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Review

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Cerebrovascular disorders and Fabry disease

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Abstract

Fabry disease (FD) is an X-linked lysosomal storage disorder caused by pathogenic variants in the GLA gene encoding for alpha-galactosidase A. Renal, cardiac, and cerebrovascular involvement are the leading complications in early adulthood and are associated with severe morbidity and mortality. Cerebrovascular manifestations in FD manifest as ischemic stroke and transient ischemic attack and less frequently as hemorrhagic strokes. Many patients may develop their stroke not only before other major complications but also before the diagnosis of FD is made. This review will describe the frequency and characteristics of cerebrovascular disease in FD, the complex pathophysiological mechanisms, the neuroimaging findings, the value of screening studies in young patients with stroke, and the controversies regarding the beneficial effect of ERT for the prevention of cerebrovascular disease in FD.

Keywords: Fabry disease, cerebrovascular disorders, ischemic stroke, hemorrhagic stroke, transient ischemic attack

INTRODUCTION

Fabry disease (FD) is an X-linked lysosomal storage disorder caused by pathogenic variants in the *GLA* gene encoding for alpha-galactosidase A (α-GAL A). FD is characterized by progressive and multisystemic lysosomal accumulation of glycosphingolipids involving peripheral nerves, gastrointestinal tract, skin, heart,

kidneys, and brain. As a consequence, a myriad of progressive signs and symptoms may be present, including neuropathic pain, hypohidrosis, exercise intolerance, gastrointestinal symptoms, hearing loss, tinnitus, angiokeratoma, "cornea verticillata", left ventricular hypertrophy, proteinuria, decreased renal function, and stroke[1-4]. Estimates of the prevalence of FD range from approximately 1 in 117,000 to 1 in 37,000 live male births for classic FD and up to 1 in 1,400 in some newborn screening projects when atypical FD variants are included[5-7].

Symptoms usually begin in childhood and adolescence, particularly in the classical Type 1 phenotype, and are mainly characterized by gastrointestinal symptoms, anhidrosis, and neuropathic pain, and progressively lead to kidney and heart involvement, as well as stroke. Misdiagnosis is common[8], with a long delay between onset of symptoms and diagnosis[9]. Renal, cardiac, and cerebrovascular involvement are the leading complications in early adulthood and are associated with severe morbidity and mortality. By contrast, patients with the Type 2 later-onset phenotype have residual enzyme activity and, therefore, present with delayed clinical manifestations. Cardiac or renal involvement may be observed in these patients after their fourth decade of life and stroke may also occur as an isolated manifestation[10-12].

Enzyme replacement therapy (ERT) has been available for the treatment of FD since 2001 and is the standard of care[13]. Two ERT formulations are available currently: agalsidase alfa[14] and agalsidase beta[15]. Additionally, an α-GAL A pharmacological chaperone, migalastat, can be used to treat certain patients with an amenable *GLA* mutation[16].

This review will describe the frequency and characteristics of cerebrovascular disease in FD, the complex pathophysiological mechanisms, the neuroimaging findings, the value of screening studies in young patients with stroke, and the controversies regarding the beneficial effect of ERT for the prevention of cerebrovascular disease in FD.

PATHOPHYSIOLOGY OF VASCULAR DAMAGE IN FD

Vasculopathy in FD is the result of overlapping abnormalities in the vessel wall, the blood components, and the circulation[17,18].

Vasculopathy and Gb3

Two primary hypotheses have been proposed for the pathogenesis of vasculopathy in FD. The first underlines the pathologic effects of globotriaosylceramide (Gb3) on the endothelial cells, while the second stresses the deleterious effect of globotriaosylsphingosine (lyso-Gb3) on the muscular layer of blood vessels [Figure 1]. Following alpha-GAL A deficiency, Gb3 accumulates within caveolae of endothelial cells, resulting in endothelial nitric oxide synthase (eNOS) uncoupling and superoxide (O2-) production. Nitric oxide is consumed to form peroxynitrite (ONOO-), which leads to the formation of 3-nitrotyrosine (3NT). Gb3 accumulation is sufficient to account for the dysregulation of eNOS[19], as demonstrated in alpha-GAL A knockout mice[20]. Studies on cerebral blood flow have reported either decreased or enhanced flow. These seemingly contradictory findings might be due to eNOS uncoupling with secondary oxidative stress[21,22].

A pro-oxidant state occurs in FD associated with both Gb3 and Lyso-Gb3 accumulation leading to tissue damage through vasculopathy, endothelial free radical formation, and altered oxidative responses[23,24].

Vasculopathy and chronic inflammation

Tissue deposition of glycolipids is not considered a sufficient explanation of the pathophysiology of FD. Gb3 and lyso-Gb3 can also induce a chronic inflammatory state leading to vascular damage, as previously

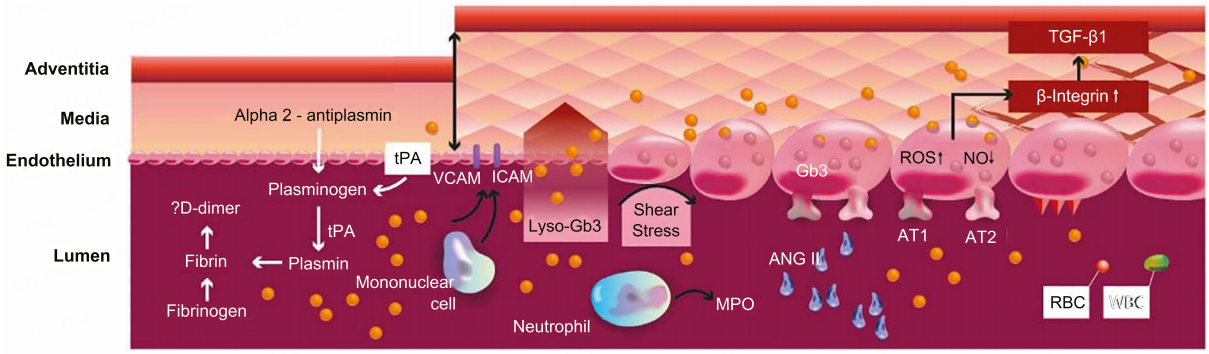

Figure 1. A visual summary of the mechanism detailed in the section of pathophysiology. Image adapted by authors from ref[17,38]. tPA: Tissue plasmínogen activator; VCAM: vascular cell adhesion molecule; ICAM: intercellular adhesion molecule; Lyso-Gb3: globotriaosylsphingosine; ROS: reactive oxygen species; NO: nitric oxide; ANG: angiotensin; AT-1: angiotensin type 1 receptor; AT-2: angiotensin type 2 receptor; MPO: myeloperoxidase; RBC: red blood cells; WBC: white blood cells.

reviewed[25]. The classical natural T killer cells recognize both Gb3 and lyso-Gb3 as self-antigens presented by the major histocompatibility complex to antigen-presenting cells[26]. Recognition of these glycolipids induces the release of various proinflammatory cytokines such as interferon-gamma, tumor necrosis factor alpha, and interleukins 4, 5, 9, 10, 13, and 17[27,28]. This proinflammatory status in patients with FD leads to endothelial cell activation, inducing a cascade of effects that lead to a prothrombotic state characterized by dysfunctional platelets, higher secretion of von Willebrand factor, increased release of microparticles, and the activation of plasminogen[29-32]. Moreover, increased expression of endothelial adhesion molecules has also been reported[33,34].

Ca^{2+}-activated K^+ channels

The endothelium controls vascular diameter through the contractile status of the smooth muscle of blood vessels. This process is mediated by the release of nitric oxide, prostaglandins, and the endothelium-derived hyperpolarizing factor (EDHF). Endothelial hyperpolarization responses are mediated by Ca^{2+}-activated K^+ channels (K_{Ca}) in response to calcium mobilization under shear stress stimulation. The hyperpolarization current is then transmitted to the medial muscular layer, inducing muscle relaxation and vasodilation. Gb3 accumulation reduces both K_{Ca} expression and function. Downregulation of pathways that control K_{Ca} expression is observed, including extracellular signal-regulated kinase (ERK) and activating protein-1 (AP-1) pathways, leading to endothelial dysfunction in FD. Moreover, channel activity is inhibited by decreasing intracellular levels of phosphatidylinositol 3-phosphate, which is a channel agonist[35,36].

Lyso-Gb3 and the medial muscular layer

Aerts *et al.* described higher concentrations of plasmatic lyso-Gb3 in patients with FD[37]. A second hypothesis of vascular damage in FD considers that the circulating lyso-Gb3 effect on the arterial medial layer is the main and primary event, inducing smooth muscle hypertrophy, increased shear stress, and vessel lumen reduction[38]. It is hypothesized that the increased shear stress induces the upregulation of angiotensin II; this molecule interacts with the angiotensin 1 receptor (AT1) to produce a complex cascade of events including the overexpression of adhesion molecules, cytokines, and chemokines. Moreover, AT1 not only induces a proinflammatory effect on leucocytes, endothelial cells, and vascular smooth muscle cells, but also reduces nitric oxide formation with a subsequent increase of reactive oxygen species[39].

After binding to the AT1 receptor, angiotensin II activates integrin-mediated signaling and overexpression of the transforming growth factor beta, thereby inducing alterations not only of extracellular matrix quality and quantity, but also of the cytoskeletal protein composition and filament organization. These changes

decrease vessel compliance. This inflammatory process, along with oxidative stress, weakens the vessel wall as it activates protease-mediated extracellular matrix degradation and apoptosis of smooth muscle cells. Progressive weakening of the vessel wall results in elongation, dilatation, and aneurysm formation[38,40,41] [Figure 1].

Basilar artery dolichoectasia

Basilar artery diameter is significantly enlarged in FD patients[42-44]. It was postulated that a low sympathetic innervation of intracranial vessels in the posterior circulation is the reason for the selective involvement of this vessel. Vertebrobasilar dolichoectasia is an additional risk factor for ischemic brain lesions and small vessel disease[45]. Brain infarctions in patients with basilar artery dolichoectasia may develop due to major distortion and obstruction of perforating arteries, thrombosis, and emboli arising from this dolichoectatic vessel[46].

Cardioembolic stroke

In addition to the previously described mechanisms, stroke in the distribution of large vessels is predominantly due to cardiac embolism, mainly due to arrhythmias and cardiomyopathy. Cardiac involvement is the main cause of mortality in FD[47]. Hypertrophic cardiomyopathy is a hallmark of FD and evolves into myocardial replacement fibrosis[48]. With FD progression, a reduction of left ventricular end-diastolic volume is seen, resulting in a lower cardiac output[49,50]. The severe involvement of the conduction system is the cause of bradycardia, asystole, episodes of ventricular tachycardia, and intermittent atrial fibrillation, all of which markedly increase the risk of sudden death and cardioembolic stroke[51].

Why are females affected in FD?

The reason why females with FD are affected has been reviewed[52] and the authors indicated that symptomatic females primarily secrete the mature 46KDa enzyme, with only small amounts of the mannose 6-phosphorylated form. Therefore, the capacity for enzyme cross-correction of affected cells is limited[53].

A second possible explanation is that α-GAL A released by the mixed cellular population of the female mosaic is more susceptible to dephosphorylation by plasma phosphatases[54].

PREVALENCE OF STROKE IN FD

Cerebrovascular manifestations in FD are mainly ischemic stroke and transient ischemic attack (TIA). Hemorrhagic strokes and microbleeds are less frequent, while cerebral venous thrombosis and subarachnoid hemorrhages are only occasionally seen[55,56].

Studies on the prevalence and incidence of stroke in FD yielded variable results[57], likely reflecting differences in genetic variants, sample size, gender, and age of the investigated cohort, as well as in the imaging methods used in the investigation.

The first published studies regarding stroke prevalence in FD were conducted in the 1990s. Morgan *et al.* analyzed 12 patients with FD and found that three of them had had a stroke (25%)[58]. Grewal identified eight patients with stroke in a group of 33 patients with FD (24%, age range: 6-64 years). Among these patients, stroke involved small perforating arteries and was evenly distributed between the anterior and the posterior circulation[59].

A retrospective study of central nervous system involvement in FD, including 43 patients, reported a prevalence of stroke of 24% in males (mean age: 33 years) and 28% in females (mean age: 53 years).

Moreover, TIA was described in 20% of males and 17% of females. Lacunar infarcts involving both the anterior and the posterior circulation were the predominant type of stroke, while only one female suffered a hemorrhagic stroke[60].

In Australian patients with FD, a prevalence of stroke of 31% in males and 5% in females was reported[61]. A retrospective analysis of a Dutch cohort of patients with FD from a single center in Amsterdam yielded a prevalence of stroke or asymptomatic lacunar infarcts detected on magnetic resonance imaging (MRI) of 32% (n = 13, median age: 56 years) in females and 48% (n = 12, median age: 46 years) in males[62]. A retrospective Japanese study including 65 patients identified ten subjects (15%, 7 males and 3 females) with ischemic strokes[63].

In 2001, MacDermot *et al.* analyzed 60 women with FD and identified 4 patients with stroke and 17 with TIA (combined prevalence of 21.5%)[64]. In a cross-sectional study, the same authors reported a cohort of 98 males and 60 females, with a respective frequency of stroke of 24% (mean age: 40 years) and 7% (mean age: 42 years)[65]. In addition, a study comprising only women included 54 participants with a brain MRI; 7% of them had lacunar strokes, but it is unclear whether they were symptomatic[66].

With the goal of increasing the sample size, several studies used data from collaborative international registries, such as the Fabry Outcome Survey (FOS) and the Fabry Registry (FR). In 2005, Mehta and Ginsberg evaluated the prevalence of stroke and TIA among 388 patients in FOS; the prevalence was higher in females (15.7%) than in males (11.1%)[67]. About half of these patients suffered a stroke or a TIA at an age younger than 44 years.

A later study identified that 91 (13.2%) of the 688 patients (330 males, 358 females) registered in FOS by March 2005 had suffered a stroke or TIA. The prevalence of ischemic strokes among males and females registered in FOS was 20.1 and 7.8 times higher than expected in a comparable general population, respectively[68].

A more recent FOS study including 1,453 patients identified that cerebrovascular events were almost equally frequent in males (25%; n = 172/699) and females (21%; n = 159/754)[47].

A study analyzing the FR cohort included 2,446 patients. Overall stroke prevalence was 5.6% (n = 138): 6.9% in males, with a mean age of 39 years, and 4.9% in females, with a mean age of 45 years. The prevalence of hemorrhagic strokes was 13.2%, whereas the prevalence of ischemic strokes was 86.8%. For ischemic strokes, up to 70% were lacunar. Moreover, 21.7% of the patients who had a stroke were younger than 30 years old. Most patients had had a stroke before any cardiac or renal event, or it was their only clinical manifestation. In addition, 38% of females and 50% of males experienced their first stroke before being diagnosed with FD. Thus, most patients had either not experienced other major complications or had not been diagnosed with FD before their stroke[69].

Atrial Fibrillation in FD

Atrial fibrillation incidence in FD is variable depending on the choice of diagnostic modality, with 12-lead ECG and Holter monitoring showing lower detection rates (2.9%-10% per year) compared with higher rates (19%-31% per year) on continuous rhythm monitoring[70].

The worldwide incidence and prevalence of AF is increasing in the general population. Higher rates of AF were observed due to advancing age, improved survival from co-existing disease, and increasing co-

morbidity[71]. These same drivers are shared in those who have FD, including increasing age, improved survival with ERT, but concurrently an increasing number of FD co-morbidities[70].

SCREENING OF FD IN PATIENTS WITH STROKE

The prevalence of FD in young patients with stroke has been an area of great interest. However, the studies yielded conflicting results, most likely due to the selection criteria of patients (cryptogenic strokes *vs.* all types of strokes or the inclusion of white matter lesions), as well as the genetic data interpretation.

Initially, the number of patients with FD that could be identified among young patients with strokes was overestimated because benign variants or variants of unclear significance were erroneously interpreted[72,73].

In a prospective study, Rolfs *et al.* analyzed 721 patients aged 18 to 55 years with cryptogenic strokes in Germany. FD was estimated to be the etiological factor in 4.9% of males and 2.4% of females. Nevertheless, the pathogenic variants were not reported[72]. Multiple investigations followed the study of Rolfs, but none of them could reproduce its results.

A meta-analysis included 8,302 patients who participated in nine studies (four about strokes of undetermined origin and five about strokes of all etiologies). Eight studies limited the age to young patients (18-55 years old), and the ninth study did not have an age limit. The investigators concluded that FD may explain approximately 1% of all strokes in the young population, including 3%-5% of cryptogenic strokes[73]. The study with no age limit, which included all types of strokes as well as white matter lesions, found no patients with FD at all[74]. An important limitation of this meta-analysis is that the authors did not critically analyze the genetic variants reported in the individual studies, which in many cases corresponded to benign variants or variants of unclear significance[73].

The Stroke in Young Fabry Patients (SIFAP) study is the largest multicentric observational study ever performed and included 5,023 young patients with stroke (both cryptogenic and non-cryptogenic). Definitive FD was detected in 0.5% of patients (n = 27). Nevertheless, some of the reported variants are now still considered benign or likely benign[12]. None of the patients presented signs and/or symptoms of classical FD.

In recent years, significant improvement was made in the genotype-phenotype correlation of young patients with stroke included in screening studies of FD, and as a consequence, a lower prevalence of 0.1%-0.3% was estimated[75,76]. This prevalence may be higher in young patients with either cryptogenic or recurrent stroke[75].

A prospective, multicentric study of stroke and FD in young adults (18-55 years old) included 311 patients with either cryptogenic or non-cryptogenic strokes. One female (0.3% of the total group, 1% of the cryptogenic ischemic strokes) had the pathogenic variant c.888G>A/p.Met296Ile/Exon 6 on the *GAL* gene. Her only other manifestation of FD was angiokeratoma[75].

An additional systematic review included screening studies published between 1995 and 2017. The aim of the review was not only to present the prevalence of FD in the mentioned population, but also to reanalyze the genetic data to exclude benign or likely benign variants, and perform genotype-phenotype correlations. Data from 3,904 males and 2,074 females were analyzed. In males, the investigators found a pre-analysis prevalence of 0.67% (n = 26) of patients with FD; among them, 21 had either benign variants or variants of unknown significance, including p.D313Y, p.A143T, p.E66Q, and g.1136C>T(5'-44C>T). Therefore, the true

prevalence of FD dropped to 0.13%. Among the 5 males with pathogenic variants, 3 exhibited the Type 1 phenotype while 2 displayed the Type 2 phenotype. Similarly, a prevalence of 1.11% of patients with FD was found in females (n = 23), but when the benign variants were excluded, only 3 presented pathogenic variants with the Type 1 phenotype and the actual prevalence dropped to 0.14%, similar to that in males[76]. The authors found that most FD patients identified in stroke clinics had the Classic phenotype and, therefore, should have been diagnosed earlier by their pediatricians and family doctors[76].

Moreover, similar clinical characteristics of stroke patients were identified in the Fabry Registry. When the most recent available follow-up examination after their first stroke was analyzed, 59.8% of males and 25.5% of females had stage 3 to 5 chronic kidney disease. Moreover, 66.1% of males and 59.5% of females had left ventricular hypertrophy. These data also suggest that most patients had type 1 phenotype[69].

A recent study evaluated 172 patients with ischemic stroke using an exome-based panel of 349 genes and identified pathogenic *GLA* variants in 2 patients (1.2%) with known FD[77].

All these studies demonstrate the need for a careful assessment of screening results based on the diagnostic methods used, a detailed interpretation of genetic data, and recognition of population selection criteria. Nevertheless, the interpretation of screening results remains a controversial issue, as demonstrated by a recent meta-analysis indicating that p.D313Y might induce an atypical neurological phenotype in patients with FD[78]. In our opinion, the investigation into FD is warranted in young patients with cryptogenic stroke.

NEUROIMAGING FINDINGS IN FD

Stroke and white matter hyperintensities [Figure 2A and B]

Ischemic strokes and TIAs are the most common cerebrovascular manifestations in FD and can be attributed to either large or, more frequently, small vessel disease, with cortical and subcortical locations, respectively. Some authors describe that stroke in FD similarly affects both the anterior and the posterior circulation[55,59], while others underline a predominant involvement of the posterior circulation[79].

Hemorrhagic stroke is a rare complication in FD, accounting for about 10% of stroke events, with a predilection for male patients and mostly associated with hypertension or end-stage renal failure. On the contrary, chronic cerebral microbleeds are more common, affecting 11% to 30% of FD patients[80] [Figure 2C]. They can be detected in brain MRI using echo gradient-weighted images, T2-weighted and susceptibility-weighted imaging[81]. A study of 36 adult patients with FD identified that 44.4% without dialysis or previous strokes had MRI evidence of small vessel disease, and 11% of them showed cerebral microbleeds[82].

Small vessel disease is commonly seen in patients with FD, manifested as subcortical stroke and white matter hyperintensities (WMH) [Figure 2A and B]. The latter represents the most frequent brain imaging feature of FD and indicates lesions not referable to focal acute cerebrovascular events[83]. WMHs could range from small, scattered, and punctuate T2-weighted hyperintense foci to bilateral diffuse, patchy, and confluent lesions. WMH occurrence is similar in males and females, with no predilection for a specific brain region[81,84]. Autopsies performed in patients with FD revealed that deep WMHs are either lacunar infarctions or are associated with small arterioles narrowing[85].

Marchesoni *et al.* identified asymptomatic WMHs in 7 children with FD (15.9%), compared with 3 children (6.5%) in an aged-matched control group (P = 0.01). Brain abnormalities revealed deep gray matter and infratentorial involvement[86].

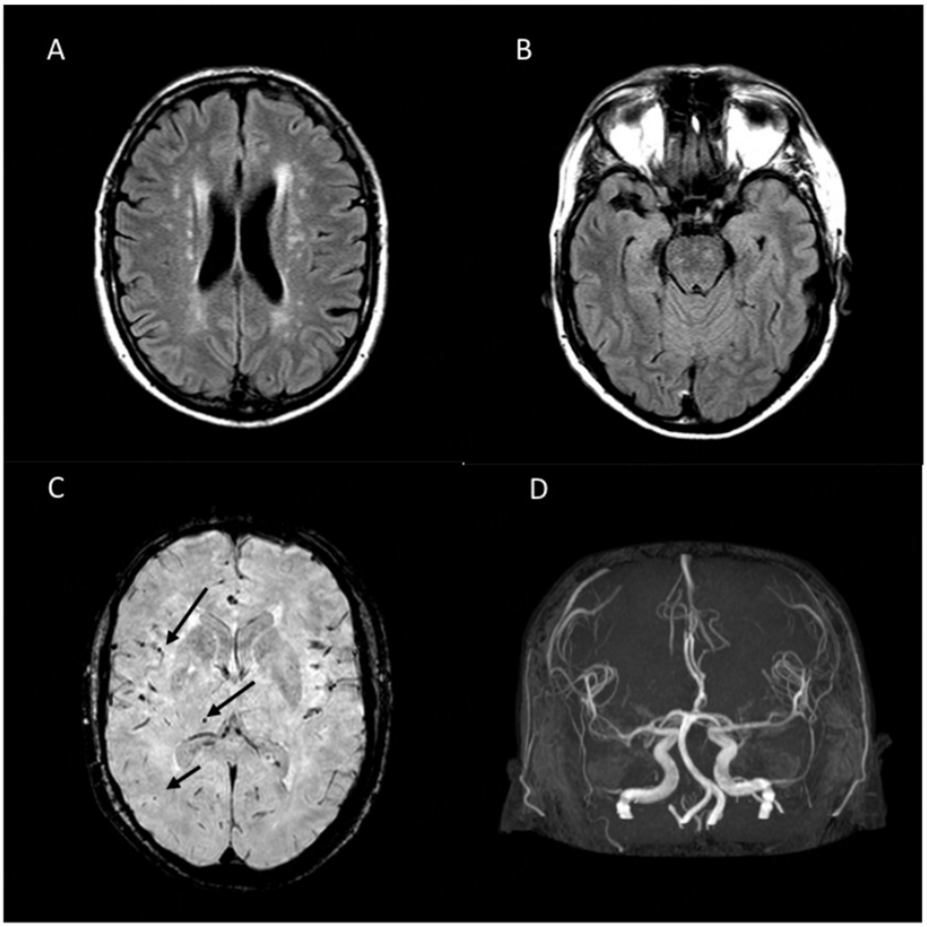

Figure 2. Brain MR T2 Flair axial reconstruction in a 36-year-old man with Fabry Disease showed white matter hyperintensities located bilaterally in the (A) periventricular and (B) pontine regions; (C) SWI axial recconstruction identified punctate microbleeds (black arrows) in the right thalannus, right frontal and right occipital lobes; (D) Intracranial time of flight MR angiography sequence coronal reconstruction revealed the presence of mild elongation and tortuosity of the basilar artery. MR: Magnetic resonance; SWI: susceptibility weighted imaging.

WMHs are not specific and may be misdiagnosed as multiple sclerosis (MS) or other demyelinating conditions[87]. In a study comparing brain MRI from FD patients *vs.* matched patients with MS, WMHs involving the juxtacortical and infratentorial regions as well as the corpus callosum were more frequently observed in MS patients[88]. Moreover, the history of multiorgan involvement, the absence of oligoclonal bands in the cerebrospinal fluid, the relative sparing of corpus callosum, and the lack of spinal cord lesions are useful in differentiating FD from MS[89,90].

Perivascular spaces

MRI-visible perivascular spaces (PVS) seem to be a promising marker of small vessel disease associated with possible impaired interstitial fluid drainage in FD. In a study including 33 patients with FD (median age: 44 years; 44.1% male) and 20 healthy controls (median age: 33.5 years; 50% male), FD was associated with more severe basal ganglia PVS and a higher total PVS score. Impaired interstitial fluid drainage might be a newly recognized mechanism of white matter injury in FD[91].

Pulvinar sign

The symmetric hyperintensity of the lateral pulvinar nucleus on unenhanced T1-weighted brain MRI is known as the pulvinar sign (PS). The pathogenesis of the PS in FD is still unclear and may represent dystrophic calcifications, likely due to chronic regional hyperperfusion[92,93]. It has been initially described as a common neuroradiologic sign in patients with FD[92,94]; nevertheless, PS is not a specific finding and it has been reported in other conditions, including metabolic disorders (Krabbe or Tay-Sachs disease), Fahr disease, disturbances of the calcium-phosphorus metabolism, central nervous system infections, or after chemoradiation therapy[95]. In a recent study, PS was detected in only 4 of 133 patients with FD (3.0%); all the patients were adult males with chronic renal failure on enzyme replacement therapy (ERT)[95]. These results suggest that the true incidence of PS is considerably lower than previously thought. In addition, the PS has a low sensitivity for the diagnosis of FD, is not modified by ERT, and is not associated with any specific FD genotype[94,95].

Vertebrobasilar artery involvement

Alterations of the posterior circulation system include tortuosity, diffuse ectasia, elongation, and/or focal aneurismal dilatation involving the vertebral and basilar arteries [Figure 2D][96]. The underlying mechanisms of such abnormal vessel dilatation have been described in the corresponding section of this review. It is worth noting that the prevalence of vertebrobasilar dolichoectasia has also been described in young patients with other uncommon causes of acute strokes[97].

Recommended MRI sequences

MRI sequences suggested include T1-weighted fluid-attenuated inversion recovery (FLAIR) and T2-weighted sequences to quantify chronic WMH load and to identify lacunar and territorial strokes; T2* MRI (gradient echo, susceptibility-weighted imaging) to identify macro and microbleeds; diffusion-weighted imaging to assess stroke and time-of-flight sequences to evaluate the diameter of cerebral vessels without using contrast[55].

In adults with FD, due to the higher prevalence of strokes in comparison to the general population and the presence of silent lesions, a consensus guideline proposes to perform a brain MRI every three years in all males at baseline and in females over 30 years old[98]. By contrast, given the rarity of stroke in the pediatric population with FD, the latest consensus guidelines advise against performing a brain MRI as baseline practice in children, except in cases with neurological symptoms[99].

Computed tomography scans may be used in the acute setting or when MRI is contraindicated.

Advanced imaging techniques

Quantitative volumetric MRI studies evaluate the presence of brain-tissue volume loss in FD patients with mild-to-moderate central nervous system involvement. Reduced grey matter density has been recently reported at the level of the thalami and hippocampus, bilaterally, reflecting direct neuronal involvement independent from vascular pathology[100].

Diffusion tensor imaging has been shown to detect brain tissue alterations, allowing for an accurate quantification of microstructural white matter changes. FD patients, including those without white matter lesions seen on conventional MRIs, may present an elevated total brain parenchymal diffusion constant compared to controls. Increased mean diffusivity values in FD patients were found in the temporal, frontal, and parietal lobes. This increase, presumably due to an elevated water content of brain tissue, may be identified independently from white matter lesions and could be interpreted as a biomarker of early stages of microvascular injury[101,102].

A proton magnetic resonance spectroscopy study was performed in FD patients using a multi-voxel analysis, with the objective of investigating changes in the N-acetylaspartate/creatine (NAA/Cr) ratio indicating possible neuronal degeneration and loss. FD patients showed a diffuse reduction of the NAA/Cr ratio, affecting both cortical and subcortical structures. These alterations were independent of the presence of WMH and were attributed to a possible metabolic dysfunction, secondary to Gb3 neuronal accumulation rather than a vascular alteration[103].

The connectome analysis of brain networks in patients with FD, using diffusion and resting-state functional MRI data, revealed both a structural disconnection (due to mild but widespread axonal damage) and a functional reorganization, associated with cognitive performances[104].

Future longitudinal studies on volumetric MRI, diffusion tensor imaging, and proton magnetic resonance spectroscopy are necessary to elucidate the possible presence of brain volume differences, microstructural changes, and metabolic dysfunction in FD.

COGNITIVE INVOLVEMENT AND PARKINSONISM IN FD

Cognitive involvement, ranging from mild reduced attention and executive dysfunction to full dementia, was identified in some patients with FD. It predominates in patients with more severe disease and a history of cerebrovascular disease[105-109]. The studies evaluating this problem have yielded conflicting results; while several investigations identified cognitive defects with male predominance[110,111], other investigators failed to identify cognitive decline in FD[79,111-115]. Moreover, executive dysfunction was identified in patients with FD, but differences with control population disappeared after controlling for depression[116,117]. Differences in these results are likely due to the characteristics of the evaluated cohort regarding gender, associated cerebrovascular disease, and depression, as well as the varied neuropsychological techniques used in each study. All these variables need to be controlled in future prospective studies of cognition in FD.

Parkinsonism is rarely seen in patients with FD, particularly in the absence of cerebral small vessel disease. Bradykinesia and impaired fine manual movements have been reported in both males and females with pathogenic *GLA* variants[118].

Moreover, in autopsies series, the storage of glycosphingolipids was documented in neuronal and glial tissue including substance nigra[119].

Nevertheless, it is still not possible to ascertain whether this PD phenotype is related to Gb3 deposition versus cerebrovascular lesions in the nigrostriatal network and the simultaneous presence of the two mechanisms may be considered[120].

TREATMENT

Whether ERT is beneficial for the prevention of stroke is still a controversial topic. It was initially considered that ERT was ineffective in reducing the risk of stroke, as it does not cross the blood-brain barrier. Nevertheless, autopsies performed in FD patients on ERT treatment indicate an almost complete clearance of endothelial glycolipids, but persistent storage in smooth muscle vascular cells, in addition to intimal fibrous thickening and adventitial fibrosis[108,121]. It should be stressed that these patients were severely affected by their disease, and ERT was started very late, possibly at an irreversible stage of vascular damage.

Recent studies suggest a protective effect of ERT after an initial latency period of 6 months[122]. In a meta-analysis including seven cohort studies and two randomized, controlled studies (7,513 participants: 1,471 on ERT *vs.* 6,042 on native treatment), the stroke recurrence ratio in the ERT treatment group (including both agalsidase alfa and beta) was 8.2% *vs.* 16% in the native treatment group ($P = 0.03$)[123].

It is worth noting that ERT has been shown to reduce both the burden of disease[124,125] and the risk of thromboembolic events, including stroke[126]. The beneficial effect of ER, in patients naïve to specific treatment, on stabilizing and improving cardiomyopathy, especially with prompt initiation of therapy, also has a preventive effect on cardioembolic stroke[127].

In patients with FD, classical cardiovascular risk factors (smoking, hypercholesterolemia, diabetes mellitus, sedentarism, and hypertension) should be treated intensively, both for primary and secondary prevention[128]. We recommend aspirin or clopidogrel in patients who suffered an ischemic stroke or TIA. Although no clinical trials are available regarding primary prevention, we also indicate antithrombotic medications in FD patients with MRI lesions Fazekas grade 2 or 3[129].

We usually use clopidogrel when aspirin is not tolerated and recommend statins in primary and secondary prevention for their pleiotropic effects[17,98,130].

Anticoagulation is reserved for patients with confirmed atrial fibrillation or cardioembolic stroke.

DECLARATIONS

Authors' contributions

Made substantial contributions to conception and design, and participated in original draft writing and final revision: Moreno-Martínez D, León-Cejas L, Reisin R

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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