihypertensive drugs before a stroke. History of diabetes was defined as a previous diagnosis of Type 1 or Type 2 diabetes (fasting glucose level ≥1.26 g/L), or use of an antidiabetic drug. For tobacco use (any type of smoking: cigarettes, cigars, pipe), patients and controls were classified as current smokers or former/never smokers. Former smoking referred to a consumption stopped for more than 3 months. Use of statins and oral contraceptive pill (combined or progestative only) was recorded.

A detailed lipid profile that includes total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and triglyceride concentrations was performed on selected patients at the discretion of the neurologist for each patient. Lipid assessment was performed on the day after admission to the hospital. A 20-mL blood sample was drawn into a disodium EDTA tube (after the subjects had fasted for at least 10 hours), stored at room temperature, and centrifuged within 4 hours. Cholesterol and triglyceride concentrations were measured using enzyme assays. HDL cholesterol was measured after sodium phosphotungstate/magnesium chloride precipitation. LDL cholesterol was determined by Friedewald's equation only if triglyceride levels were lower than 4.56 mmol/L (4 g/L).