Causative Classification of stroke System (CCS) to investigate pathogenesis of ischemic stroke in Fabry disease: a pilot experience

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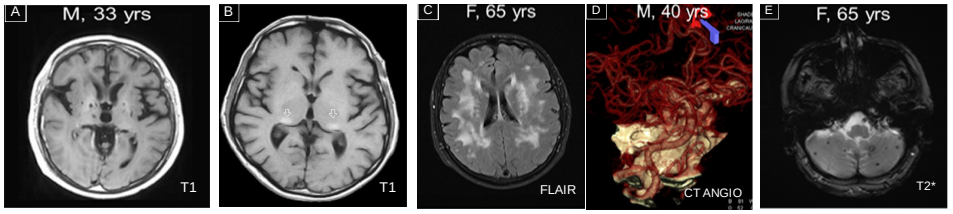
Introduction and aimes

Fabry disease (FD) is a rare X-linked disorder resulting from a defect in α-galactosidase A gene and the consequent storage of glycosphingolipids (Gb3) in organs. In Central Nervous System FD vasculophaty causes an increased risk of TIA and strokes (Fig. 1).
We aimed to define the characteristics and mechanism of ischemic stroke in a clinical series with FD.

Fig.1 *Central nervous system involvement in Fabry's disease*



A) Lacunar (and territorial) strokes; B) Pulvinar's sign; C) White matter disease; D) Basilar artery dolichoectasia; E) Cerebral microbleeds

Methods

We conducted a retrospective observational study of 70 consecutive patients referred to the Multidisciplinary Center for FD of Careggi University-Hospital, Florence.
We used the computerized CCS[1] (Causative Classification System for ischemic stroke) available at https://ccs.mgh.harvard.edu/ccs_form.php to assess ischemic stroke's pathogenesis.

Tab.1 *Early Fabry's disease symptoms*

	N=70
Angiokeratoma	27 (38.6%)
Acroparesthesia Mean age at onset (years)	40 (57.1%) 13 (±12.98)
Hypohidrosis	25 (35.7%)
Hyperthermia	7 (10.0%)
Cornea verticillata	31 (44.3%)
Proteinuria	25 (35.7%)
Hearing loss	27 (38.6%)
Sudden hearing loss	6 (8.6%)

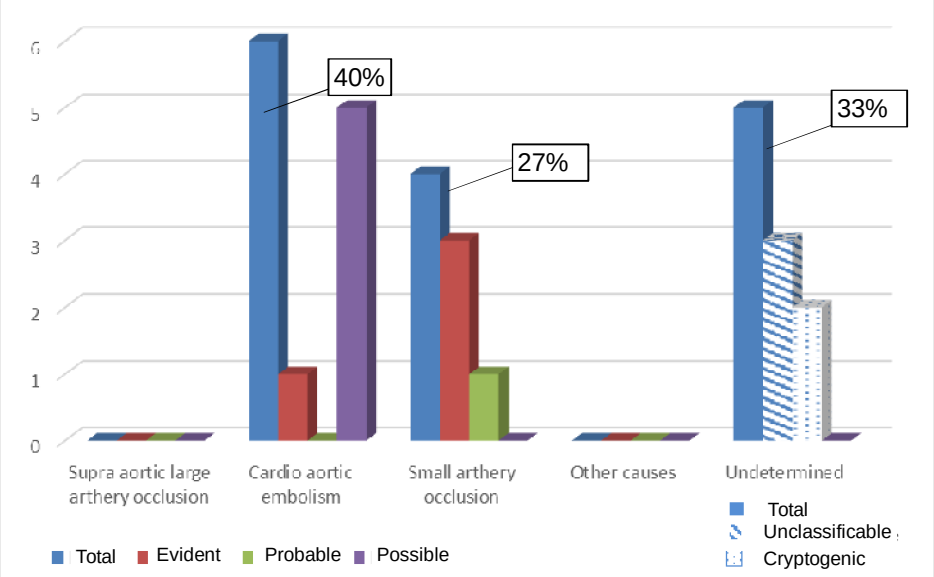
Tab.2 *Major organ involvement*

	N=70
Stroke	15(21.4%)
Hypertrophic cardiomyopathy	38(54.3%)
Angina	11(15.7%)
Myocardial infarction	2(2.9%)
Bradyarrhythmia	6(8.6%)
Pacemaker	4 (5.7%)
Tachyarrhythmia	12(17.1%)
Creatinine (mg/dl, mean)	3.19 (±12.75)
Dialysis	4 (5.7%)
Kidney transplant	3 (4.3%)
Deep venous thrombosis	4 (5.7%)

Results

From December 2010 to August 2016, 70 consecutive patients (female: 64.3%; mean age 49.1 ± 17.3 SD years) with enzimatic and/or genetic diagnosis of FD underwent to a follow up visit (Tab. 1, 2). The frequency of ischemic stroke was 21.4% (female: 66.7%) with a mean age at onset of 48.9 ± 18.9 SD years (min 19.7, max 91.7 years).
Two of 15 strokes (13.3%) were classified as cryptogenic on CCS (Fig. 2). Cardioembolism was represented in 6 cases (40.0%), with 5 possible and 1 evident cardioembolic sources. Small artery occlusion was represented in 4 patients (26.7%), with 1 probable and 3 evident lacunar strokes. Three patients were unclassified because the CCS categories "possible cardioembolism" and a "possible small artery occlusion" were coexistent.

Fig.2 *Ischemic stroke pathogenesis in Fabry's patients using CCS*



Cardioembolism (40%) and small artery occlusion (33%) are two important ischemic stroke's mechanism in Fabry's disease.

Screening for Fabry's disease only in cryptogenic stroke could exclude from the diagnosis some Fabry's patients.

Conclusions

In our experience, ischemic stroke is an important complication of FD that occurs in 21.4% of FD patients. The recorded age for troke onset (48.9 years) is higher than as expected from previous studies[2]. Researching FD as the possible cause of stroke only in adults with
the classical definition of juvenile stroke (<45 years) may avoid the diagnosis in a significant proportion of patients. Using CCS, cerebrovascular mechanisms more frequently associated with stroke are "possible cardioembolism" and "evident small artery occlusion", according to the current knowledge about stroke pathogenesis in FD patients.
On the other hand, cryptogenic stroke, where FD Is frequently researched[3], accounts only for a small proportion of cases. According to this, screening for FD only in cryptogenic strokes could exclude from diagnosis some Fabry patients.

References

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