Prevalence of Fabry Disease in Young Patients with Stroke in Argentina

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Background: Fabry disease (FD) is an underdiagnosed cause of stroke in young adults, but the frequency of this association is largely unknown. We estimated the prevalence of FD in a nationwide cohort of young adults who had stroke and transient ischemic attack (TIA) in Argentina. *Methods:* This was a prospective, multicenter study of stroke and FD in young adults (18-55 years) conducted in Argentina between 2011 and 2015. Patients were enrolled if they had had a TIA or an ischemic or hemorrhagic stroke within the previous 180 days. FD was diagnosed by measuring α-galactosidase A activity (males) and through genetic studies (females). *Results:* We enrolled 311 patients (54% men, mean age: 41 years). Ischemic events occurred in 89% of patients (80% infarcts, 9% TIA) and hemorrhagic strokes in 11%. One female (.3% of the total group, 1% of the cryptogenic ischemic strokes) had the pathogenic mutation c.888G>A/p.Met296Ile /Exon 6 on the *GAL* gene. Her only other manifestation of FD was angiokeratoma. Eighteen females had nonpathogenic intronic variations: c.-10C>T, c.-12G>A, or both. Two patients had the nonpathogenic mutation D313Y, while a third had the likely benign mutation S126G. *Conclusions:* FD was identified in 1 patient (.3%) in this first Latin American study. The patient presented with a late-onset oligo-symptomatic form of the disease. A large number of nonpathogenic mutations were present in our cohort, and it is essential that they not be mistaken for pathogenic mutations to

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avoid unnecessary enzyme replacement treatment. **Key Words:** Fabry disease—stroke—young—cerebrovascular disease—mutations.

Introduction

Stroke is a leading cause of death and disability worldwide.[1] From 5% to 10% of all strokes occur in patients under 45 years old, generating considerable morbidity and mortality in this age group. The crude annual incidence rate of stroke in young adults is estimated at between 8 and 19 per 100,000,[2] whereas mortality rates range between 2.9% at 1 year and 26.8% after 20 years.[3] The causes of stroke in this group are very diverse but remain undetermined in up to 40% of patients after extensive workup.[4] Moreover, only limited information exists regarding stroke in young adults in Latin America.[5-9]

Fabry disease (FD) is an X-linked lysosomal storage disorder characterized by decreased or absent activity of lysosomal enzyme α-galactosidase A (α-GAL A); it has been identified as an underdiagnosed etiology of stroke in the young.[10] The prevalence of CVA in FD patients identified in the Fabry Outcome Survey (FOS) was 11% in males and 15% in females, a prevalence 12 times higher than observed in a comparable non-Fabry population.[11] In the global Fabry Registry, 6.9% of males and 4.3% of females with FD had had an ischemic or hemorrhagic stroke. Furthermore, 50% of males and 38% of females had their stroke before the diagnosis of FD was made.[12] Among patients with FD and no history of stroke or transient ischemic attack (TIA), 44% had silent brain infarcts on brain magnetic resonance imaging (MRI).[13] Rolfs et al reported that 4.9% of males and 2.4% of females with cryptogenic stroke younger than 55 years suffered from FD, which corresponds to approximately 1.2% of young stroke patients overall.[10]

Several other studies screening for FD in young stroke patients throughout the world have yielded conflicting results.[14-22] We herein report the Argentinean Initiative for the Study of Young patients with Stroke and Fabry disease (AISYF Study), the first national, multicenter, prospective study to investigate the association between stroke and FD in young Latin American adults.

Methods

Study Design and Patient Selection

We performed a prospective, multicenter, nationwide study of ischemic and hemorrhagic stroke and FD in young adults in Argentina. The study was conducted at 22 centers across the country, coordinated by the Department of Neurology at Hospital Británico de Buenos Aires between January 2011 and December 2015. Patient enrollment required written informed consent.

We ultimately enrolled 311 patients between the ages of 18 and 55 years with either a TIA (defined as a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction),[23] an acute ischemic stroke (defined as a focal neurological deficit due to infarction of central nervous system tissue),[23] or an intracerebral hemorrhage (defined as a focal neurological deficit associated with focal collection of blood within the brain parenchyma).[24] Patients were enrolled within 180 days of their cerebrovascular event. We excluded patients with ischemic stroke following subarachnoid hemorrhage, cancer, or trauma, as well as patients with a hemorrhagic stroke due to a vascular malformation (e.g., aneurysm, arteriovenous malformation, or cavernous hemangioma) or when suspected to be related to cancer, trauma, or anticoagulation. We also excluded patients with either an epidural or subdural hemorrhage.

Stroke Subtype Classification and Etiological Workup

After informed consent was obtained from the patients, demographic data, cardiovascular risk factors, the presence of signs and symptoms of FD, and clinical and neuroimaging data were registered in a database. Head computed tomography or MRI had been performed in all patients before enrollment. After enrollment, all patients underwent comprehensive etiological investigations, including brain and vascular imaging, electrocardiography, echocardiography, extensive laboratory testing, and FD enzymatic and genetic studies. Information on comorbidities and vascular risk factors were collected prospectively using a standardized prespecified case report form. All variables analyzed were checked for completeness, range, and outliers. Trial of ORG 10172 in acute stroke (TOAST) criteria were used to define the clinical subtypes of ischemic stroke.[25] Intracerebral hemorrhage was categorized by location.[24,26] Demographic information and comorbid conditions of our patients will be reported separately.

Diagnosis of Fabry Disease

Measurement of α-GAL A activity (in all males) was determined using dried blood spots on filter paper[27] and performed at the Instituto de Estudios Inmunológicos y Fisiopatológicos (IIFP) Facultad de Ciencias Exactas, Universidad Nacional de La Plata-Consejo Nacional de Investigaciones Científicas y Técnicas, La Plata, Argentina. When deficient activity was detected, confirmation of the enzymatic result was performed in leukocytes from whole blood. Sequencing of the *GLA* gene was per-