Screening for Fabry Disease in Patients with Ischemic Stroke at Young Age.

The Italian Project on Stroke in Young Adults (IPSYS)

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Background

Fabry disease (FD) is a rare, X-linked, lysosomal storage disorder caused by a total lack or a 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. Screening studies conducted so far in cohorts of young patients with ischemic stroke of undetermined origin have reported a wide range of FD prevalence (0.0% to 3.9%), which is likely the consequence of differences in the study populations, stroke subtypes, and screening methods. Therefore, whether routine screening for FD in young patients with IS of unknown origin is warranted is still matter of debate.

Subjects and Methods

We analyzed data from consecutive patients with first-ever IS of undetermined origin who were 18 to 45 years of age, as part of the multicenter Italian Project on Stroke in Young Adults (IPSYS). Fourteen out of the 23 centers included in the IPSYS network participated to the present analysis. As per 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 from screening patients that suffered from an IS secondary to endocarditis, cardiac tumour, spontaneous dissection of the carotid or vertebral arteries, cerebral vasculitis, hematological disorders, monogenic diseases causing stroke, and illicit drug abuse. According to the screening protocol, all these patients underwent full genetic sequencing of the α-GAL-gene for mutation analysis.

Results

A group of 350 consecutive patients admitted for acute IS qualified for inclusion. All gave consent to participate. The characteristics of this cohort are reported in Table 1. The mean age was 36.9 ± 6.8, and 192 (54.9%) were men. None of the patients turned out to have causative mutations in the GLA gene responsible for classical FD. Two patients carrying the D313Y genetic variant in the GLA gene (Gly937Ala alteration at cDNA level) had normal α-Gal A activity in plasma and no evidence of other FD manifestations.

Discussion

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 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.

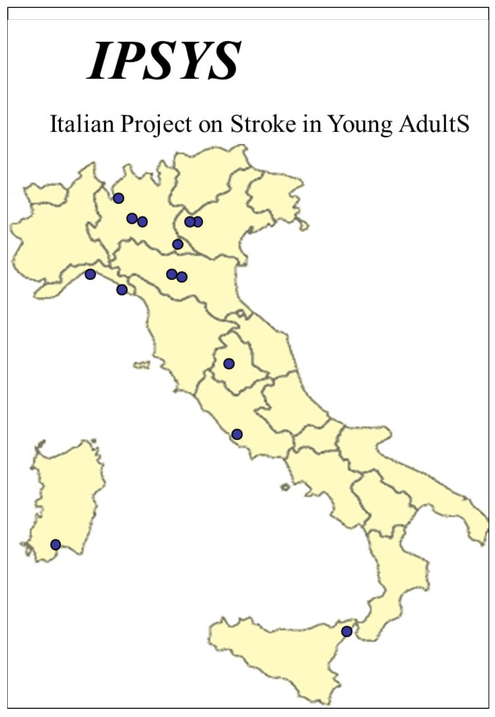

Fig.1: IPSYS Project

Variable	
	mean ± SD
Age, yrs	36.9 ± 6.8
	n (%)
Men	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	58 (36.7)
Family history of stroke	121 (34.6)
History of ischemic heart disease	7 (2.0)
Stroke etiologic subtypes (TOAST CRITERIA)	
Large vessels 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)

Table 1: Demographic and clinical characteristics of the study group.

Trial	Patients Screened, n	Patients With Fabry Disease, n (%)		Age (Range)	Mean Age at First Stroke
		Men	Women		
Rolfs et al	721	21 (4.9)	7 (2.4)	18–55	38.4 (men); 40.3 (women)
Brouns et al	103	0	0	16–60	51.3
Wozniak et al	154	1* (0.6)	…	15–49	Not stated
Brouns et a	1000 (573 ischemic stroke)	2 (0.4)	3 (0.7)	18–60	48.2
Rolfs et al	5023 (3396 ischemic stroke)	11 (0.4)	16 (0.8)	18–55	Not stated
Baptista et al	493 (364 ischemic stroke)	7 (2.3)	5 (2.6)	18–55	45.4
Marquardt et al	1046	0	0	24–103	…
Sarikaya et al	150 (135 ischemic stroke)	0	0	18–55	43
Dubuc et al	100 ischemic stroke	1 (1.0)	0	16–55	40.5
Kilarsky et al	994 lacunar stroke	0 (0.0)	0 (0.0)	<70	56.7
Fancellu et al	178 any stroke (plus)	1 (0.5)	1 (0.5)	18-55	48.4
Romani et al	108 ischemic stroke/TIA	1 (0.9)	2 (1.8)	18-60	48.0
Song et al	357 ischemic stroke/TIA	0 (0.0)	0 (0.0)	18-55	Not stated
Goeggel et al	624 ischemic stroke/TIA	1 (0.2)	1 (0.4)	16-55	Not stated
Poli et al	353 ischemic stroke (IPSYS)	0 (0.0)	0 (0.0)	18-45	37.3

*All patients in this study were men

Modified from Kolodny E et al. Stroke 2015;46:302-313

Table 2: Incidence of Fabry Disease among younger patients with stroke in epidemiologic studies

1. Kolodny E, Fellgiebel A, Hilz MJ, et al. Cerebrovascular involvement in Fabry Disease. Current status of knowledge. Stroke 2015;46:302-313
2. Pezzini A, Grassi M, Lodigiani C, et al; Italian Project on Stroke in Young Adults Investigators. Predictors of migraine subtypes in young adults with ischemic stroke. The Italian Project on Stroke in Young Adults (IPSYS). Stroke. 2011;42:17-21
3. Kilarski LL, Rutten-Jacobs LCA, Bevan S, et al, UK Young Lacunar Stroke DNA Study. Prevalence of CADASIL and Fabry Disease in a cohort of MRI defined younger onset lacunar stroke. PloS ONE 2015;10:e0136352

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