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Review Article

Fabry Disease and Early Stroke

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Fabry disease, an X-linked lysosomal storage disorder, results from deficient activity of the enzyme α-galactosidase A. Affected males with the classic phoenotype have acroparaesthesias, hypohidrosis, and corneal opacities in childhood and develop renal failure, cardiac hypertrophy or strokes in the third to fifth decade of life. Some female heterozygotes are asymptomatic, some as severely affected as males. The natural history of Fabry patients includes transitory cerebral ischaemia and strokes, even in very young persons of both genders. The mechanism is partly due to vascular endothelial accumulation of GL-3. White matter lesions on MRI occur. Both males and females can be safely treated with enzyme replacement; and thus screening for Fabry disease of young stroke populations should be considered. There are, however, no hard data of treatment effect on mortality and morbidity. The analyses of results from ongoing studirs will add to the decision on whether or not to screen young stroke patients for Fabry disease. Finally, stroke prophylactic therapy should be used liberally in patients of both genders with verified Fabry disease. This includes primary prevention such as lifestyle counseling, targeting blood pressure, managing atrial fibrillation, diabetes mellitus, hyperlipidaemia, and ASA.

1. Introduction

Fabry disease is a rare X-linked inborn error of glycosphingolipid metabolism resulting from reduced production of lysosomal (α-galactosidase A (α-Gal A)) [1]. The enzymatic deficiency leads to lysosomal accumulation of glycosphingolipids, primarily globotriaosylceramide (GL-3), particularly in vascular endothelial cells throughout the body. Affected males and symptomatic heterozygous females with the classical phenotype have manifestations in childhood or adolescence including angiokeratoma, acroparesthesia, gastrointestinal manifestations, and corneal opacities. With advancing age, the progressive vascular involvement results in renal insufficiency, cardiac disease, and strokes [1]. Patients with Fabry disease have a shortened life expectancy due to the development of a specific vasculopathy. Male patients typically develop renal impairment in their third or fourth decade of life, as well as cardiac hypertrophy and conduction abnormalities. Life expectancy is reduced with a median life expectancy between 50 and 57 years for the male population [2–4]. In females, the disease is more variable, with less involvement of the kidneys, but life span is shortened as well [2, 3, 5]. In female patients, cardiac disease and cerebral white matter lesions dominate and contribute to morbidity and mortality.

Stroke is a common and serious clinical manifestation of Fabry disease. Recent evidence, from papers on natural history of Fabry and postmarketing surveillance databases of Fabry patients treated with enzyme replacement therapy, has indicated that stroke may appear even in young patients [6, 7], and stroke has been seen in some patients as the first disease event [7]. Although patients with Fabry disease are known to experience transient ischaemic attacks (TIAs) and strokes at an early age [8, 9], there are few quantitative markers of disease burden in the central nervous system. Fabry patients frequently exhibit white matter lesions, which can be detected by conventional neuroimaging methods (reviewed in [10]). Recently, magnetic resonance diffusion tensor imaging has been used to quantify these abnormalities [11]. However, the risk of clinical cerebrovascular manifestations, such as stroke and TIAs, is difficult to predict. Thus, because of the various ways by which different studies defined cerebrovascular complications, the stroke incidence and median age at first stroke cannot be readily compared across studies.

The approval of r-hα-GAL-A treatment has subsequently put a pressure on both clinicians and authorities to begin therapy in affected individuals, and therefore a number of questions may never be answered by randomized placebo-controlled trials. Consequently, the only realistic possible sources to obtain future long-term data is to rely on the postmarketing surveillance databases run by the pharmaceutical companies who market the enzyme products, that is, Fabry Outcomes Survey (Shire Inc) and Fabry Registry (Genzyme Inc). The Fabry Registry provides information on the worldwide largest cohort of patients with Fabry disease. Both databases are ongoing, observational databases that track the natural history and outcomes of patients with Fabry disease. Patient and physician participation is voluntary. All patients provide informed consent and may decline to participate or withdraw consent at any time. The treating physicians determine the actual frequency of necessary assessments according to a patient's individualized need for medical care and routine followup. However, there is a recommended schedule of assessments for the enrolled patients. This schedule encompasses assessments of cerebrovascular and neurological manifestations of the included patients with Fabry disease.

Although these databases provide only surrogate sources of information on the clinical outcome of therapy, the level of evidence is more conclusive than clinical experience with singular cases, and the two databases have already provided useful information on the baseline phenotype in women, information that has not been possible to obtain by other means in this rare disease [8, 12].

2. Mechanisms for Stroke in Patients with Fabry Disease

The understanding of the pathophysiology of the vasculopathy in Fabry disease is limited, as recently reviewed by Rombach et al. [13]. the removal of glycosphingolipid from various cell types has been reported in studies investigating the efficacy of enzyme replacement therapy [14–17]. However, it has become apparent that the removal of stored glycosphingolipid from the endothelial cells, as identified by conventional histological examination, does not prevent the progression of vascular disease in many patients [18, 19]. Thus, the traditional concept that prominent storage in endothelial cells is primarily responsible for the vascular dysfunction cannot be held. Several investigators have attempted to unravel the components that contribute to the general vascular damage. Most studies have been performed in limited patient populations, usually focusing on one aspect of the vascular dysfunction rather than on the complex interplay of all the different factors involved.

The mechanisms underlying the stroke pathogenesis in Fabry disease have thus not been clearly delineated. Progressive accumulation of GL-3 within the endothelium of intracranial blood vessels is thought to play a primary role in the vasculopathy and risk of ischaemic stroke [20]. However, other factors such as the presence of a prothrombotic state, abnormalities in cerebral blood flow velocity, autonomic dysfunction [21], and increased production of reactive oxygen species were also identified as being contributing to the development of stroke in patients with Fabry disease [13, 21–24]. Another different mechanisms contributing to the strokes could be emboli or other consequences of cardiac arrhythmias [7], that are some of the most important and common cardiac manifestations in Fabry patients of both genders [25].

The role of vascular or autonomic dysfunction as a pathogenic mechanism for stroke in Fabry patients by compromising cerebral blood flow velocities and cerebral autoregulation has been elegantly studied by Hilz et al. [21]. They used transcranial Doppler sonography in 22 Fabry patients and 24 controls and assessed the resistance index, pulsatility index, cerebrovascular resistance, spectral powers of oscillations in RR intervals, mean blood pressure, and mean cerebral blood flow velocities. They hypothesized that the decreased cerebral blood flow velocities might result from downstream stenoses of resistance vessels and dilatation of the insonated segment of the middle cerebral artery due to reduced sympathetic tone and vessel wall pathology with decreased elasticity. Furthermore, the augmented gain between blood pressure and cerebral blood flow velocities oscillations indicates an inability to dampen blood pressure fluctuations by cerebral autoregulation. Thus, both reduced cerebral blood flow velocities and impaired cerebral autoregulation are likely to be involved in the increased risk of stroke in patients with Fabry disease.

The normal function of GL-3 is still a mystery, and the potential contribution of secondary metabolic phenomena to the evolution of Fabry disease is unknown [2]. Enzyme replacement therapy with intravenous infusion of r-hα GAL-A has been found to consistently decrease GL-3 levels in plasma and clear lysosomal inclusions from vascular endothelial cells. Whether this occurs to the same extent in brain vasculature is unknown. The effects of enzyme therapy on other tissues are not obvious, and therefore recommendations for the treatment include commencement early in the course of the disease in order to be optimally effective in preventing initial or progressive organ failure and to establish which complications of the disease that do not respond to intravenously delivered enzyme [20].

The conclusion from the review by Rombach et al. [13] was that the smooth muscle cell is the primary cell involved in the vasculopathy of Fabry disease and that in an early stage of Fabry vasculopathy, angiotensin II production becomes upregulated. The proliferation of smooth muscle cells and GL-3 storage results in a higher intima-media thickness. Increased reactive oxygen species production as well as enhanced nitric oxide production may result in different findings with respect to endothelial activation markers, which can be severely enhanced in the context of other vascular risk factors. Selective angiotensin I receptor blockade may be an interesting option for optimal nitric-oxide-mediated vasodilatation and should be explored as adjunctive therapy [13]. Therefore, further studies not only on both the uptake of α-GAL A in brain vasculature and tissue, but also on the vasculopathy are needed in order to

optimise the management of the stroke risk and consequent treatment in patients with Fabry disease.

3. Cerebral Imaging in Fabry Disease Patients

The cerebral involvement in Fabry disease can be visualized on conventional magnetic resonance imaging (MRI) as multiple lesions located in the deep white matter and in the subcortical grey matter of both hemispheres. The cerebral lesion burden visible on these imaging methods increases with age and can precede the onset of neurological symptoms [26]. Females who are carriers of the disease might show MRI abnormalities similar to those of affected males [27, 28]. More recent studies, using proton emission tomography [29] and proton MRI spectroscopy [30], have suggested that metabolic abnormalities can be found even in the absence of cerebral lesions in patients with Fabry disease. This was substantiated [31] in 8 patients (4 males) with Fabry disease by the use of brain proton MRI/MR spectroscopic imaging examinations to obtain measures of total brain volumes, total brain lesion volumes, and magnetization transfer ratios in white matter and central brain levels of N-acetylaspartate (NAA) to creatine (Cr). The authors concluded that subtle structural and metabolic tissue damage could extend beyond white matter in subjects with Fabry disease. A diffuse decrease in brain NAA/Cr could occur in Fabry subjects in relation to the degree of their CNS involvement and its evolution over time.

Moore et al. [32] studied neuroradiologic records of 104 hemizygous patients with Fabry disease for the presence of hyperintensity on the T1-weighted images. Additional CT, gradient-echo (T2*-weighted), and fat-suppression MR studies were reviewed to characterize further the T1 abnormality in selected patients. Overall, 22 patients (23%) demonstrated pulvinar hyperintensity on T1-weighted images; the frequency increased with age to over 30% by age 50 years. They concluded that hyperintensity in the pulvinar on T1-weighted images is a common finding in Fabry disease, likely reflecting the presence of calcification, and exclusive involvement of the pulvinar may be distinctively characteristic to Fabry disease. Increased cerebral blood flow in the posterior circulation, particularly the thalamus, suggested that the dystrophic calcification was secondary to cerebral hyperperfusion and selective vulnerability of the pulvinar and adjacent thalamic nuclei. Thus, according to the authors, the finding of isolated pulvinar hyperintensity on T1-weighted images should suggest Fabry disease, particularly when seen in conjunction with other nonspecific neuroradiologic manifestations of the disease.

This finding was later supported by Burlina et al. [33] who investigated the pulvinar sign and its relationship with other clinical findings in a total of 36 patients (16 males, 20 females) from 14 families. The pulvinar sign was found in 5 male patients but not in any of the investigated female patients. Seven patients had had at least one stroke (territorial or lacunar), but there was no correlation between the occurrence of stroke and the pulvinar sign. All patients with the pulvinar sign had hypertrophic cardiomyopathy. Four patients out of five with the pulvinar sign were on dialysis or had had a kidney transplantation. They suggested that the pulvinar sign is a highly specific sign of Fabry disease, found in male patients with cardiac signs and severe kidney involvement, and very recently, they also demonstrated the pulvinar sign in a female Fabry patient (Burlina, personal communication).

The importance of the pulvinar sign was recently challenged by Fellgiebel et al. [34], who could not find similar results in a comprehensive study on the diagnostic utility of different MRI and MR angiography measures in Fabry disease. They investigated 25 clinically affected patients with Fabry disease (age 36.5 ± 11.0 years) and 20 age-matched controls by structural MRI, MR angiography, and diffusion tensor imaging. They determined individual white matter lesion volumes, global mean diffusivity, and mean cerebral artery diameters. Using receiver-operating characteristic analyses, they were able to demonstrate that enlarged diameters of the middle cerebral artery, posterior cerebral artery, carotid artery, and basilar artery significantly separated patients with Fabry disease from controls. A total of 87% of the individuals were correctly classified by basilar artery diameters (sensitivity 95%, specificity 83%), while neither white matter lesion volumes nor global mean diffusivity values could significantly separate patients from controls. In their study, basilar artery diameters were superior to all other MR measures for separating patients with Fabry disease from controls with an accuracy of 87%, and they therefore recommended that future studies should adopt basilar artery measurements for early detection and monitoring of brain involvement in Fabry disease. All in all, the latter could speak in favour of performing further investigations to reveal if the dilated vasculopathy in Fabry disease could be a screening marker to detect Fabry disease in a cohort of other cerebrovascular diseases, especially in cryptogenic stroke in young individuals.

4. Prevalence of Stroke in Fabry Patients

Several studies have estimated the incidence of stroke in various small cohorts of patients with Fabry disease. Vedder et al. [2] reported that 12 of 25 males (48%) and 13 of 41 females (32%) had experienced a cerebrovascular accident or lacunar stroke, at a median age of 46 and 52 years, respectively. Gupta et al. [35] reported that 4 of 54 female Fabry patients (7%) had experienced strokes, at a median age of 51 years, and Mehta et al. [26] found that 24 of 216 males (11%) and 27 of 172 females (16%) had experienced either a TIA or a stroke. Grewal et al. reviewed various types of imaging data and reported that 8 of 33 Fabry patients (24%) had experienced strokes at a median age as low as 26.5 years [36].

From the FOS Registry, the overall prevalence of ischaemic stroke or TIAs was 13% [37], events tending to occur at an earlier age with 12 times higher number of ischaemic strokes in the male 25–44 years age group compared to what could be expected in the general population. A significantly higher proportion of patients with Fabry disease, who had

a history of cerebrovascular complications, had valvular heart disease, left ventricular hypertrophy, arrhythmias, or hypertension compared to those with no history of such complications. Not surprisingly, Sims et al. [7] found in the Fabry Registry that patients who had strokes were much more likely to have reported a medical history of various risk factors for strokes, as compared to other patients. Compared to nonstroke patients, those who had strokes were more likely to report TIAs (36.2% versus 5.4%), arrhythmias (32.6% versus 12.7%), or hypertension (52.9% versus 20.5%). Furthermore, similar percentages of male and female stroke patients reported a history of TIAs. Male stroke patients were more likely than females to have reported a history of arrhythmias. A greater percentage of females who had strokes reported a history of hypertension (32 of 52, 61.5%), as compared to males (41 of 86, 47.7%). Among the two subpopulations of patients with strokes at <30 years (all of whom had ischaemic strokes) and those with haemorrhagic strokes, respectively, the proportion of patients with a history of TIAs or arrhythmias was generally similar to that observed in the overall population of Fabry stroke patients. Finally, patients with hemorrhagic strokes were more likely to have reported a history of hypertension (11 of 16, 68.9%) than patients with a stroke below 30 years of age (8 of 30, 26.7%), and overall, 73 of 138 Fabry stroke patients (52.9%) had a history of hypertension.

Thus, the presence of hypertension should be a warning sign for future strokes in young Fabry patients and be treated vigorously with antihypertensive drugs, antiplatelet drugs, and statins if appropriate, in order to prevent strokes. Another warning sign is cardiac affection, in particular arrhythmia as mentioned above.

5. Prevalence of Fabry Disease among Young Patients with Stroke

A screening study of 721 young German patients (age 18 to 55) who had strokes of unknown aetiology reported that 4.9% of males and 2.4% of females had Fabry disease [38]. Based on these findings, it was estimated that 1% to 2% of all stroke patients within this age range could have Fabry disease [28]. Others have suggested that this percentage may be higher [39] or lower [40]. A very recent study [41] was published from Portugal, where during one year, all patients aged 18 to 55 years with first-ever stroke, who were admitted into any of 12 neurology hospital departments, were prospectively enrolled (n = 625) and assessed for presence of a *GLA* mutation. Alpha-galactosidase activity was further assayed in all patients with *GLA* mutations. Four hundred ninety-three patients (mean age, 45.4 years; 61% male) underwent genetic analyses: 364 with ischaemic stroke, 89 with intracerebral hemorrhage, 26 with subarachnoid hemorrhage, and 14 with cerebral venous thrombosis. Twelve patients had missense *GLA* mutations: 9 with ischaemic stroke, including 5 patients with an identified cause of stroke (2 with cardiac embolism, 2 with small vessel disease, and one with other cause), 2 with intracerebral haemorrhage, and one with cerebral venous thrombosis. Leukocyte α-galactosidase activity was subnormal in the hemizygous males and subnormal or lownormal in the heterozygous females. The estimated prevalence of missense *GLA* mutations was thus 2.4% (95% CI, 1.3% to 4.1%).

The Stroke Prevention in Young Men Study enrolled men (15 to 49 years) with first ischaemic stroke in the Baltimore-Washington area in 2004 to 2007 [42]. Frozen plasma samples were assayed for α-Gal A activity, and DNA from patients with consistently low plasma α-Gal A activities was sequenced. In the study sample of 558 men (42% African-American; median age 44 years), stroke was cryptogenic in 154 (40% African-American). Ten patients had low plasma α-Gal A activities, but DNA sequencing identified alterations in the α-Gal A gene in only 2 of these patients. Their study suggested a low yield of screening for Fabry disease in young men with an initial ischaemic stroke regardless of aetiology. The yield of screening in recurrent cryptogenic ischaemic stroke in young adults still remains unclear. There is therefore a need for a large sample size replication of the findings of the German study [28], which suggested a prevalence of 24.3% for unrecognized Fabry disease among men with recurrent cryptogenic stroke. Because Fabry disease is a treatable condition and the diagnosis has implications for other family members, the decision to screen for Fabry disease should be made on an individual basis. A better understanding of the natural history of cerebrovascular manifestations of Fabry disease may provide valuable information about which patients may be at greatest risk for stroke. Such information can also raise the awareness of Fabry disease within the broader medical community and highlight the importance of improved monitoring and management options. Despite a low diagnostic yield, screening for *GLA* mutations should probably be considered in different types of stroke. Restricting investigation to patients with cryptogenic stroke may underestimate the true prevalence of Fabry disease in young patients with stroke.

6. The Special Case of Females with Fabry

In recent years, the involvement in heterozygous females has been more extensively documented [1, 5, 8, 9, 12, 43]. Heterozygotes for the classic phenotype of Fabry disease can be asymptomatic throughout life or have as severe manifestations as affected males [1, 5, 8, 9, 12, 42–44]. Most mutation-confirmed heterozygotes have the corneal opacities, which are observed by slit-lamp microscopy and are a useful diagnostic finding. About 53 to 70% of heterozygous females will have episodic neuropathic pain as reported in several studies [5, 8, 12, 42–44]. So the findings of pain in the extremities, which is exacerbated by fever, exercise, and stress, together with the typical eye changes are significant diagnostic findings. Other findings in Fabry heterozygotes include sparse angiokeratoma, hypohidrosis, gastrointestinal pain and cramping, and diarrhea. Interestingly, female Fabry patients were shown to have a higher prevalence of strokes or TIAs of 16% compared to 11% in males in the FOS registry

natural history paper [3], perhaps because fewer of them die from renal failure.

7. Diagnosing Fabry Disease

The diagnosis of Fabry disease in males is reliably made by demonstrating the α-Gal A enzymatic deficiency [45]. However, in heterozygous females, the α-Gal A enzymatic activity can range from very low to high normal values due to random X-inactivation [45–47]. To accurately identify heterozygote, the family's mutation must be identified. Suspect heterozygotes with no family history of Fabry disease require α-Gal A gene sequencing for diagnostic confirmation. In a few cases, this is also difficult if the patient does not display a mutation on sequencing, as in case of large deletions (Feldt-Rasmussen et al., unpublished observation). In such cases, eye examination, neurological assessment, and kidney biopsy can be of importance.

8. Screening for Fabry Disease?

The frequency of the classic phenotype has been estimated at ~1 in 40,000 males [1], and recent newborn screening studies have found the incidence of classically affected males to be ~1 in 24,620 by screening over 147,700 consecutive newborn males in Taiwan [48, 49] and ~1 in 37,000 newborn males screened in Italy [50]. In the latter study, 12 male neonates had deficient α-Gal A activities and specific mutations, revealing a surprisingly high Fabry disease incidence of one in 100 males. Of the 12 neonates with α-Gal A deficiency, 11 had mutations predicting the later-onset phenotype for an 11:1 ratio of later-onset/classic phenotypes [50]. No similar studies have been done in females. These figures have given rise to a discussion as to whether or not newborn screening for Fabry males should be done due to availability of a safe treatment option and probably an efficient one if started early in life to prevent progressive irreversible tissue and organ damage.

While waiting for such decision, it may rather be worthwhile for clinicians to consider screening of specific patient populations for Fabry disease [51]. These considerations should include young people with stroke or TIAs at least those without other known aetiology. It seems that approximately 1-2% of young stroke patients are demonstrated with Fabry disease. The recruitment to the sifap1 (stroke in young Fabry patients) study provides the largest prospective case series of young stroke patients reported so far. Results are expected to provide novel information on the prevalence of Fabry in the population as well as characteristics of the patients. The further analyses of results of this study will therefore possibly add to the decision on whether or not to screen young stroke patients for Fabry disease [52].

However, screening for Fabry disease among young stroke patients would only be meaningful if it can be verified that subsequent enzyme replacement or other therapy can prevent further stroke episodes. Currently, such information is not available from any of the published studies on treatment efficacy [53–55].

9. Treatment Options

As mentioned previously, ERT replacement in Fabry disease is now a treatment option in most countries [18, 53, 54], although a production limitation in Fabrazyme has been known for a while, an issue which is not yet solved. One of the drawbacks of the treatment is the fact that it needs intravenous infusion, another one is the price. Whether or not to start treatment early, particularly in males, to prevent progression of organ manifestations or in some cases to wait and see is still not agreed upon internationally. One of the difficulties in obtaining proper evidence is the rarity of the disease and the relatively short treatment and follow-up period in the existing trials.

Apart from that, trials are going on concerning the use of chaperone therapy, which is oral, but only effective in certain genotypes. It may, however, also prove efficient in patients with other genotypes as adjunctive therapy to ERT, and gene therapy is another imminent therapy ready for clinical testing [52]. In addition, it is becoming increasingly important to use also other treatments, for example, primary stroke prevention including lifestyle counseling and blood pressure and lipid lowering drugs, but additionally ACE inhibitors, angiotensin I and II receptor antagonists [13], and finally anti-inflammatory agents [24] and vitamin D receptor agents [56] may prove effective in slowing down the progression of the vasculopathy and not only be used for renal protection.

The evidence for providing firm algorithms for initiation of therapy in males and females, respectively, is not available, and they are therefore currently arbitrary and diverging between countries and treatment centers.

10. Conclusion

Fewer patients than previously with Fabry disease die from renal failure mainly due not only to a better general renal care but also to ERT, and therefore more of them live to experience other complications such as cardiac arrhythmias, left ventricular hypertrophy, hypertrophic cardiomyopathy, and stroke occurring with advancing age in both genders [1, 5, 9, 12, 44, 57]. Thus, pediatricians, neurologists, cardiologists, and internists should be aware of the disease manifestations in children, adolescents, and young adults, particularly because the earlier the diagnosis is suspected and confirmed and the earlier treatment, including ERT is initiated, the more effective is the therapy [18, 53, 56, 58]. Thus, it is important to add primary stroke prevention including lifestyle counseling, blood pressure and lipid-lowering drugs, and additionally ACE inhibitors, angiotensin I and II receptor antagonists [13], in order to slow down the progression of the vasculopathy and not only be used for renal protection. Targeted screening for Fabry disease among young individuals with stroke seems to disclose unrecognized cases and may therefore very well be recommended as routine in the future. For this to be verified, the results of the sifap study is much awaited [52].

Disclosures

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