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The Diagnostic and Therapeutic Challenges of Fabry Nephropathy—A Review of the Literature, Illustrated by a Clinical Case

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Abstract

Fabry Disease (FD) is a rare lysosomal storage disorder characterized by α-galactosidase A (α-Gal A) enzyme deficiency, resulting in glycosphingolipid accumulation. Its clinical spectrum ranges from severe classical to milder non-classical or late-onset phenotypes. Renal involvement, termed Fabry Nephropathy (FN), can vary from mild proteinuria to kidney failure. FN diagnosis, especially in nonclassical cases with a genetic Variant of Unknown Significance (VUS) in the *GLA* gene, poses challenges. Measurement of plasma lyso-Gb3 levels is gaining importance in FN diagnosis, while renal biopsy with electron microscopy remains the gold standard in equivocal cases. Treatment options include Enzyme Replacement Therapy (ERT) and chaperone therapy, demanding careful candidate selection due to high treatment costs. Research has predominantly focused on classical FD, revealing modest treatment benefits. However, evidence for treating patients, especially females, with milder nonclassical or late-onset phenotypes is scarce, emphasizing the necessity for placebo-controlled clinical trials in these subgroups. Meanwhile, participation in global FD registries can improve our understanding of disease management.
Case Presentation: A woman in her late sixties presented with moderate chronic kidney disease, mild proteinuria, and microscopic hematuria. Her family history included a prevalence of renal, cardiac and cerebrovascular diseases. Kidney biopsy revealed characteristic myelin figures and zebra bodies in podocytes, strongly suggestive of FN. Genetic analysis identified a VUS in

the *GLA* gene (c.655A > C, p.Ile219Leu), introducing diagnostic uncertainty. Further investigations revealed severe cardiac involvement. Considering the recurring difficulty presented by the finding of a VUS in the *GLA* gene during FN assessments, along with the uncertainty regarding the need for treatment in nonclassical or late-onset FD phenotypes, especially in women, this case becomes a central focus for a thorough review of the literature. This review aims to propose a practical algorithm that integrates clinical, biochemical, and genetic markers for FN screening and diagnosis. Additionally, it explores treatment benefits in nonclassical or late-onset FD phenotypes, with a focus on female patients.

Keywords

Fabry Disease, Fabry Nephropathy, Variants of Unknown Significance, Diagnosis, Treatment Selection, Lysosomal Storage Disorder, *α*-Galactosidase A, Glycosphingolipid Accumulation, Enzyme Replacement Therapy, Migalastat

1. Background

In 1898, the German dermatologist Johannes Fabry and the British surgeon William Anderson independently documented a hereditary skin condition featuring generalized angiokeratomas accompanied by albuminuria, later termed Fabry Disease (FD) [1] [2]. FD is a rare lysosomal storage disorder resulting from *α*-Galactosidase A (*α*-Gal A) enzyme deficiency, leading to glycosphingolipid accumulation throughout the body [3] [4]. The Galactosidase (*GLA*) alpha gene on the X-chromosome encodes *α*-Gal A [5] and pathogenic mutations in this gene can lead to absent or reduced *α*-Gal A levels, thereby determining disease severity [6]. The phenotypical spectrum ranges from severe classical FD to milder nonclassical or late-onset FD [7] [8]. In the classically affected hemizygous male, who has no detectable *α*-Gal A activity, FD becomes symptomatic during childhood or adolescence with various symptoms, such as angiokeratoma, acroparesthesia, cornea verticillata, hypohidrosis and proteinuria. Typically, around the fourth to fifth decade of life, severe complications such as progressive renal failure, cardiomyopathy, cardiac arrhythmias and cerebrovascular disease occur, resulting in a shortened lifespan [9] [10] [11]. Due to X-linked inheritance, women usually exhibit milder FD phenotypes and might even remain asymptomatic until later in life. However, some women can still present a classical phenotype, showing the full spectrum of disease manifestations [12] [13]. This variability is explained by skewed X-inactivation, where the predominant expression of the mutant *GLA* allele leads to more severe disease outcomes [14]. The importance of the specific mutations at play is highlighted by reports of homozygous and compound heterozygous females revealing varying disease severity [15] [16] [17]. In general, studies indicate a lifespan shortened by an average of

approximately 10 years among women with FD [10] [12].

Reported FD prevalence (1 in 40,000 to 1 in 117,000) likely underestimates true prevalence due to undiagnosed cases with nonclassical FD phenotypes [18] [19]. This was highlighted by a series of newborn screening studies, revealing a birth prevalence of 1 in 1.250 [20]. Nevertheless, it is important to note that diagnosis in these studies was based on the presence of variants in the *GLA* gene and/or reduced α-Gal A activity, which are not exclusively indicative of FD. The actual prevalence likely falls in between. Enzyme Replacement Therapy (ERT) has been available for over two decades [21] [22], while the introduction of oral chaperone treatment later expanded therapeutic options [23].

Diagnosis and treatment decisions are usually straightforward in classical FD with a (likely) pathogenic *GLA* mutation. However, this case report highlights challenges in diagnosing and treating patients with milder and nonspecific FD symptoms. We present a case of an elderly female patient with moderate chronic kidney disease, where genetic analysis revealed a *GLA* gene, Variant of Unknown Significance (VUS). To address these difficulties, we included a literature review on the diagnosis and treatment of kidney disease in FD, hereinafter referred to as Fabry Nephropathy (FN).

2. Case Report

A woman in her late 60s was referred to the UZ Brussel nephrology outpatient clinic due to proteinuria and hematuria detected during routine dipstick analysis. Her electronic medical records revealed a consistent presence of hematuria and proteinuria over the preceding four years. In her 40s, she was diagnosed with ovarian cancer for which she had undergone omentectomy and chemotherapy. Additionally, she had been receiving treatment for arterial hypertension since that time.

She was born and raised in Morocco. Her father lived into his 80s and enjoyed good health throughout his life. Her mother experienced cardiac problems over an extended period and died in her 70s due to a myocardial infarction. Among her three brothers, one passed away in his 40s due to unspecified kidney disease, another in his 60s due to a stroke, and her remaining brother, now in his 50s, had cardiac issues requiring a pacemaker, with no reported kidney disease. Her daughter, in her 40s, and two grandchildren were in good health.

At the time of presentation, she was asymptomatic, and her comprehensive patient history did not reveal any unexplained symptoms. Her medication included eprosartan and an oral vitamin B complex. Physical examination revealed obesity with a body mass index of 41 kg/m^2 and an elevated blood pressure of 155/75 mmHg. Blood analysis indicated mild kidney disease, with a serum creatinine level of 1.1 mg/dL, corresponding to an eGFR CKD-EPI of 56 mL/min/1.73m^2. Urine analysis showed the presence of microscopic hematuria and micro-albuminuria at 62 mg/g creatinine. Further investigations, including serum protein electrophoresis, complement analysis, screening for rheumatoid

factor and cryoglobulins, as well as testing for antineutrophil cytoplasmic antibodies, antinuclear antibodies and anti-GBM antibodies, yielded normal results. Kidney MRI revealed normal-sized kidneys with bilateral simple cortical cysts, the largest of which measured approximately 3.5 cm. The differential diagnosis included *COL4A*-related kidney disease, IgA nephropathy, or another unspecified mild glomerulonephritis.

Subsequently, a kidney biopsy was performed. Evaluation of nine glomeruli under light microscopy (**Figures 1(A)-(C)**) revealed normal mesangial cellularity. Certain regions showed hyperplastic podocytes containing clear isometric intracytoplasmic granules. Tubules displayed dedifferentiation and regenerative

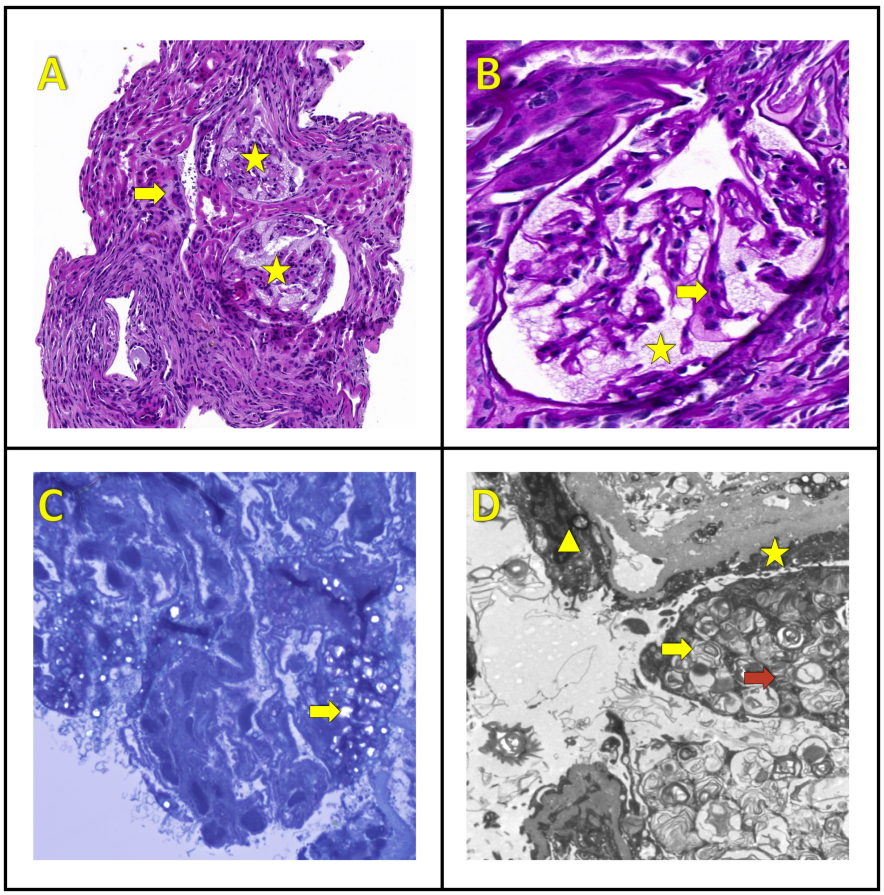

Figure 1. Renal biopsy examination. (A) Light microscopy illustrates preserved overall architecture with slight interstitial fibrosis (arrow). Two glomeruli exhibit enlarged foamy podocytes (stars) (Hematoxylin eosin stain, 100× magnification). (B) Light microscopy provides an in-depth view of a glomerulus, revealing a normal mesangium (arrow). It also exhibits diffuse global enlargement and a foamy appearance of podocytes (star) (Hematoxylin-eosin stain, 200× magnification). (C) Light microscopy shows enlarged but empty lysosomes within podocytes, resulting from the use of lipid solvents during processing (arrow) (Toluidine blue stain, 200× magnification). (D) Electron microscopy, utilizing processing without lipid solvents as in (C), displays affected podocytes with distinct myelin figures featuring concentric layers (yellow arrow) and elongated striped zebra bodies (red arrow). These changes are accompanied by foot process effacement (star). An unaffected podocyte is also visible (triangle) (6200× magnification).

changes, with areas of slight interstitial fibrosis and mild tubular atrophy. Arterioles exhibited discreet hyalinosis, while medium-sized arteries displayed medial thickening and intimal fibrosis. Immunofluorescence microscopy did not detect any immune deposits.

Electron microscopy revealed segments of glomeruli with a preserved capillary wall architecture (**Figure 1(D)**). Endothelial cells showed no abnormalities. The glomerular basement membrane was thin and regular. Podocytes exhibited an excess of cytoplasm, foot process effacement, and the formation of cytoplasmic vacuoles with lamellar material arranged in successive layers with a striated appearance. The mesangium and glomerular basement membrane were devoid of deposits.

The electron microscopical image was identified as characteristic of FD, prompting genetic testing. Genetical analysis revealed a VUS within the *GLA* gene (c.655A > C, p.Ile219Leu). While this variant was absent in population databases like GnomAD, it had been reported in one female with clinically diagnosed FD [24].

Further investigations indicated the absence of vestibulocochlear, ophthalmological, or gastrointestinal involvement. Electrocardiography showed a sinus rhythm with a normal PR interval (190 ms), and T wave inversion in the anterolateral leads. Levels of cardiac troponin T (59 ng/L) and NT-proBNP (619 pg/mL) were elevated. Transthoracic echocardiography revealed left ventricular hypertrophy and a Left Ventricular Ejection Fraction (LVEF) of 40% - 45%, with hypokinesia of the basal and mid-anterolateral ventricular wall and akinesia of the inferolateral ventricular wall. Coronary angiography was normal. Cardiac magnetic resonance imaging confirmed left ventricular hypertrophy with a septal diameter of 19 mm, a reduced LVEF (38%) and late gadolinium enhancement in the septum and basal inferolateral segment.

According to the Galafold® amentability table [25], the identified *GLA* gene mutation was considered amenable to treatment with migalastat. Following a multidisciplinary evaluation, treatment was considered worthwhile, mainly because of cardiac reasons. Treatment was initiated shortly after.

3. Discussion and Review of the Literature

This case highlights the intricate diagnostic challenges associated with nonclassical FD phenotypes when a VUS is present in the *GLA* gene. Given the rarity of FN, many nephrologists may not be familiar with its presentation and diagnosis.

Prior to the availability of treatments for FD, large-scale analyses in Europe and the United States identified approximately 20 known FD patients per 100,000 patients on Renal Replacement Therapy (RRT), with males comprising nearly 90% of the cases. Typically, FD patients started RRT in their late thirties to early forties, but survival rates of FD patients on RRT remained notably lower compared to other patients, primarily due to cardiovascular complications [19] [26].

3.1. Pathophysiology of FN

FN's pathophysiology centers on continuous glycosphingolipid buildup across all glomerular cell types, initiating early in life and potentially even before birth, well before onset of proteinuria or declining kidney function [27] [28] [29] [30]. Notably, podocytes, due to their limited regenerative capacity, exhibit the most pronounced disturbances among the different glomerular cell types. Initially, glycosphingolipid accumulation causes podocyte expansion, a process that continues until around ages 25 to 30 in classical FD. Beyond this threshold, podocytes struggle to accommodate the increasing glycosphingolipid load, leading to increased podocyte stress, evident as foot process effacement, and ultimately culminating in podocyte loss. Podocyte loss initially leads to segmental and later global glomerulosclerosis [31]. In women with FN, skewed X-inactivation can result in a podocyte mosaicism. This means that glycosphingolipid deposits are only present in podocytes in which the X-chromosome carrying the *GLA* mutation is dominant [32].

The process of glycosphingolipid accumulation is observable microscopically through cytoplasmic vacuolization in all glomerular cell types, with podocytes notably displaying a foamy appearance [33]. Electron microscopy reveals multilamellar inclusions of glycosphingolipids, appearing as myelin figures composed of concentric layers, alongside zebra bodies exhibiting an elongated striped appearance [34]. Recent research suggests the involvement of pathogenic pathways beyond glycosphingolipid metabolism, resulting in the buildup of α-synuclein, exacerbating lysosomal dysfunction. This α-synuclein accumulation remains unresponsive to current treatments. This finding may explain the limited potential of existing therapies to reverse glomerular damage, while also offering a potential avenue for future therapeutic interventions [35].

3.2. Screening and Diagnosis of FN

While guidelines exist for identifying FN in individuals with a classical FD phenotype or affected family members [36] [37], diagnosis becomes less straightforward when these criteria are not met. In such cases, it is advisable to consider FN as a possibility when unexplained kidney disease occurs, particularly in males under 50 and females with potential FD-related symptoms [38] [39].

Several clues can heighten suspicion for FN. Proteinuria is present in 25 to 30% of cases, more often in advanced FN [13] [40]. However, its sensitivity for early FN detection is limited [41] and it may even be absent in advanced stages [42]. Glomerular hematuria, although atypical, may occasionally occur [43]. Urine microscopy offers a noninvasive and inexpensive approach to reveal FN indicators like podocyturia [30] [44] [45], lipid particles with a distinctive Maltese cross pattern under polarized light microscopy [33] [46], and Mulberry cells—distal tubular epithelial cells containing glycosphingolipid accumulations [47]. Additionally, renal cysts, mainly parapelvic cysts, are found in up to half of the cases [48]. Although these features can raise suspicions of FN, their diagnostic value

remains uncertain, as there is ongoing debate about their sensitivity and specificity [49].

Diagnosis of FD in males involves assessing α-Gal A activity in leukocytes, with reduced levels suggesting FD and levels below 5% indicating a classical phenotype [50]. In heterozygous females, skewed X-inactivation can result in normal α-Gal A activity in leukocytes for up to one-third of patients [51]. However, in females with FD, disease severity does not correlate with residual α-Gal A activity, rendering this marker devoid of diagnostic or prognostic significance in women [52].

In recent years, there has been a lot of attention on the diagnostic and prognostic value of glycosphingolipid substrates of the α-Gal A enzyme, like globotriaosylceramide (Gb3) and its hydrophilic deacylated variant, globotriaosylsphingosine (lyso-Gb3). Urinary Gb3-levels can be increased in patients with FN, but lacks specificity as increased urinary Gb3-levels have also been described in patients with cardiac disease or nephrotic syndrome in the absence of FD [53] [54]. Similarly, plasma Gb3-levels are associated with a high rate of false-positives when used for screening purposes [55]. The measurement of the more soluble lyso-Gb3 in plasma emerged as a more reliable marker, exhibiting a stronger correlation with disease severity compared to the inconsistent relationship observed between Gb3 levels in plasma or urine and disease severity in both genders [56]. Plasma lyso-Gb3 rises and reaches a plateau during childhood in males with FD and females with a classical FD phenotype, making it a useful diagnostic tool [8] [57]. Additionally, plasma lyso-Gb3 levels can differentiate between classical and nonclassical phenotypes in men using a cutoff of approximately 45 to 50 nmol/L (normal range 0.3 - 0.5 nmol/L) [8] [58] and can identify subgroups at heightened risk of severe FD manifestations [59].

Genetic analysis is crucial for diagnosing FD in females and confirming FD in males [36] [37] [38] [39]. It often reveals a VUS in the *GLA* gene which, in the absence of symptoms or signs of organ involvement, may correspond to milder FD phenotypes or absence of the condition. The introduction of ERT prompted numerous screening studies, often supported by the pharmaceutical industry, revealing unexpectedly high counts of *GLA* gene variants. A 2014 systematic review by Van der Tol *et al.* reported pooled prevalence rates of 0.04% among newborns and 0.62% within high-risk populations [20]. To prevent overtreatment, it is crucial to differentiate individuals with a *GLA* VUS who have FD from those with unrelated symptoms.

To address this concern, an international panel of FD experts has established organ biopsy as the definitive gold standard to confirm glycosphingolipid accumulation in uncertain cases [60]. In the context of FN, this entails confirming the presence of characteristic lysosomal glycosphingolipid inclusions within the glomerulus using electron microscopy. Simultaneously, the use of chloroquine and amiodarone should be ruled out, as these medications can induce similar storage patterns [49]. A validated standardized scoring system for FN has been

developed, covering both disease-specific lesions (related to lipid deposition) and general markers of progression (fibrosis and sclerosis) [61]. Nevertheless, kidney biopsy should not be reserved for uncertain cases as histology can provide valuable information on potential simultaneous processes which need treatment and to assess the extent of glomerular damage which does not always correlate well with the serial measurements of eGFR. More extensive damage can influence treatment decisions.

Based on the aforementioned clinical, biochemical and genetic markers, we have proposed an algorithm to guide in the screening and diagnosis of FN (**Figure 2**).

Following this diagnostic algorithm, we were able to confirm the FN diagnosis in our patient. The identified VUS within the *GLA* gene (c.655A > C, p.Ile219Leu),

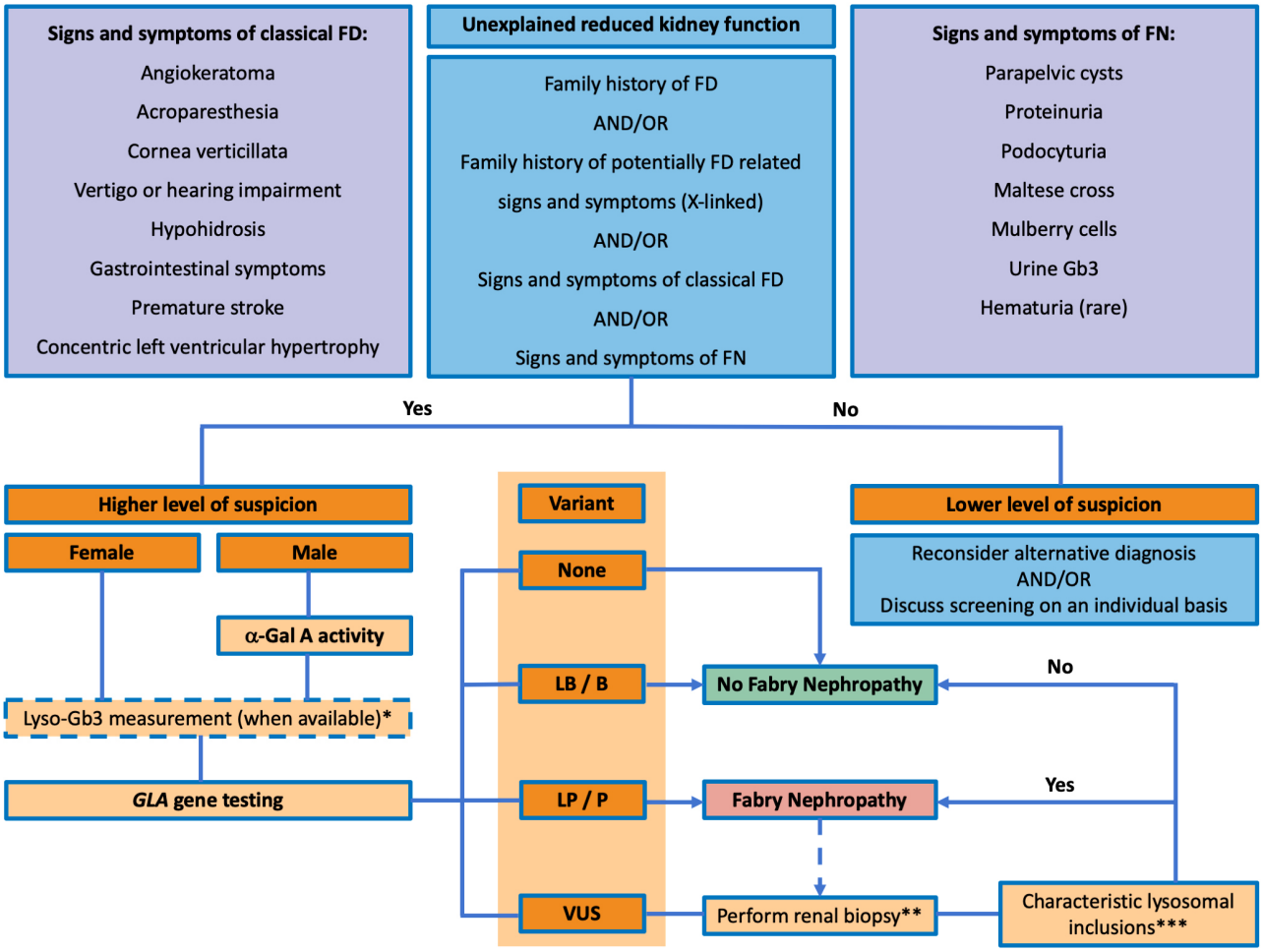

Figure 2. Suggested algorithm for FN screening and diagnosis. *Lyso-Gb3 measurement is not required for diagnosis, but when available lyso-Gb3 should be measured in both males as well as females for confirmation of diagnosis and prognostication. **Renal biopsy is necessary in cases of VUS to confirm diagnosis but can be performed in cases with a pathogenic mutation as well for prognostication. ***Electron-dense multilamellar glycosphingolipid inclusions (myelin figures exhibiting concentric layers and elongated striped zebra bodies) in the absence of drug use known to induce these lysosomal inclusions such as chloroquine or amiodarone. Abbreviations: α-Gal A: Alpha-Galactosidase A, FD: Fabry Disease, FN: Fabry Nephropathy, GLA: Galactosidase Alpha, LB/B: Likely Benign/Benign, LP/P: Likely Pathogenic/Pathogenic, VUS: Variant of Unknown Significance.

in conjunction with typical electron microscopy findings, the patient's clinical phenotype, and family history, aligns with the American College of Medical Genetics and Genomics (ACMG) criteria, indicating likely pathogenicity [62].

3.3. Selecting Patients for Treatment

The treatment landscape for FD offers two main therapeutic options: ERT and migalastat. ERT, available since 2001, addresses the deficiency of the α-Gal A enzyme and includes agalsidase-α (Replagal®) and agalsidase-β (Fabrazyme®) [21] [22]. However, intravenous ERT can lead to immune responses, reducing its effectiveness and causing infusion-related reactions [63]. A newer pegylated ERT, pegunigalsidase alfa (Elfabrio®), offers improved stability and reduced immunogenicity [64]. On the other hand, migalastat (Galafold®), introduced in 2016, is an oral chaperone treatment that restores α-Gal A activity in patients with responsive *GLA* mutations [23]. Migalastat has demonstrated good tolerability, but only approximately 30% - 35% of FD patients have *GLA* mutations amenable to migalastat treatment. A list of these amenable mutations, based on *in vitro* tests in human embryonic kidney cells, is available online (https://www.galafoldamenabilitytable.com/, last updated 27th of August 2021) [25]. Unlike ERT, migalastat is primarily excreted in urine and is not recommended for patients with an eGFR below 30 mL/min/1.73m^2. Migalastat has demonstrated a lower incidence of severe renal, cardiac and cerebrovascular complications at 1.5 years of treatment when compared to ERT [65].

Identifying FD patients who would benefit from ERT or migalastat remains challenging. Observational studies on the natural course of renal involvement in FD have primarily focused on classical FD phenotypes, revealing annual Glomerular Filtration Rate (GFR) decline rates of approximately −3 mL/min/1.73m^2 in males, and −1 mL/min/1.73m^2 in females [10]. In females, this decline mirrors the age-related GFR-decline typically observed from the fourth to sixth decade onward in the general healthy population. However, another observational study including more women showed that almost 40% experienced a more rapid kidney function decline [66]. From these studies, proteinuria emerged as the strongest predictor for the rate of eGFR decline and the progression to kidney failure. Higher levels of proteinuria, defined variably as approximately ≥ 1 g/24h and ≥ 1.2 - 1.5 g/g creatinine, were linked to annual GFR decline rates ranging from −5.6 to −6.9 mL/min/1.73m^2 in males and −1.3 to −4.6 mL/min/1.73m^2 in females [10] [66].

Both ERT and migalastat effectively reduce glycosphingolipid accumulation in the kidney [67] [68]. Given ERT's longer history, most research has revolved around ERT. These studies predominantly included male patients with classical FD phenotypes and highlighted ERT's potential to slow or halt kidney function decline in both genders [69] [70] [71] [72]. The impact of ERT in these studies was most pronounced when commenced early, prior to the onset of irreversible organ damage [73] [74] [75] [76]. Pooling these data, meta-analyses indicate that

the effectiveness of ERT in stabilizing kidney function is somewhat limited. The benefits of ERT for FN primarily manifest in male FN patients with an eGFR below 60 mL/min/1.73m^2, while no discernable differences in the rate of kidney function decline were observed between treated and untreated women [77] [78]. This absence of a clear treatment effect in women with FN, especially those exhibiting a nonclassical FD phenotype, is apparent in the European Fabry Working Group consensus. This consensus recommends ERT for classical FD phenotypes in both genders but only considers it for females with nonclassical FD phenotypes [79].

Research on migalastat in FN has produced conflicting results. Long-term observational studies spanning up to nine years have shown that migalastat treatment stabilizes kidney function without significantly affecting proteinuria, with annual kidney function decline rates ranging from −0.3 to −1.4 mL/min/1.73m^2 in females [80] [81]. However, two single-center studies reported an accelerated kidney function decline among patients receiving migalastat treatment, possibly linked to the inclusion of patients with more severe kidney and cardiac involvement. These studies also identified a correlation between systolic blood pressure below 120 mmHg and accelerated kidney function decline, potentially exacerbated by the higher Angiotensin Converting Enzyme Inhibitors (ACEIs) and Angiotensin Receptor Blockers (ARBs) usage [82] [83]. This latter stands in contrast to studies indicating that lowering proteinuria below 0.5 g/g creatinine by using ACEIs and ARBs correlated with stabilization of kidney function in conjunction to ERT [42] [84]. It is generally accepted however, that in addition to ERT or migalastat, adjunctive treatment of FN needs to include managing blood pressure, hyperlipidemia and proteinuria [85]. Emerging studies are exploring Sodium-Glucose Cotransporter Inhibitors (SGLT2Is) in FN [86].

Given the absence of strong evidence demonstrating clear treatment benefits on kidney function, especially in females with nonclassical or late-onset phenotypes, it was determined that neither ERT nor migalastat treatment would provide substantial advantages beyond conservative treatment for the patient described in this case report concerning her kidney involvement. However, it is important to note that she also presented with severe Fabry cardiomyopathy. When it comes to cardiac involvement, expert consensus lacks specific directives for treatment initiation or precise timing, primarily emphasizing early initiation while recognizing limitations in advanced disease stages or extensive myocardial fibrosis. Unfortunately, it does not provide guidance on determining the point at which treatment becomes less beneficial [87]. Several meta-analyses have highlighted ERT's efficacy in stabilizing or reducing left ventricular mass in both genders, even in the absence of ventricular hypertrophy at baseline [77] [88]. It should be mentioned that there is limited availability of untreated data on left ventricular mass in FD [89]. Regarding migalastat, data are limited but have shown a decrease in left ventricular mass [87]. Additionally, studies suggest that migalastat may be more effective in improving left ventricular hypertrophy com-

pared to ERT treatment [23] [90]. Following a multidisciplinary meeting, it was decided to initiate migalastat treatment for the patient in this case report, primarily for cardiac reasons.

4. Conclusions

Diagnosing and managing FN, especially in cases with nonclassical FD phenotypes lacking family history or clear FD-related signs, presents significant challenges. It is currently recommended to screen all individuals with unexplained chronic kidney disease, particularly younger individuals with unexplained symptoms potentially linked to FD. However, indicators such as urine microscopy abnormalities, renal cysts and proteinuria, while heightening suspicion for FN, lack the necessary sensitivity and specificity for a definite FN diagnosis. When available, lyso-Gb3 can be measured to identify individuals with a classical FD phenotype and differentiate between classical and nonclassical FD phenotypes in men. The integration of massively parallel sequencing techniques into clinical practice has improved the diagnosis of genetic kidney diseases, revealing monogenic causes for a substantial portion of previously unexplained chronic kidney disease cases [91]. Including the *GLA* gene in multigene panels is likely to enhance FN diagnoses, especially among females with nonclassical FD phenotypes. Nevertheless, this broader approach also increases the likelihood of detecting VUS within the *GLA* gene. In such cases, a reliable FN diagnosis can be confirmed through a kidney biopsy. Unfortunately, comprehensive data on the natural progression of FN is scarce. Studies evaluating disease progression in untreated patients were halted with the advent of treatment availability [89], leaving a gap in our understanding, especially in females with nonclassical phenotypes. Though limited, existing data from this subgroup, suggest a relatively mild kidney disease without progression to kidney failure [7].

Regarding treatment, multiple options exist for FD, but none provide a cure and, at best, aim to modify the disease course. Evidence supporting treatment efficacy primarily derives from observational studies, with only a limited number of single-arm clinical trials and even fewer small placebo-controlled trials. These studies hint at potential benefits, such as slowing or halting kidney function decline in men, and possibly in women, with a classical FD phenotype. Additionally, they suggest a potential for reducing or stabilizing left ventricular mass in both genders. However, there is a lack of randomized clinical trials demonstrating significant reductions in critical clinical endpoints, such as kidney failure, cardiovascular events, and stroke. Furthermore, these studies rarely compare antiproteinuric treatment alone to treatment with ERT or migalastat.

In the absence of conclusive evidence supporting consistent treatment efficacy for all FD patient subgroups, questions arise regarding the justification for adopting expensive, intensive treatment regimens without individualized evaluation [92]. This concern is particularly pertinent for females with nonclassical or late-onset FD phenotypes. Our case highlights the need for international place-

bo-controlled trials [93], which were previously deemed ethically problematic due to the availability of treatment. However, it is equally ethically questionable to initiate treatment without robust evidence of its effectiveness.

Additionally, an alternative approach to advancing our understanding of FD involves enrolling patients in international FD registries, even in cases where treatment is not warranted. Unfortunately, existing international registries are primarily funded by pharmaceutical companies, driven by post-authorization requirements for orphan drug marketing in Europe. Regrettably, these registries tend to be primarily focused on the drugs themselves, rather than taking a comprehensive disease-oriented approach.

As advocated by Hollak *et al.* [94] [95], pharmaceutical company-driven registries can lead to data fragmentation, limited accessibility, and compatibility issues that may hinder independent third-party analysis, potentially introducing bias into resulting publications. To address this, it is imperative that FD registries be designed independently of pharmaceutical industry influence. Such registries should aim to provide open access to real-world data, fostering transparency and facilitating a more comprehensive and unbiased understanding of FD management.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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