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REVIEW

Stroke and Fabry disease

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Abstract Fabry disease (FD) is a rare inherited disorder of the metabolism, associated with renal, cardiac, and cerebrovascular complications. Ischemic and hemorrhagic stroke in FD present with a similar proportion to that observed in the general population, but usually at an early age. Ischemic stroke may result from cardiac embolism, large and small vessel disease, while hemorrhagic stroke is usually attributed to hypertension. Deposition of glycosphingolipids in endothelial cells results in a specific FD vasculopathy that contributes to the different vascular phenotypes. Neuroimaging features of cerebrovascular involvement in FD include white matter lesions, dolichoectasia, and the "pulvinar sign", a T1 MRI hyperintensity of the posterior thalamus. The role of enzymatic replacement therapy in the prevention of stroke remains to be established, but its utilization should be considered in FD stroke patients, for prevention of renal and cardiac complications, together with general prevention measures. Enzymatic replacement therapy increased our awareness of FD, underlining the importance of incomplete phenotypes in specific settings such as stroke. An overview of studies on the prevalence of FD in stroke patients is presented. Available data suggest that prevalence of FD is similar to some of the rare causes of stroke usually considered, and that classic features of the disease may be absent or more subtle. Moreover, FD should be considered in both cryptogenic and all-cause stroke. The role of FD in stroke on a multifactorial basis and the identification of a putative "stroke variant" are questions that need to be further elucidated in future studies.

Keywords Stroke · Fabry disease

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Introduction

Over the past several years, new research findings have led to increasing attention to central nervous system manifestations of Fabry disease (FD) [1]. The advent of enzymatic replacement treatment (ERT), available since 2001 [2], promoted increased awareness of the diagnosis of this rare disorder and underlined the importance of FD in specific settings, such as stroke. In fact, phenotypic heterogeneity in FD suggests that it is likely that some patients with isolated manifestations may remain undiagnosed [3]. While the incidence of FD has been estimated to be approximately 1 in 40,000, epidemiological data suggest that prevalence of later-onset phenotypes may be as high as 1 in 4,600 [4]. On the other hand, several recent studies suggest that prevalence of FD in young stroke patients may be similar to some of the rare potential causes usually considered in this setting [5–9]. Furthermore, it is at least conceivable that FD may play a role in stroke on a multifactorial basis [10].

Stroke is an important feature of FD, but the low prevalence of the disorder suggests that, for the stroke neurologist, recognizing FD among patients with stroke may be more relevant than possessing a comprehensive knowledge of FD. In this paper we address the characteristics of stroke in FD and the different FD cerebrovascular imaging phenotypes, and, subsequently, we perform an

overview of available data on the prevalence of FD in stroke patients.

Stroke in Fabry disease

Fabry disease

FD (Anderson-Fabry disease: Online Mendelian Inheritance in Man No. 301500) is a rare, panethnic, X-linked lysosomal storage disorder of glycosphingolipid metabolism due to mutations in the alpha-galactosidase (α-GAL) gene (*GLA*). Deficient plasma and leucocyte α-GAL activity leads to accumulation of globotriaosylceramide and related glycosphingolipids in tissues, including in vascular endothelial and smooth muscle cells, resulting in progressive organ dysfunction [11]. Classic FD phenotype features dermatologic (angiokeratomas, i.e. small, raised, dark-red spots, that occur singly or in clusters, usually in the lower back, groin, buttocks and upper thighs, Fig. 1), ophthalmologic (cornea verticillata, i.e. whorl-like corneal rays emanating from a single vertex, detectable by slit lamp examination, and rarely of visual significance), and neurologic involvement (painful neuropathy and hypohidrosis) [12]. Early neural damage primarily involves the small fibers of the peripheral and autonomic nervous systems, with associated childhood symptoms, such as intermittent acroparesthesia, episodic crises of pain and fever, hypohidrosis and heat/cold intolerance, resulting in impaired quality of life [13–15]. Audiovestibular and gastrointestinal symptoms have also been reported frequently in different FD series [16, 17]. Major causes of morbidity and mortality are usually attributed to the late renal (proteinuria and progressive renal failure), cardiac (hypertrophic cardiomyopathy) and cerebrovascular complications [12]. Early diagnosis is particularly relevant as ERT not only improves quality of life, but also prevents renal and cardiac complications, and may have a beneficial effect upon abnormal cerebral blood flow [12, 18, 19].

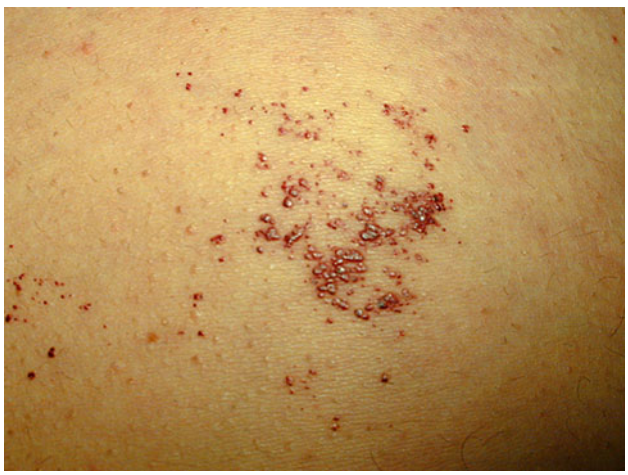

Fig. 1 Typical FD angiokeratomas over the buttocks of a female heterozygote for GLA gene mutation R118C, originally reported as associated with a late onset mild phenotype. Courtesy of Professor JP Oliveira, Genetics Department, Faculdade de Medicina da Universidade do Porto, Portugal

Incidence of stroke in Fabry disease

It has been estimated that during the course of FD 16% of patients will experience a stroke [17]. Nevertheless, although using different definitions of cerebrovascular complications, several studies reported higher incidences of stroke in FD [16, 20]. In the large cohort of the Fabry Registry ($n = 2{,}446$) stroke occurred in 6.9% of males and 4.3% of females [3]. In fact, stroke also occurs in women. Besides, white matter lesions (WML), the likeliest candidate marker of central nervous system vascular involvement, seem to present with comparable degrees in both genders [21]. These findings highlight the fact that female heterozygotes for this X-linked condition are not mere carriers, but are at risk of its life-threatening complications, namely stroke. Furthermore, females seem to be more likely than males to experience a stroke as their only FD clinical event [3].

Stroke has been considered a manifestation of end-stage FD. Nevertheless, patients with FD are known to experience strokes at an early age, when compared to the general population, in the Fabry Registry median age at first stroke was 39.0 years in males and 45.7 years in females [3]. Besides, cerebrovascular involvement in FD has been reported in the first and second decades [22, 23]. In spite of this, as in the general population, in patients with FD the incidence of stroke seems to increase with increasing age [3].

Type of stroke and pathophysiologic mechanism in Fabry disease

Ischemic and hemorrhagic stroke in FD seem to present with similar proportion to that observed in the general population [24], and transient ischemic attacks (TIA) seem to be a risk factor for stroke [3]. Hypertension has been considered the most important risk factor for stroke in FD, and its effect is probably potentiated by underlying vessel degeneration secondary to deposition of glycosphingolipids [3, 10]. It has been associated with small and large vessel disease, and it is thought to be responsible for the majority of cases of hemorrhagic stroke [1, 23–26]. In the Fabry Registry, patients with stroke were more likely to report a previous history of hypertension compared to FD nonstroke patients, 52.9% versus 20.5%, respectively [3]. Hypertension is attributed to renal dysfunction; nevertheless, FD

nephropathy is associated with only a moderate prevalence of hypertension, when compared to other chronic kidney diseases [26]. In the Fabry Outcome Survey ($n = 391$) the prevalence of hypertension was 57% among men and 47% among women [25]. Although poorly understood, accumulation of glycosphyngolipids may lead to progressive dysfunction of both small and large arteries of the brain [27]. Various abnormalities in cerebral blood flow [28], and in intracranial vessel walls [29] have been identified, and these may not be exclusive to the arterial system. Nevertheless, cerebral venous thrombosis was reported in a single case identified in a FD screening, without other features of FD, not allowing any further discussion on this issue [8]. Several mechanisms may contribute to FD vasculopathy, including: impaired endothelial function [29], dysregulated nitric oxide pathways [30], increased lipid levels and homocysteinemia [31], raised levels of leukocyte adhesion molecules [32], and a prothrombotic state [33] (for a detailed review on FD vasculopathy see reference 10). Dolichoectasia is frequently found in FD, particularly in posterior circulation large vessels, and may be related to mechanical weakening of the vessel wall, caused by glycosphingolypid deposition, and hypertension [5, 24, 28]. Pathophysiologic mechanisms of stroke frequently associated with dolichoectasia include: emboli formation and occlusion of penetrating arteries of the brainstem. Cardiac involvement in FD may also predispose to stroke, and previous history of arrhythmias is associated with stroke [3]. Although several cardiac disturbances can be observed, hypertrophic cardiomyopathy seems to be the characteristic cardiac phenotype [34]. Features that should raise diagnostic suspicion include several electrocardiographic clues, such as a short PR interval without a δ wave and a prolonged QRS interval, supraventricular and ventricular arrhythmias. Concentric left ventricular hypertrophy may be demonstrated on echocardiography, as well as selective thinning of the postero-inferior left ventricular wall. Delayed enhancement in this segment on cardiac MR is suggestive of FD. Echocardiographic and MR findings have been shown to be due to intramyocite accumulation of glycosphingolipids [35].

Prognosis and treatment of stroke in Fabry disease

Recurrent stroke is common in FD. A review of 51 cases indicated a stroke recurrence rate of 76% for male patients and estimated median time to first recurrence to be 6.4 years [24]. The same study indicated that when death was directly linked to the cerebrovascular event, death rates were 34.5% and 30%, respectively, for male and female patients. However, significant morbidity and mortality from concurrent complications of FD has been reported in patients experiencing strokes [3, 24]. According to the Fabry Registry, at the most recently available follow-up examination after their first stroke, 60% of males and 25.5% of females exhibit stage 3–5 chronic kidney disease and 66.1% of males and 59.5% of females have left ventricular hypertrophy [3]. Although not formally studied, there is no reason to suppose that the burden of disability arising from strokes in FD differs from that of cerebrovascular disease in the general population.

Treatment strategies in FD involve combined efforts from multiple specialties. The diagnosis and care of these patients is usually best handled at tertiary care centers. Prevention of stroke seems to be particularly important. Antiplatelet agents have been used for primary and secondary stroke prevention in FD, but their effectiveness in this setting has not been proved [36]. The same holds true for anticoagulants that may be necessary if embolic events that stem from cardiac causes are a concern. Aggressive blood pressure control is mandatory, and statin therapy should be considered [36, 37]. Adequate intake of vitamins should be promoted, especially in cases of hyperhomocysteinemia [38]. Evaluation of comorbid prothrombotic risk factors may help to identify those with higher stroke risk. Although there are no evidence based data, feasibility of thrombolysis in acute ischemic stroke in FD was recently illustrated, for the first time, in a case report [39].

In the past decade ERT has been used successfully in FD patients. For both agalsidase alfa (Replagal®, Shire Human Genetic Therapies, Inc., Cambridge, MA) and beta (Fabrazyme®, Genzyme Corporation, Cambridge, MA) enzyme preparations, initial studies were performed in a mouse model of FD. Subsequent placebo-controlled and open-label trials showed reduction in neuropathic pain and gastrointestinal symptoms and partial reversal of the vascular abnormalities [40]. Available evidence suggests that ERT may prevent, or help in normalizing, renal and cardiac complications. Whether this therapy changes the natural history of strokes attributable to FD is unclear. Strokes occurred during ERT with both preparations available and WML were shown to progress [41, 42], although anecdotal reports suggest that ERT may halt or reverse this process [43, 44]. Regardless of these data, ERT seems to improve cerebrovascular blood flow [18]. If age plays a role on the effect of ERT on stroke and WML progression is an issue that remains to be elucidated, but it seems reasonable to assume that treatment should probably be started before irreversible vascular damage has been done (for a comprehensive review on ERT see reference 40). Recognizing the importance of ERT, for the first time in 2011, the American Heart Association/American Stroke Association included in its guidelines ERT for patients with ischemic stroke or TIA and FD (*New recommendation, Class I*; *Level of Evidence B*) [45].

Cerebrovascular imaging phenotypes of Fabry disease

WML are widely accepted as the most prominent imaging finding in FD. WML in FD occur typically at a younger age than in patients without FD, and evidence of microvascular involvement in pediatric cases has been demonstrated [46]. In a longitudinal MRI study of 50 patients with FD (mean age 33 years) 52% had WML. Furthermore, all patients older than 55 years had WML, suggesting that age may also play a role [27]. Although a higher susceptibility of the posterior circulation has been proposed, WML present with an asymmetric widespread pattern generally indistinguishable from the pattern seen in age-related WML (Fig. 2) [21, 46–48]. WML in FD seem to progress [43, 49], and may be associated with silent ischemic stroke and cognitive dysfunction, similar to age-related WML. Nevertheless, a recent study showed only mild cognitive deficits, mainly in the attention domain, even in patients with extensive WML [50]. Further studies are needed to clarify if these deficits might precede significant cognitive decline. On the other hand, diffusion weighted imaging measures demonstrate brain tissue alterations in normal appearing white matter, even in patients with few WML [47, 51], showing a more promising ability to quantify clinically relevant alterations, similar to what has been found in age-related WML [52, 53]. Further evidence of small vessel involvement may be present, including lacunar infarcts (Fig. 2a) [52], and microbleeds demonstrated on MR gradient echo images (Fig. 2b) [54], similar to those found in age-related WML. Clinical significance of these features remains to be determined, but it is conceivable that they may contribute to cognitive impairment. Grey matter infarcts and brain atrophy have also been reported in association with WML [55, 56]. Although vascular dysfunction seems to be the underlying defect in WML, MR spectroscopy studies suggested that metabolic tissue alterations and neuronal dysfunction exist beyond cerebrovascular lesions [57, 58]. Differential diagnosis of WML occurring in FD with other diseases associated with WML is important, as sometimes patients may be misdiagnosed with other inherited small vessel disorders or multiple sclerosis [51, 59].

Stroke in patients with FD, when compared to the general population, seems to be more common in the posterior circulation [24, 29]. This may be related to a selective involvement of large vessels, with tortuosity, elongation and ectasia, of the vertebrobasilar system [24]. Nevertheless, anterior circulation vessels do not seem free of abnormalities [55]. These features, previously demonstrated in autopsy studies and conventional angiography, can now be depicted by CT or MR angiography (Fig. 3). Basilar artery diameter seems to be superior to other MRI measures for separation of FD patients from controls. Furthermore, this measure seems to differentiate FD stroke patients from age-matched non-FD stroke patients [60], and therefore, might be useful as a screening tool for FD in stroke patients.

The so-called pulvinar sign on MRI, a T1-hyperintensity of bilateral posterior thalamus, although not pathognomonic, as previously described [61, 62], seems to be rather specific of FD and to correlate with hypertrophic cardiomyopathy and severe renal involvement, but not with stroke [63]. Its frequency seems to increase with age, and a possible explanation implicates increased cerebral blood flow in the posterior circulation and selective vulnerability of the posterior thalamus. Microvascular mineralization is corroborated by some cases of hyperdensity on brain CT scans [61]. The vast majority of patients reported with the pulvinar sign are men, and although its significance is not

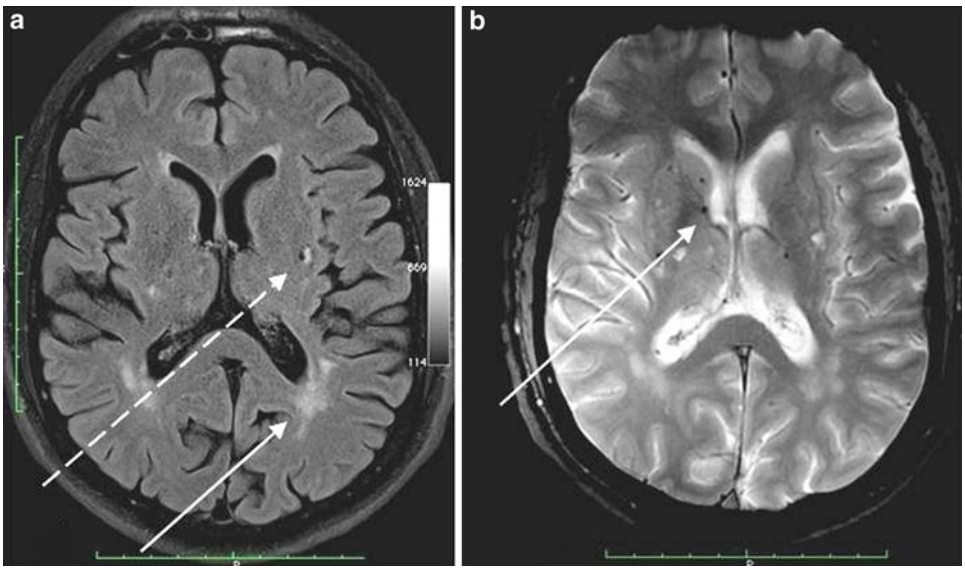

Fig. 2 Brain MRI axial sections of a 53-year-old male patient with FD. Diagnosis was established after stroke, despite presence of mild cardiac and renal involvement (*GLA* gene mutation F113L; plasmatic α-GAL 0.4 nmol/h/ml plasma, leucocyte α-GAL 0.8 nmol/h/mg protein). Deep white matter lesions (*white arrow*) and lacunar infarcts (*dashed arrow*) are depicted on FLAIR sequence (**a**), and microbleeds on T2* gradient echo image (**b**)

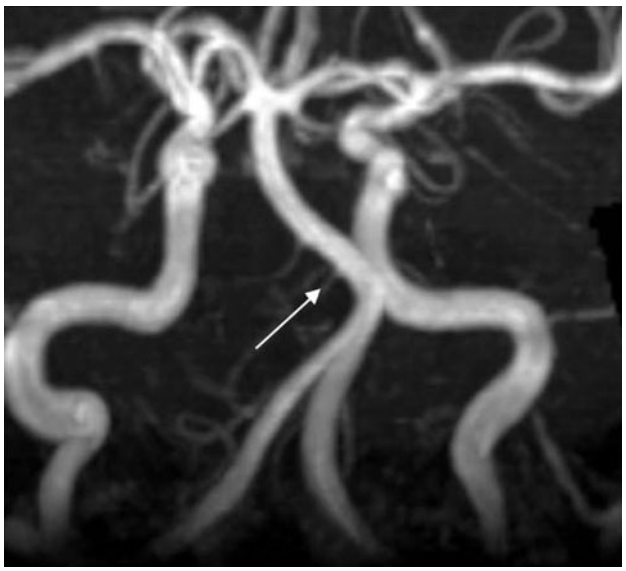

Fig. 3 TOF magnetic resonance angiography of the intracranial vessels of a 23-year-old male patient with FD presenting with a classic phenotype (*GLA* gene mutation Del239I [g. 10206del3 (ATA)]; plasmatic α-GAL 0.27 nmol/h/ml plasma, leucocyte α-GAL 0.38 nmol/h/mg protein). Tortuosity and elongation of the basilar artery (*white arrow*). Courtesy of Dr. Elsa Azevedo, Neurology Department, Hospital São João, Porto, Portugal

completely understood, it may be a marker of disease severity [64].

Stroke and Fabry disease

Screening for FD in high-risk populations became an important concern when ERT became available. Studies were undertaken in different settings portraying severe complications of FD, including renal insufficiency, left ventricular hypertrophy, and stroke [65]. In spite of this, we still need more data to understand the relationship between FD and stroke, and we have to be able put together data from these different screenings and data from FD registries. This purpose must, however, take into account that registries are surveillance observational databases run by pharmaceutical companies, based on voluntary participation of physicians and patients, and thus might be biased towards patients with most severe disease and classic phenotypes.

In the Fabry Registry, patients with strokes were diagnosed later than patients without, and most of them had not experienced renal or cardiac events before their first stroke, thus suggesting that the classic features of the disease may be absent or more subtle in these patients [3]. On the other hand, atypical phenotypes have been reported recently with increasing frequency [66], some of them with stroke as the presenting feature [39, 67], and because its clinical recognition requires a high index of suspicion, the diagnosis of FD is often delayed or missed. Therefore, the true prevalence of FD in young stroke patients remains unknown. In spite of this, several published studies [5–9], and several on-going [68–71], address this issue. Unfortunately, these studies differ in several aspects that preclude their analyses as a whole [72]. A prospective study of FD in young adults with cryptogenic stroke was first published in 2005 and suggested that up to 5% of these patients might have FD [5], however, *GLA* gene mutations identified in these cases were never reported. Moreover, in a smaller retrospective study of similar patients, no *GLA* gene mutations were found in any of the subjects who had low enzyme activity on dried blood spot assay [6]. The study underlined that false positives cannot be excluded with this technique, but a subsequent study that assayed α-GAL on frozen plasma samples in men also did not detect mutations in several patients with low enzyme activity [7]. In spite of this, it is generally accepted that enzyme measurements are sufficient for FD diagnosis in men, but genetic testing is needed in women. Therefore a two-step approach, using both diagnostic procedures, in reverse order according to the gender, is usually undertaken. However, this approach will probably miss cases with residual α-GAL activity, with more subtle or absent manifestations of FD. Mutational analysis for both genders will be needed to overcome these limitations. Three recently published studies screened FD in all-cause young stroke patients, assuming that this approach might decrease selection bias and would be more appropriate to identify possible interactions between FD and environmental risk factors [7–9]. Data from these studies showed that several of the index patients had an identified cause of stroke (cardiac embolism, small and large vessel disease) suggesting that screening should not be restricted to patients with cryptogenic stroke. Curiously, dissection was reported in three female mutation confirmed patients. Table 1 presents a summary of all published studies on FD in stroke patients. Estimated prevalences for males ranged from 0.36% to 4.9% and for females from 2.4% to 2.6%. It is likely that the initially reported prevalence of almost 5% is due to inclusion of patients with recurrent stroke [5], instead of studying only first-ever stroke patients [7, 8]. Preliminary data from the ongoing SIFAP study [68], a large survey on different countries including more than 5,000 patients, suggested an estimated FD prevalence in stroke patients of approximately 0.9% (A. Rolfs et al. personal communication 2011).

A detailed discussion of mutation pathogenicity is beyond the scope of the present paper, but it is important to mention that *GLA* gene mutations reported in these studies include not only mutations that possibly behave similar to late onset variants, A143T and R118C [4], but also mutations of controversial pathogenicity, D313Y [73], and a

Table 1 Screening Fabry disease in young stroke patients: summary of studies published in the literature

Study reference	Study population	Type and cause of stroke	Type of study and two-step screening method	Main results and estimated prevalence (%)	*GLA* gene mutations	Type and cause of stroke in patients with mutations
Rolfs 2005 [5]	$n = 721$ Male/female 18–55 years Germany	Ischemic stroke: Cryptogenic Hemorrhagic stroke: Cryptogenic	Prospective (multicenter nationwide) 1. Plasma α-GAL enzyme assay 2. Genotyping for males with low enzyme activity and all females	32 men with low enzyme activity 21 men with *GLA* gene mutations (4.9%) 10 women with low enzyme activity 7 women with *GLA* gene mutations (2.4%)	Not reported	Ischemic stroke: $n = 24$ Cryptogenic Hemorrhagic stroke: $n = 4$ Cryptogenic
Brouns 2007 [6]	$n = 75$[a] Male/female 16–60 years Belgium	Ischemic stroke: Cryptogenic Hemorrhagic stroke: Cryptogenic	Retrospective (single center) 1. α-GAL enzyme activity on dried blood spot 2. Genotyping for males with low and females with low normal enzyme activity	1 man with low enzyme activity (normal exonic DNA sequencing) 2 women with low enzyme activity (normal exonic DNA sequencing)	No mutations	–
Wozniak 2010 [7]	$n = 558$ Male 15–49 years United States	First-ever: Ischemic stroke All cause	Retrospective (population-based) 1. Plasma α-GAL enzyme assay 2. Genotyping for males with low enzyme activity	10 men with low enzyme activity 2 men with *GLA* gene mutations (0.36%)[b]	A143T: $n = 1$ D313Y: $n = 1$	Ischemic stroke: $n = 2$ Cryptogenic: $n = 1$ Not reported: $n = 1$
Baptista 2010 [8]	$n = 493$ Male/female 18–55 years Portugal	First-ever: Ischemic stroke Hemorrhagic stroke CVT All cause	Prospective (multicenter nationwide) 1. Genotyping for all males and females 2. Plasma and leucocyte α-GAL enzyme assay for patients with *GLA* gene mutations	7 men with *GLA* gene mutations (2.3%) Enzyme activity subnormal 5 women with *GLA* gene mutations (2.6%) Enzyme activity subnormal/low-normal	R118C: $n = 6$ D313Y: $n = 6$	Ischemic stroke: $n = 9$ Cryptogenic: $n = 4$ Small vessel disease: $n = 2$ Cardiac embolism: $n = 2$ Other cause (Dissection): $n = 1$ Hemorrhagic stroke: $n = 2$ CVT: $n = 1$
Brouns 2010 [9]	$n = 622$[a] Male/female 18–60 years Belgium	Ischemic stroke Hemorrhagic stroke All cause	Prospective (multicenter nationwide) 1. α-GAL enzyme activity on dried blood spot 2. Genotyping for males with low enzyme activity and all females	12 men with low enzyme activity (normal exonic DNA sequencing) 3 women with *GLA* gene mutations (2.4%)	A143T: $n = 2$ S126G: $n = 1$	Ischemic stroke: $n = 3$ Cryptogenic: $n = 1$ Other cause (Dissection): $n = 2$

CVT cerebral venous thrombosis

[a] Patients with TIA, unexplained WML, and vertebrobasilar dolichoectasia were excluded from this analysis, as small numbers of patients and considerable heterogeneity among the different groups may be responsible for biases

[b] Mutation D313Y was assumed by the authors to correspond to a pseudomutation and thus reported estimated prevalence was 0.18%

novel FD mutation, S126G. Nevertheless, recent laboratory data lent further support for a pathogenic role for mutation D313Y [8], and the discovery of previously unreported mutations in this setting should not be surprising, because most FD families have private mutations and new mutations are frequently found [74]. Several of the index patients identified in these studies showed α-GAL enzyme activity much above the levels that cause the classical FD phenotype, and the limited family data available support the concept that reported mutations are not major disease-causing mutations [72, 75]. The question of how to treat these patients still needs to be elucidated, as none of the clinical trials of ERT included patients with substantial residual enzyme activity. One may argue that a specific ERT regimen, tailored to the individual patient, may be the answer, but this hypothesis has never been tested. Alternative FD therapeutic approaches in progress, such as gene therapy or chemical chaperones, will possibly foster further insights in the future. Currently, institution of secondary prevention measures, based on a thorough investigation of the cause of the index stroke, and careful monitoring of the patient are of the utmost importance. Collaborative efforts will be essential to obtain evidence on which therapeutic decisions and genetic counseling can be based.

The question of which stroke patients should be screened for FD remains unanswered. Classic FD phenotypes are probably rare, but their identification should be relatively straightforward, provided that the clinician is familiar with classic FD features, such as angiokeratomas (Fig. 1). However, atypical phenotypes, namely those presenting with stroke, with absent or more subtle classic features of FD may raise other difficulties. Furthermore, family history may be notably absent in these cases [72, 75], and thus screening should not be restricted to patients with family history, as was recently proposed [76]. This approach will probably underestimate the true prevalence of *GLA* gene mutations, especially those associated with relatively high residual α-GAL activity that may interact with other genetic and environmental vascular risk factors. Additional information provided by simple tests, such as proteinuria and left ventricular hypertrophy, probably should be considered, but its role in decision-making remains to be elucidated. The pulvinar sign has never been reported in index patients, in line with the assumption that these patients have mild FD phenotypes, but imaging data deserve to be taken into account, as a higher frequency of infarctions in the posterior circulation, vertebrobasilar dolichoectasia, and WML have been reported to be more frequent in patients with FD [5, 8]. Patients with evidence of small vessel disease, particularly those without hypertension, with stroke in the posterior circulation, seem to deserve additional attention, as more than 10% might have FD [8]. In the future, case–control and family segregation studies will be needed to clarify data provided by FD screenings. Until then, FD should be considered in young patients with all cause of stroke, as available data suggest that it may be as frequent as some of the rare potential causes usually considered in this setting [77, 78].

Conclusion

A better understanding of the clinical history and phenotype of FD patients with stroke is needed in order to identify patients at higher risk of experiencing a stroke and allow more accurate management. The role of ERT in prevention of stroke remains to be established. Nevertheless, its utilization in patients with stroke and FD should be considered for prevention of severe disease manifestations.

Although available studies suggest that the prevalence of FD in stroke patients is very low, stroke neurologists are supposed to recognize this entity in patients with cryptogenic stroke, and also in those with an identified cause of stroke. Elucidating the role of *GLA* gene mutations on stroke on a multifactorial basis and identifying a putative FD "stroke variant" are questions that need to be further elucidated.

Conflict of interest M.V.B. has received speaker's fees from Genzyme Corp. M.V.B. coordinated the PORTYSTROKE study that was sponsored by an unrestricted grant from GENZYME–Portugal. M.V.B. served as an advisor on the Global Fabry Neurology Advisory Board, sponsored by Genzyme Corp.

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