Nontraditional Lipid Variables Predict Recurrent Brain Ischemia in Embolic Stroke of Undetermined Source

Patricia de la Riva, MD,* Maitane Zubikarai, MD,† Cristina Sarasqueta, MD,‡ Mikel Tainta, MD,*,§ Amaia Muñoz-Lopetegui, MD,* Naiara Andrés-Marín, MD,* Félix González, MD,* Noemi Díez, MD,* Ana de Arce, MD,* Alberto Bergareche, MD,*,‡ Adolfo Lopez de Munain, PhD,*,†,‡,‖ and Maite Martínez-Zabaleta, MD*,†

Objective: The aims of this study are, first, to calculate the risk of brain ischemia recurrence and embolic source diagnosis in the follow-up of patients with ESUS (embolic stroke of undetermined source) and, second, to identify the predictors of these events including cardiologic, laboratory, and clinical factors. *Methods:* A retrospective observational cohort study of stroke patients admitted to the stroke unit in a single tertiary hospital from 2012 to 2014 was performed. Patients fulfilling ESUS criteria were identified and followed by medical history review until March 2016. Statistical analysis comprised Kaplan–Meier analysis and Cox proportional hazards multivariate analysis including clinical characteristics, cardiologic data, and blood test results. *Results:* One hundred and thirteen patients, 8.3% of the overall stroke patients, filled ESUS criteria and they were younger, had less vascular risk factors, and suffered milder strokes than the remainder of stroke patients. Median follow-up of ESUS was 25.6 months. Risk of brain ischemia recurrence was 8.4, 10.8, and 15% at 12, 24, and 36 months, respectively, and was associated to age (HR 1.07, $P = .027$) and to a higher total cholesterol (TC)/high-density lipoprotein (HDL)-cholesterol (HR = 1.38, $P = .002$) and low-density lipoprotein (LDL)-cholesterol/HDL-cholesterol ratios (HR = 1.48, $P = .001$). The risk of major embolic source diagnosis was 6.7, 7.8, 13.6% at 12, 24, and 36 months, and was associated to female sex (HR = 6.05, $P = .021$). *Conclusions:* Brain ischemia recurrence increases with age and increased values of nontraditional lipid variables, TCHDLr and LDLHDLr, in ESUS patients, and women are more frequently diagnosed with a major embolic source in the follow-up. **Key Words:** Ischaemic stroke—cardioaortic embolism—prevention—statins—lipid profile—cholesterol.

From the *Department of Neurology, University Hospital Donostia, San Sebastián, Spain; †Faculty of Medicine, University of the Basque Country, Leioa, Spain; ‡Neurosciences Area, Biodonostia Institute, San Sebastián, Spain; §CITA-Alzheimer Foundation, San Sebastian, Spain; and ‖Center for Biomedical Research in Neurodegenerative Diseases Network (CIBERNED), San Sebastián, Spain.

Received January 10, 2017; revision received March 15, 2017; accepted March 21, 2017.

The work was performed in the Neurology Department of Donostia University Hospital in San Sebastian, Spain.

Address correspondence to Patricia de la Riva, MD, Department of Neurology, University Hospital Donostia, Paseo Dr. Beguiristain 109, 20014 Donostia, Guipuzcoa, Spain. E-mail: patricia.delariva@gmail.com, https://twitter.com/PatriciaDlrv.

1052-3057/$ - see front matter

http://dx.doi.org/10.1016/j.jstrokecerebrovasdis.2017.03.024

Introduction

In 2014, the term *embolic stroke of undetermined source* (ESUS) was coined by the Cryptogenic Stroke (CS)/ESUS International Working Group with specific diagnostic criteria[1]: a visualized nonlacunar brain infarct in the absence of (1) extracranial or intracranial atherosclerosis causing greater than or equal to 50% luminal stenosis in arteries supplying the area of ischemia; (2) a major risk cardioembolic source; and (3) any other specific cause of stroke (e.g., arteritis, dissection, migraine/vasospasm, drug misuse). Major risk sources of cardioembolism included the following: permanent or paroxysmal atrial fibrillation (AF), sustained atrial flutter, intracardiac thrombus, prosthetic cardiac valve, atrial myxoma or other cardiac tumors, mitral stenosis, recent (<4 weeks) myocardial infarction, left ventricular ejection fraction less than 30%, valve vegetations, or infective endocarditis. Lacunar stroke was defined as a subcortical brain infarct less than or equal to 1.5 cm in largest dimension in the distribution of the small, penetrating cerebral arteries.

To date, antiplatelet therapy is indicated in patients with a stroke of undetermined cause as secondary prophylaxis. However, as recurrence rates in this group of patients are relatively high and considering recent evidence suggests the origin may eventually be embolic,[2,3] a potential benefit of anticoagulants in reducing the risk of stroke recurrence has been suggested for this group of patients and subsequently for ESUS.

Nevertheless, ESUS is a relatively new term and very little data exist about the real course of these patients after the stroke event. We therefore conducted this study with the aim of, first, calculating the risk of stroke recurrence or embolic source diagnosis in the follow-up of ESUS patients and, second, more importantly, identifying the predictors of these events including cardiologic, laboratory, and clinical factors.

Methods

Study Population

A retrospective observational cohort study was carried out at a single tertiary center, Donostia University Hospital. The study population and data were derived from the institutional registry based on the National Stroke Registry RENISEN, a registry funded by the Cerebrovascular Diseases Group of the Spanish Neurological Society, with the aim of facilitating collaborations between different centers and providing a tool for individual registry.

The study included all patients with a stroke admitted to the stroke unit within 24 hours after symptom onset between January 2012 and December 2014. Patients with transient ischemic attack (TIA) or hemorrhagic stroke were excluded. Stroke was confirmed by neuroimaging, magnetic resonance imaging, or head cranial tomography.

ESUS Definition and Follow-Up

The criteria proposed by the CS/ESUS International Working Group[1] were applied to identify ESUS patients. Patients with cryptogenic stroke and incomplete cardiac study were excluded from the ESUS group.

After that, ESUS patients who survived the index stroke and were discharged were followed retrospectively by electronic medical history review from the stroke until March 2016. ESUS patients received standard neurological care, and additional diagnostic studies, such as transesophageal echocardiogram or repeated Holter ECG (electrocardiography) study, were performed or not according to their own physician criteria. A stroke neurologist performed all medical history reviews.

Data Collection

Prospectively recorded data in all stroke patients included the following: (1) demographics: sex and age, medical history, previous disability; (2) cardiovascular risk factors: hypertension, diabetes mellitus, smoking history, alcohol consumption; (3) previous medication; (4) time of stroke onset; (5) duration of hospitalization; and (6) stroke characteristics and patient disability at discharge and at 90 days after stroke onset.

Stroke severity was assessed by means of the National Institutes of Health Stroke Scale (NIHSS) score,[4] disability was measured with the modified Rankin Scale Score[5] and a score of 2 or less indicates functional independence. The $CHADS_2$ score and the CHA_2DS_2-VASc score were calculated as previously reported.[6,7]

Some other data were retrospectively gathered for the purpose of the study in ESUS patients:

- Laboratory investigations including creatinine, urea, glucose, total cholesterol (TC), low-density lipoprotein-cholesterol (LDL-C), high-density lipoprotein-cholesterol (HDL-C), triglycerides (TG), vitamin B12, folates, leukocytes, neutrophils, uric acid, and C-reactive protein.

Lipid profile was extended with nontraditional variables that have been independently linked with cardiovascular risk: TC/HDL-C ratio (TCHDLr),[8] TG/HDL-C ratio (TGHDLr),[9] and LDL-C/HDL-C ratio (LDLHDLr).[10]

Blood tests were performed the next morning after hospital admission for the index stroke.

- Cardiologic data included left atrial dilatation (diameter over 3.8 cm); left ventricle dilatation (diastolic diameter over 5.3 cm); left ventricle hypokinesia; mitral valve dysfunction or malformation including prolapse, sclerosis, stenosis, and insufficiency; atrial septal aneurysm; patent foramen ovale; left ventricular ejection fraction; left atrial or ventricular thrombus; PR interval; supraventricular extrasystolia; atrioventricular block; and heart rate.