Screening for Fabry disease in patients with ischaemic stroke at young age: the Italian Project on Stroke in Young Adults

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Sirs,

Fabry disease (FD) is a rare, X-linked, lysosomal storage disorder caused by a total lack or deficiency of the α-galactosidase A (α-GAL A) enzyme, encoded by the *GLA* gene. Cerebrovascular complications are a major cause of morbidity and early mortality in both male and female patients with FD [1]. Ischaemic stroke (IS), caused by cerebral vasculopathy or cardiac embolism, is the most prevalent type and occurs at an earlier age than is usual in the general population. Screening studies conducted so far in cohorts of young patients with IS of undetermined origin have reported a wide range of FD prevalence (0.0–3.9%), which is probably the consequence of differences in the study populations, stroke subtypes and screening methods [2]. Therefore, it is still a matter of debate whether routine screening for FD in young patients with IS of unknown origin is warranted.

This study is part of the Italian Project on Stroke in Young Adults (IPSYS) project, a countrywide network of neurological centers with a special interest in cerebral ischaemia at a young age across Italy, aimed at recruiting patients with first-ever acute stroke who fulfill the following criteria: (i) age 18–45 years and (ii) computed tomography- or magnetic resonance imaging-proven cerebral infarction, in the setting of a hospital-based, multicenter, observational study [3,4]. Fourteen of the 23 centers included in the IPSYS network participated in the present analysis. According to the IPSYS protocol, IS due to sinus venous thrombosis, vasospasm after subarachnoid hemorrhage, cardiac surgery, occurring as an immediate consequence of trauma, and iatrogenic strokes were excluded. For the present analysis, we also excluded patients who suffered from an IS secondary to endocarditis, cardiac tumor, spontaneous dissection of the carotid or vertebral arteries, cerebral vasculitis, hematological disorders (hemoglobinopathy, polycythemia vera, essential thrombocytopenia, thrombocytosis, thrombotic thrombocytopenic purpura, heparin-induced thrombocytopenia, antiphospholipid syndrome), monogenic diseases causing stroke (i.e. cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) and illicit drug abuse. Informed consent was provided by all study participants.

According to the screening protocol, all patients underwent full genetic sequencing of the α-GAL A gene for mutation analysis. Peripheral blood was collected, using EDTA as an anticoagulant. DNA samples were isolated from whole blood by column extraction (GenElute Blood Genomic DNA Kit, Miniprep; Sigma-Aldrich, St. Louis, MO, USA). Seven pairs of primers were designed for the analysis of seven target regions containing the seven exons of the GLA gene and the regulatory sequences flanking them. Polymerase chain reaction products were purified and sequenced to identify suspected mutations, using an automated DNA sequencer at BMR Genomics (Padova, Italy). We did not plan to measure leukocyte α-GAL A activity in males, except in those cases in which molecular screening had revealed variants of unknown significance.

A group of 350 consecutive patients admitted for acute IS qualified for inclusion. The characteristics of this cohort are reported in Table 1. The mean age was 36.9 ± 6.8 years and 192 (54.9%) were men. None of the patients had causative mutations in the GLA gene responsible for classical FD. Two females (aged 31 and 41 years, respectively) carrying the D313Y genetic variant in the GLA gene (Gly937Ala alteration at cDNA level), had normal α-GAL A activity in plasma, no evidence of other FD manifestations (in particular,

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Table 1 Demographic and clinical characteristics of the study group

Variable	
Age (years)	36.9 ± 6.8
Male	192 (54.9)
Hypertension	65 (18.5)
Diabetes mellitus	12 (3.4)
Current smokers	143 (40.9)
Hypercholesterolemia	87 (24.8)
History of migraine	
No migraine	244 (69.7)
MO	56 (16.0)
MA	37 (10.6)
Oral contraceptives[a]	58 (36.7)
Family history of stroke	121 (34.6)
History of ischaemic heart disease	7 (2.0)
Stroke etiologic subtypes (TOAST criteria)[b]	
Large-vessel atherosclerosis	30 (8.6)
Cardioembolism	122 (34.8)
Small-vessel occlusion	43 (12.3)
Stroke of other determined etiology	75 (21.4)
Stroke of undetermined etiology	80 (22.9)

Data are given as mean ± SD or *n* (%).
[a]In females; [b]According to Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria. MO, migraine without aura; MA, migraine with aura.

acroparaesthesia, hypohidrosis, gastrointestinal symptoms, angiokeratoma, cornea verticillata, cardiac or kidney disease, and/or cerebral magnetic resonance imaging/magnetic resonance angiography abnormalities, including white matter hyperintensities, dolichoectasia or pulvinar sign) in their previous medical history as well as over an 84-month (case 1) and 20-month (case 2) follow-up after the index event, and no relatives with clinical features consistent with the hypothesis of FD.

For many patients with FD, IS is the first serious clinical manifestation of the disease and may be the event that leads to a diagnosis. Clinicians should be therefore aware of FD as a cause of early IS. In line with other previous reports, however, we were unable to identify any patients with FD in our cohort, in spite of the screening procedure based on molecular genetic testing that we used, which is expected to overcome the limitations of α-GAL A activity assay. This reinforces the prevailing idea that systematic screening for FD is not warranted even in young patients with IS of undetermined origin, and that an appropriate clinical/neuroradiological assessment should guide clinicians in the diagnostic process. In this regard, research should focus more on the application of clinical, biochemical and neuroimaging markers for patient stratification [2,5].

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Disclosure of conflicts of interest

The authors declare no financial or other conflicts of interest.

Role of the sponsor

The sponsor had no role in the design and conduct of the study; the collection, management, analysis and interpretation of the data; the preparation, review or approval of the manuscript; or the decision to submit the manuscript for publication.

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Appendix 1

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