

# FABRY DISEASE: CLINICAL CHARACTERISTICS, DIAGNOSIS AND MANAGEMENT

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## Abstract

Fabry disease (FD) is an X-linked, lysosomal storage disorder characterized by the decreased activity of the lysosomal enzyme, alpha-galactosidase A ( $\alpha$ -Gal A), related to mutations in the GLA gene (Xq21.3-q22). Deficient enzyme activity results in the accumulation of neutral glycosphingolipids and globotriaosylceramide (Gb3) in the plasma and cellular lysosomes of different tissues and organs throughout the body. Multi-system manifestations, such as progressive renal failure, cardiac disease, cerebrovascular disease, small-fiber and large-fiber peripheral neuropathy, and skin lesions, among other abnormalities complete the phenotype of FD. Diagnosis is based on the finding of reduced  $\alpha$ -Gal A activity in leukocytes or plasma or the detection of Gb3 accumulation in plasma, urine or biopsy specimens, while it is confirmed by molecular genetic testing. Regarding the disease prognosis, end-stage renal disease and life-threatening cardiovascular or cerebrovascular complications limit the life-expectancy of untreated males and females compared to the general population. However, disease-specific treatments are currently available, including enzyme replacement therapy and small-molecule chaperone treatment. In adjunction to symptomatic management, these therapeutic options have the potential to modify the disease course and halt progression. Furthermore, other treatments such as substrate reduction therapies, mRNA-based therapies and gene therapies are being developed and tested in clinical trials. In this era when available FD-specific treatment options are actively expanding, increased clinical suspicion and prompt and accurate diagnosis of FD are critical for the early initiation of individualized treatment and change in the prognosis of FD patients.

**Key words:** Fabry disease, alpha-galactosidase A, globotriaosylceramide, enzyme replacement therapy, chaperone treatment

## Introduction

Fabry disease (FD) is an X-linked metabolic disorder characterized by decreased activity of the lysosomal enzyme, alpha-galactosidase A ( $\alpha$ -Gal A), related to mutations in the GLA gene (Xq21.3-q22) [1]. Deficient enzyme activity results in the accumulation of neutral glycosphingolipids and globotriaosylceramide (Gb3) in the plasma and cellular lysosomes of different tissues and organs throughout the body [2]. Hence, FD is categorized as a lysosomal storage disorder [3] with multi-system manifestations, such as progressive renal failure, cardiac disease, cerebrovascular disease, small-fiber and large-fiber peripheral neuropathy, and skin lesions, among other abnormalities [4].

FD is considered a rare disease (OMIM: # 301500) with an estimated annual incidence of 1 in 80,000 live births [5]. However, true prevalence might be underestimated due to later-onset subtypes of FD and under-diagnosed cases. Despite being highly variable among different countries, a prevalence of approximately 1 in 3,000 individuals has been suggested [2]. Diagnosis is based on the finding of reduced  $\alpha$ -Gal A activity in leukocytes or plasma and is confirmed by molecular genetic testing [6]. Regarding the disease prognosis, end-stage renal disease and life-threatening cardiovascular or cerebrovascular complications limit the life-expectancy of untreated males and females with reductions of 20 and 10 years, respectively, versus the general population [2].

However, disease-specific treatments are currently available, including enzyme replacement therapy and small-molecule chaperone treatment. In adjunction to symptomatic management, these therapeutic options have the potential to modify the disease course and halt progression [7]. Furthermore, other treatments such as substrate reduction therapies, mRNA-based therapies and gene therapies are being developed and are currently being tested in randomized-controlled clinical trials [7].

In this narrative review, we aim to present the pathophysiology of FD, outline the main clinical characteristics that FD patients may exhibit and discuss the diagnostic and management considerations in FD.

### 1. Pathophysiology

Fabry disease is caused by the deficiency of  $\alpha$ -Gal A, a lysosomal enzyme encoded by the GLA gene on the X-chromosome (region Xq22.1). Almost 1,000 mutations in the GLA gene have been described including missense and nonsense mutations [8]. The list of FD-associated mutations is continuously expanding, since novel GLA mutations or mutations that were previously considered non-pathogenic are being described and associated with FD diagnosis [9]. A potential limitation in the characterization of these mutations is the fact that many of them are private, being isolated in certain families only, further complicating the genotype-phenotype correlation [10].

Male patients carrying a FD-associated mutation in their single X-chromosome (hemizygous mutation) are expected to be impacted more severely and manifest FD-associated symptoms in a more characteristic manner, resulting in the "classic" presentation of symptoms. Female carriers may also be affected to a lesser extent, manifesting milder or atypical symptoms [11]. Inactivation of the wild-type GLA allele in heterozygous female patients is considered the most probable cause for disease manifestation [12, 13]. GLA-homozygous female patients have also been described in the literature, but are considered extremely rare [14, 15]. Therefore, female sex should not be considered as an exclusion criterion for disease diagnosis. Characteristically, the term "X-linked recessive" in the description of FD inheritance has been vigorously questioned and should better be replaced by the more general term "X-linked inheritance" to include the cases of carriers that manifest disease symptoms.

The normal function of  $\alpha$ -Gal A is to participate in lipid metabolism by hydrolyzing and removing terminals  $\alpha$ 1, 3- and  $\alpha$ 1, 4-linked galactosyl residues from various glycoconjugates within lysosomes [16]. When  $\alpha$ -Gal A is deficient, the primary substrate Gb3 cannot be digested and accumulates within the lysosomes. Another deacylated form of Gb3 is

the globotriaosylsphingosine (lyso-Gb3) which also contributes to disease pathogenesis, but, importantly, serves as a biomarker for FD diagnosis and treatment monitoring [17, 18]. Other glycoconjugates that accumulate –to a lesser extent compared to Gb3– in FD are digalactosylceramide and blood group B- and P1- glycosphingolipid antigens.

The association between Gb3 accumulation and disease manifestation seems to be dependent not only on lysosome function; other cellular organelles and mechanisms are implicated as well. Gb3 also accumulates within the plasma membrane of  $\alpha$ -Gal A-deficient cells and potentially alters the function of various membrane proteins and channels [19, 20]. Mitochondrial and endoplasmic reticulum function is affected as well in FD, either directly through Gb2 accumulation or indirectly through impairment of the autophagic flux [21, 22]. Downstream results implicating fibrosis [23], inflammation [24] and increased oxidative stress [25], all contribute to the pathogenesis of the disease and its systemic manifestations.

### 2. Clinical Characteristics

FD has long been considered as an adult disease, predominately affecting male patients [2]. However, this notion could not be further from the truth. Indeed, significant morbidity in childhood has been associated with FD, even in the absence of major organ dysfunction [26]. Furthermore, both atypical symptoms and milder phenotypes exist, affecting female carriers. All organs may also be affected to varying extent, resulting in a phenotypic spectrum of disease manifestations. Characteristic symptoms of FD include neurological, cutaneous, renal, cardiac and cochleo-vestibular manifestations and are summarized in Table 1.

#### 2a. Neurological Manifestations

##### Peripheral Nervous System

Neurological manifestations in FD can be observed even from an early stage of the disease, often during childhood. Those early FD neurological symptoms mostly implicate the peripheral nervous system, involving small nerve fibers of the peripheral somatic [27] and autonomic nerve systems [28].

The neurological symptoms most commonly experienced in childhood include neuropathic pain, gastrointestinal dysmotility, hypohidrosis and heat intolerance [29]. Neuropathic pain, which has been reported during childhood by 59% of males (median age 7 year) and 41% of females (median age 9 year) in a registry-based study [30], may manifest as acroparaesthesias or acute pain crises or a combination of both [31]. Symptoms, such as chronic neuropathic pain, acroparaesthesias or perspiration disorders may

**Table 1.** Organ-specific involvement and manifestations of Fabry Disease

Organ	Involvement %	Manifestations
Peripheral Nervous System	45%	Neuropathic pain Acroparaesthesias Acute pain crisis Thermal sensation deficits Perspiration disorders Gastrointestinal dysmotility Median nerve entrapment Cramp-Fasciculation Syndrome
Central Nervous System	34%	Ischemic Stroke Transient Ischemic Attack Transient Ischemic Attack Vascular Dementia Hemorrhagic Stroke
Kidney	45%	Microalbuminuria Proteinuria Progressive renal failure
Heart	68%	Left ventricular hypertrophy Right ventricular hypertrophy Congestive heart failure Arrhythmias Myocardial ischemia
Skin	34%	Angiokeratomas Lymphoedema Hoarse facial features
Eye	38%	Cornea verticillata Cataract
Ear	19%	Hearing loss Vestibular disturbances
Miscellaneous		Chronic cough Osteopenia Anemia Azoospermia Hypothyroidism

be under-reported by the patients. Therefore, during medical history investigation, patients should be specifically asked for those symptoms. Additionally, although these symptoms are not life-threatening, they clearly impact the health and quality of life of affected children [26, 32].

Peripheral neuropathy is a typical manifestation for adult FD patients, as well. Chronic, burning pain and superimposed attacks of severe pain, when temperature changes or other stressful situations occur (such as infectious illnesses or surgery), usually develop by the age of 20 years in 60-80% of patients with FD [33]. Thermal sensation deficits also occur and are more pronounced in the feet than in hands in a length-dependent manner [34]. Initially, the thermal sensation impairment involves cold perception,

and only later warmth perception is diminished [35]. Accumulation of lipids in dorsal roots ganglion cells [36] and autonomic ganglia [37] may be accountable for these symptoms, via decompensation of Ad-and C-fiber function and absolute reduction in the intraepidermal nerve fiber density [38, 39]. Additionally, Gb3 accumulation within the endothelial cells of the vasa nervorum may precipitate thrombotic complications through laminal encroachment and occlusion and contribute to ischemic nerve damage [40]. Over time, the positive neuropathic symptoms seem to ameliorate, probably due to reduction of axonal sensory hyperexcitability and central sensitization, with disappearance of pain and progression to numbness and hypoalgesia.

Autonomic nerve dysfunction as part of the

small-fiber neuropathy may manifest with a variety of sympathetic and parasympathetic-associated symptoms. Gastrointestinal dysmotility including abdominal cramps, diarrhea and nausea is one of the most frequent and early general complaints among FD patients, affecting up to 52% of adult patients [41, 42]. Reduced tearing and saliva production may be also associated with autonomic disturbance in FD [28]. Impaired pupillary constriction with pilocarpine may also be apparent [28]. Perspiration disorders, including both hyperhidrosis and hypohidrosis, are characteristic for FD, even from the early stages of the disease, highlighting the involvement of autonomic nervous system [43]. Specifically in the case of hypohidrosis, pathogenesis lies not only to the autonomic neuropathy but partly to the sweat gland dysfunction due to Gb3 proliferation [44, 45]. Other autonomic-related symptoms include reduced increase in heart rate and blood pressure upon exercise and, less often, orthostatic hypotension [46]. However, cardiovascular autonomic involvement is considered rare in FD, while other end-organ manifestations may also significantly account for those cardiovascular decompensations [47].

Large nerve fiber dysfunction is much less common in FD [27, 48]. Motor function, position and vibration sensation are typically not affected until the later stages of the disease, through GL-3-induced cell dysfunction adding to the already negative influence of age per se in the large fiber integrity [27]. Other neurotoxic mechanisms, such as uremia due to FD-associated renal disease, may account as well for the development of large nerve fiber abnormalities.

On the other hand, median nerve is more commonly involved in FD, with a reported prevalence of carpal tunnel syndrome of approximately 25% for both male and female patients. Gb3 accumulation within the carpal tunnel structures is implicated in the pathogenesis of median nerve entrapment [49].

Cramp-fasciculation syndrome without apparent small-fiber neuropathy is another interesting and more atypical manifestation of peripheral nervous system involvement in FD, further expanding the spectrum of later-onset FD [50]. Although a clear pathologic association was not demonstrated in this reported case, the authors postulate that Gb3 deposits along the motor neuron or portions of the motor axons may account for this, otherwise unexplained, manifestation of lower motor neuron hyperexcitability [50].

### **Central Nervous System**

The hallmark of central nervous system involvement in FD is cerebrovascular disease as a result of Gb3 accumulation in the vascular endothelium and smooth muscle cells of the small blood cerebral ves-

sels [51, 52]. Other factors, such as the presence of a prothrombotic state, autonomic dysregulation and increased production of reactive oxygen species or even FD-associated cardiac arrhythmias, may also be implicated in the pathogenesis of cerebrovascular disease in affected patients. Cerebrovascular complications in FD may include transient ischemic attacks, ischemic strokes of multiple underlying mechanisms, intracerebral hemorrhage, subarachnoid hemorrhage, and vascular dementia [53, 54]. According to the Fabry registry, 6.9% of male patients and 4.3% of female patients were complicated with stroke, at a median age of 39 and 45.7 years, respectively [55]. Importantly, a significant proportion of patients may experience stroke as the first manifestation of FD disease, before experiencing any cardiac or renal events [55]. Therefore, screening for FD during etiopathogenetic investigation of stroke in young patients might be reasonable [56, 57]. In a cohort of 721 patients with cryptogenic stroke, 3.9% were diagnosed with FD [58]. In this cohort, proteinuria and infarction in the vertebrobasilar artery system were shown to be associated with FD diagnosis [58]. Dolichoectasia of the basilar artery, which is a characteristic finding of FD, may account for the high prevalence of strokes in the posterior circulation [59]. Screening gains even more clinical importance, when considering the high rates of stroke recurrence (76-86%) and the poor prognosis (mortality rate between 40-55%) of these patients [53].

Although clinically silent, white matter hyperintensities are the most common central nervous system manifestation of FD. This neuroimaging finding has been reported in 46% of FD patients, with a similar prevalence between male and female patients [60]. Cerebral white matter pathology has further clinical correlations as well, being associated with cognition and disease severity [61]. Even before apparent white matter hyperintensities in brain MRI are demonstrated, alterations of cerebral blood flow velocity are detected by transcranial doppler sonography in the posterior circulation of FD patients compared to controls [62]. Thus, cerebral hemodynamic changes detected by neurosonology may be used as a potential biomarker for the preclinical detection of neurovascular involvement in FD [62].

Another important neuroimaging finding of FD is the pulvinar sign, defined as T1-weighted symmetric hyperintensities in both lateral pulvinars. This sign is suggestive of dystrophic calcification, secondary to cerebral hyperperfusion and selective vulnerability of the pulvinar and adjacent thalamic nuclei [63]. Although previously considered pathognomonic, the prevalence of pulvinar sign is relevantly low, presenting in 3% of the FD patients among a retrospective cohort, and may also be found in other abnormal conditions, mostly when concomitant renal dysfunc-

tion is noted [64]. In fact, FD-associated pulvinar sign has been correlated with male sex and serious complications, such as hypertrophic cardiomyopathy and severe kidney involvement [65].

Apart from ischemic stroke, which is well recognized as a FD-associated complication, intracerebral hemorrhage has also been described in both classic and atypical FD patients [66]. Vessel wall remodeling and degeneration, in addition to arterial hypertension, have been associated with this dreadful manifestation. However, hemorrhagic strokes account for only 16.9 and 6.9 of all strokes in male and female FD patients, respectively [55]. Cerebral microbleeds may also be present in FD patients, with a prevalence ranging from 11% to 30% in different cohorts [67, 68]. These are predominately deep chronic microbleeds, significantly associated with white matter hyperintensities, underscoring the pathogenicity of small vessel vasculopathy for both manifestations.

Vessel fragility and possibility of rupture leading to intracerebral hemorrhage have been a matter of debate regarding the safety of recanalization therapies for acute ischemic stroke in FD patients. Despite scarcity of data, relevant published cases are in favor of intravenous thrombolysis in FD-associated stroke [69-71].

An uncommon manifestation of FD, resulting in cerebrovascular disease, is cervical artery dissection [72, 73]. Gb3 accumulation within the vessel walls renders the cervical arteries fragile and prone to dissection, even without a prominent traumatic history [74].

## 2b. Renal Manifestations

Renal involvement in FD is one of the most important causes of morbidity and mortality of the patients. The basis of the pathophysiology of renal manifestations in FD is the Gb3 depositions in the glomerular endothelium, mesangial and interstitial cells, podocytes, epithelium of the loop of Henle, as well as in the endothelial and smooth muscle cells of the renal arterioles [75, 76]. Initially, renal dysfunction may be masked by glomerular hyperfiltration, but with advancing age and Gb3 continuous accumulation, the existing nephrons cease to be able to adequately compensate for those affected, resulting in apparent kidney failure.

Microalbuminuria and proteinuria are the first signs of renal involvement in FD, typically manifesting during the second or third decade [77]. These have been shown to be present in 44% of male and 33% of female patients [78]. Furthermore, urinary protein excretion is considered to directly contribute to the progression of the Fabry nephropathy and is significantly associated with both systolic blood pressure [79] and renal disease progression in both sexes [80].

Fibrosis, sclerosis and tubular atrophy typically follow in the third to fifth decades of life, leading to rapid progression of FD-associated nephropathy and end-stage renal failure [81]. Even when chronic hemodialysis is undertaken, mortality in FD-associated nephropathy has been shown to be higher compared to other standard nephropathies, with a 5-year survival rate of 41% in FD patients compared to 68% in other pathologies [82, 83]. Furthermore, the severity of chronic kidney disease is also closely related to cardiovascular disease progression, including left ventricle hypertrophy, arrhythmias and sudden death [84]. Characteristically, according to the findings of the Fabry registry, 57% of the patients who died due to cardiovascular causes had previously received renal replacement therapy [85].

## 2c. Cardiac Manifestations

Cardiac involvement in FD may manifest with structural changes, such as left ventricular hypertrophy, arrhythmia and electrocardiographic abnormalities, and less often with coronary artery disease [86-88]. Cardiovascular system is involved in approximately 40-60% of FD patients [81].

Diastolic dysfunction and concentric left ventricular hypertrophy without left ventricular outflow tract obstruction are the most characteristic signs of cardiac involvement in FD [89]. Systolic function seems to be preserved until the later stages of disease. Septum thickness is another important finding to recognize in FD-related cardiomyopathy, since the posterior wall is more commonly affected by the fibrosis [90]. Congestive heart failure may occur at the end stage of FD [91, 92]. Right ventricular structural changes were previously considered less common. However, right ventricular hypertrophy is found in almost 40% of FD patients, equally affecting both genders [93].

Structural changes and remodeling, together with autonomic disturbance, may lead to prominent electrocardiographic abnormalities in FD patients, including a short PR interval, ST segment depression, prolonged QRS and QT intervals, atrioventricular blocks, bundle branch blocks, intermittent supraventricular tachycardia and other arrhythmias [94]. Excessive Gb3 may also accumulate in the endothelium of coronary arteries, leading to abnormal coronary microvascular function [95]. As a result, reduced exercise capacity, angina, myocardial ischemia and infarction may present as FD-associated complications [95, 96]. Arrhythmias and myocardial infarction may be the cause of sudden death in a significant proportion of patients [97]. Therefore, prompt diagnosis and management are important. Aortic root dilatation has also been demonstrated in 24% of affected male patients and was found to be associated with basilar dolichoectasia [2].

**Figure 1.** Patients with diagnosed Fabry disease presenting angiokeratomas in typical locations, such as the abdomen and thighs (Panel A & B), the inner part of the lips (Panel C) and the palms (Panel D). Angiokeratoma corporis diffusum is characteristic for Fabry disease and presents as small, red-to-purple, raised skin lesions, which are superficial angiomas due to excessive deposition of Gb3 in the vascular endothelial cells of the skin



Atypical variants of FD restricted to cardiac involvement, hence the “cardiac variant”, have also been reported in the literature [98, 99]. In patients with this variant, left ventricular hypertrophy and other cardiac manifestations present during middle age, without any other signs of FD [100]. Relatively high residual  $\alpha$ -Gal A activity, as well as certain mutations have been shown to be associated with this cardiac phenotype [101].

#### 2d. Dermatological Manifestations

A characteristic skin lesion that manifests early in the course of FD is angiokeratoma corporis diffusum [102]. Angiokeratoma presents as small, red-to-

purple, raised skin lesions, localized in the buttocks, groin, thighs, abdomen (i.e., the “swimsuit area”) and mucosal areas as well, such as the inner part of the lips or the genitals (Figure 1) [103]. These lesions are actually superficial angiomas due to excessive deposition of Gb3 in the vascular endothelial cells of the skin. The superficial dilated capillaries are also accompanied by epidermal proliferation. Angiokeratomas are benign and are found in 83% of males and 80% of females with FD [104]. With progressive age, they tend to increase in number and size. Nevertheless, angiokeratomas are not pathognomonic for FD, since they may appear in other diseases as well, such as hereditary haemorrhagic telangiectasia or Fordyce’s angiokeratoma [105].

Another cutaneous manifestation is lymphoedema, which was firstly described in the original description of FD by Anderson [106]. Although heart and renal impairment may partly account for this manifestation, actual Gb3 deposition within the cells of lymphatic vessels actually occurs, leading to the lymphatic microangiopathy [107]. Dysfunction of the lymphatic circulation subsequently leads to lymphoedema [108].

Facial dysmorphism may also be present in FD, as in other lysosomal storage disorders. Although not striking, hoarse facial characteristics, with prominent supraorbital ridges, frontal bossing, broad nasal base and thickening of the lips, can be found in males and to a lesser extent in female FD patients [109, 110]. The exact pathophysiology of facial dysmorphisms remains yet unclear; however, Gb3 accumulation within the growing facial bones and connective tissues may probably be a putative link between FD and abnormal facial appearance [109].

Other dermatological manifestations are acroparaesthesia and perspiration disorder have been previously described under FD-associated peripheral nerve involvement.

## 2e. Ophthalmological Manifestations

Cornea verticillata, revealed by slit-lamp examination, is one of the most common signs of FD disease, affecting more than 70% of the patients, including both males and females [111, 112]. Cornea verticillata actually refers to vortex opacities located in the superficial corneal layers and characteristically does not affect the visual acuity of the patient. Thus, every patient with suspected FD should be evaluated ophthalmologically for the presence of ocular manifestations, even when no relevant symptoms are reported by the patients.

Another ocular manifestation is the so-called "Fabry cataract", which is defined as a posterior subcapsular cataract consisting of posterior lens opacities with a radiating appearance [113]. Fabry cataract is a more specific finding for FD compared to cornea verticillata (which can also be found in other disorders, such as chronic amiodarone administration) and can affect males with a higher prevalence compared to female FD patients [112].

Retinal and choroidal vessels are affected as well in FD due to Gb3 accumulation within the endothelial cells and may present increased tortuosity, giving a corkscrew appearance during fundoscopic examination or fluorescein angiography [114, 115].

## 2f. Otological Manifestations

Hearing loss, tinnitus and vertigo have also been reported as otological manifestations of FD [116, 117]. Both progressive and acute hearing loss may

complicate FD patients, implicating both neurologic and vascular damage as the pathogenetic link [116]. Vestibular disturbances may also be present in a significant proportion of patients [118].

## 2g. Other Manifestations

FD, being a multi-system disorder, also presents respiratory manifestations, including exercise-induced dyspnea, chronic cough and airway obstruction [119, 120]. Furthermore, skeleton involvement may also be present in 50% of the cases, with either osteopenia or osteoporosis [121, 122]. Finally, rare cases have been reported with FD-associated anemia [123], azoospermia [124], priapism [125] and hypothyroidism [126].

## 3. Diagnosis

Significant diagnostic delays have been reported in FD, with an approximate interval of 14- and 16-years for male and female patients, respectively, between onset of symptoms and disease confirmation [78]. However, delaying diagnosis might have important clinical consequences. Irreversible damage of organs might occur, leading to a reduced response to available treatments [29]. Additionally, there is a higher risk for FD-related clinical events, such as cardiovascular or renal events, underscoring the need for early diagnosis and treatment initiation, before the onset of severe organ damage [127]. Prompt FD diagnosis requires increased awareness and clinical suspicion regarding the phenotypic spectrum of the disease. In case of suspected FD, appropriate biochemical and genetic confirmation is warranted [128]. A summary of the laboratory findings in FD, according to the phenotype, is presented in Table 2. If positive, biochemical tests are highly indicative of disease diagnosis, especially in male patients; however, diagnosis of FD is not possible without genetic confirmation for both males and females [129].

### 3a. Biochemical analysis

The activity of  $\alpha$ -Gal A can be measured in plasma or in leukocytes and the demonstration of its reduction is the mainstay of initial diagnosis in male FD patients [130]. However, in the case of the female patients, this result can be quite inconclusive, since false negative results may be quite common [131]. Genotypic analysis is more informative regarding the female patients [132]. Several pitfalls in the measurement of  $\alpha$ -Gal A activity in plasma may occur, mostly regarding the buffering and incubation of the specimens [133]. Therefore, measurement in the leukocytes is considered more accurate compared to plasma [134]. Examination of samples derived from dried blood spots is also quite applicable and accu-



**Table 2.** Summary of findings in Fabry disease

	Classical Males	Females	Non-classical Patients
Residual Enzyme Activity	Absent	Low to normal	Reduced, but not absent
Mutation	Severe (null, missense)	Carrier	Mild (missense)
Phenotype	Severe	Variable	Milder, variable
<b>Typical symptoms</b> , including angiokeratomas, cornea verticillata, acroparaesthesia	Present	Variable	Usually absent

rate, allowing for storage and delivery to reference laboratories worldwide [135].

Detection of Gb3 accumulation may also assist in the diagnosis of FD. This can be performed by the measurement of the deacylated form of Gb3 in the plasma or urine, called the lyso-Gb3, which has been proven an important biomarker for FD diagnosis and monitoring [136]. Liquid chromatography tandem mass spectrometry is considered the most reliable method for lyso-Gb3 measurement in the plasma [137]. Increased lyso-Gb3 values are indeed very suggestive for FD [138]. An additional important aspect is that lyso-Gb3 increase may also identify the clinically relevant GLA mutations among those with unknown significance [139]. One limitation is that normal Gb3 values cannot exclude FD, especially with regard to non-classical phenotypes or female patients. However, lyso-Gb3 measurement appears to be more useful in FD diagnosis compared to  $\alpha$ -Gal A activity [140].

### 3b. Genetic analysis

More than 900 mutations have been described in the GLA gene. Not all of them, however, are considered pathogenetically associated with FD. Direct molecular analysis of the GLA gene is applicable using dried blood spots. High-performance liquid chromatography and Multiplex Ligation-dependent Probe Amplification are useful methods to identify point mutations and deletions in the GLA gene [15, 141]. When a pathogenetic variant is identified, FD diagnosis can be confirmed.

Novel mutations and mutations of unknown significance present as the challenge in the molecular diagnosis of FD. For example, the mutation D313Y, which was previously considered as non-pathogenic variant, has been recently associated with FD classical phenotype and disease diagnosis [9, 142]. Despite the fact that genetic testing is considered mandatory for FD confirmation, its results should be evaluated critically and in adjunction with the clinical signs of the disease and the other biomarkers as well [129].

### 3c. Histopathological analysis

Although quite invasive, histopathological analysis of kidney or myocardial biopsies under electron microscopy may provide useful information, especially in ambiguous cases or in cases presenting novel GLA mutations or mutations of unknown significance [143]. Glomerulosclerosis and tubulointerstitial fibrosis are non-specific findings in kidney biopsies of FD patients, while Gb3 deposits in podocytes, glomerular endothelial cells, mesangial cells, tubular epithelial cells and vascular endothelial cells can also be evaluated and are more characteristic of the disease [144]. Intracellular osmiophilic, lamellar inclusions, called the “zebra bodies” are very indicative of FD, but drug-induced renal phospholipidosis may also mimic this ultrastructural appearance [145]. Lysosomal storage and “zebra bodies” may also be visualized in the cardiomyocytes during electron microscopy assay [146]. Furthermore, skin biopsies may also be used, revealing Gb3 deposits which are specific in FD patients with classical GLA mutations [147]. Importantly, the utility of skin biopsies also includes the evaluation of peripheral small fiber innervation and the involvement of peripheral nervous system as part of FD manifestations [148].

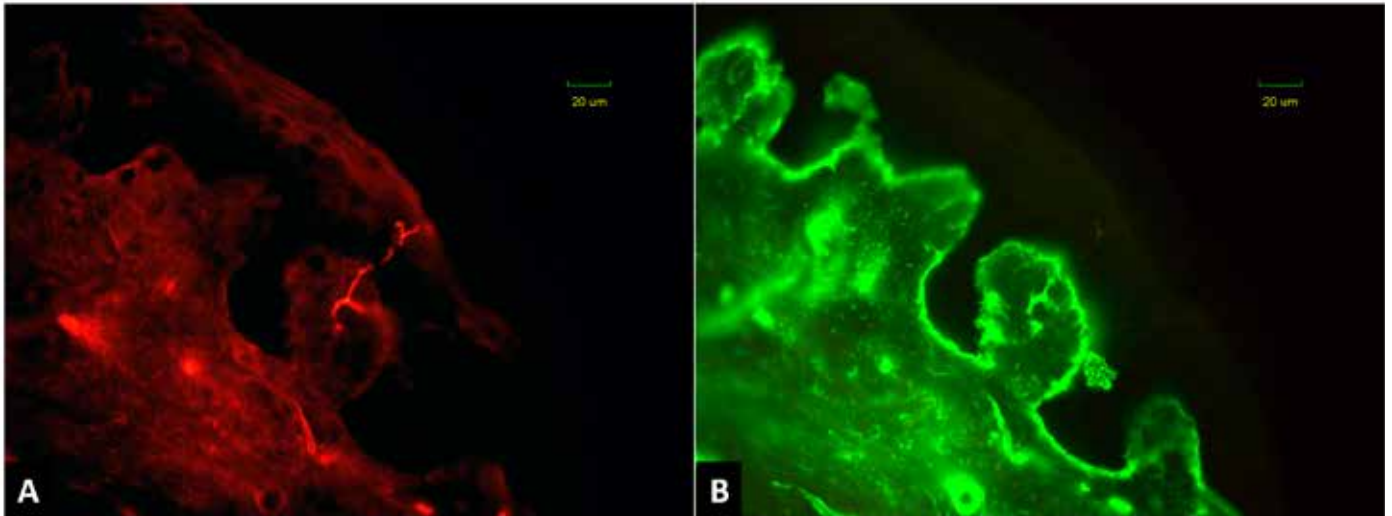
### 3d. Other diagnostic tests

During the initial diagnosis of an FD patient and throughout the entire follow-up, a variety of ancillary diagnostic tests should be performed to evaluate the involvement of each target organ.

With regards to peripheral nerve involvement, electrophysiological studies should be performed, including sympathetic skin response, thermal quantitative sensory testing, sensory and motor nerve conduction studies and electromyography [149]. Skin biopsy may also be evaluated for estimating intradermal nerve fiber density (Figure 2) [38]. Central nervous system involvement may be assessed by brain MRI, assessing for strokes, leukoencephalopathy, cerebral microbleeds or pulvinar sign [150]. Transcranial doppler ultrasonography may also early evaluate cerebral



**Figure 2.** Double immunofluorescence staining of a 3 mm skin specimen, collected 10 cm above lateral malleolus, showing reduced number of intraepidermal nerve fibers penetrating the basal membrane of the epidermis; magnification 40X; secondary staining with Cy3 (Panel A) and Daylight 488 (Panel B)



hemodynamic changes indicative of microvascular disruption [62].

Renal manifestations may be assessed by serum biochemical assays, evaluating plasma urea, creatinine, and age-corrected eGFR [151]. Initial and more subtle involvement may be determined by microalbuminuria and proteinuria [80]. Imaging techniques, such as renal ultrasound or MRI, may also be performed [152].

Electrocardiography and transthoracic echocardiography are mandatory when assessing an FD patient [86]. Transthoracic echocardiography reveals a rather symmetric pattern of myocardial hypertrophy, compared to the more common pattern of asymmetric hypertrophy of hypertrophic cardiomyopathy. Quite often, the patient may also need long-term rhythm monitoring for possible detection of rhythm abnormalities [153]. The mainstay of cardiac involvement evaluation is cardiac MRI that is able to detect cardiac hypertrophy and fibrosis [154]. Newer cardiac MR sequences, most notably native T1 mapping, can aid the differential diagnosis in unexplained myocardial hypertrophy that can be observed in other forms of cardiomyopathy, such as cardiac amyloidosis, hypertrophic cardiomyopathy or hypertensive heart disease [155]. As lipids shorten T1 time, intracellular cardiomyocyte accumulation of glycosphingolipids leads to characteristic shortening of native T1 mapping, in contrast to areas with fibrosis where it is prolonged. However, these scar areas are well identified on late gadolinium enhancement (LGE) images. Therefore, cardiac MR with native T1 mapping exhibits an advantage in Fabry disease, as it can help diagnose myocardial involvement in earlier disease stages without the need of contrast agent

administration. Notably, iron overload, in patients with thalassemia or hereditary hemochromatosis, also shortens native T1 mapping times, however the clinical context differs between the two disease entities.

Specialized dermatologist, ophthalmologist and otolaryngologist, as part of the multidisciplinary team, should also examine a FD patient at initial diagnosis and during follow-up.

## 4. Management

### 4a. Supportive Management

The so far available FD-specific treatments do not cure the disease, but rather halt its progression. Thus, supportive management continues to be the mainstay of treatment. An organized and multidisciplinary approach is desirable to provide the FD patient a holistic treatment.

Adequate pain management and avoidance of a pain crisis can be achieved by the avoidance of trigger factors, such as temperature changes or physical stress. Other conservative measures of treatment include rest, holding icepacks, or administration of acetaminophen during febrile periods. However, in the cases of chronic neuropathic pain and acroparesthesias, symptoms are more persistent and require pharmacological treatment. Carbamazepine, phenytoin and gabapentin have a proven efficacy in managing the pain in FD [156]. Serotonin-norepinephrine reuptake inhibitors and duloxetine may also be used in the management of chronic pain in FD. On the other hand, non-steroidal anti-inflammatory drugs and narcotic analgesics should generally be avoided or maybe used for the acute relief during a pain crisis [157].

Secondary stroke prevention therapy is recommended in the cases of FD-associated stroke, including antiplatelets, statins, and adequate control of other risk factors, such as arterial hypertension, diabetes mellitus or hyperhomocysteinemia [158].

Renal disease can be managed by administering angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARBs), which may limit proteinuria and also control hypertension [159-161]. Dialysis and kidney transplant should be considered in the cases of end-stage renal disease [162-164].

Symptomatic anti-anginal and antihypertensive therapy is recommended in FD cardiac involvement, including calcium antagonists, ACEis's and ARBs. B-blockers should be avoided to avoid sinus bradycardia and atrioventricular block [165]. When clinically significant arrhythmias occur, cardiac pacing and cardioverter defibrillator implantation may be necessary. In end-stage heart failure, heart transplant may be a viable option [166].

#### **4b. Disease specific therapies**

Apart from supportive care, there has been a wide range of developments in treatment of lysosomal storage disorders in general, and in FD specifically. Different steps along the metabolic pathway have been targeted as therapeutic options, including enzyme replacement therapy and chaperone therapy, while substrate reduction therapy and gene therapy are under development (Table 3).

#### **Enzyme Replacement Therapy**

Agalsidase alfa at a dose of 0.2 mg/kg biweekly and agalsidase beta at a dose of 1.0 mg/kg biweekly are authorized FD-specific treatments, replacing the deficient  $\alpha$ -Gal A enzyme in FD patients [167, 168]. Safety and efficacy of both drugs have been proven in randomized controlled clinical trials [169-172], as well as in investigator-sponsored studies independent from the industry [173-176].

The efficacies of agalsidase alfa and agalsidase beta are comparable [177, 178]. However, both treatments should be administered early in the course of FD, since the window of opportunity exists before irreversible damage is evident [179]. Both male and female patients should initiate treatment upon first evidence of early FD-associated clinical signs [179]. Significant reduction of neuropathic pain has been recorded in patients treated with both regimens [180]. Additionally, left ventricular mass was found to be reduced in treated patients [181]. Progression of renal disease may also be delayed during treatment [182, 183]. FD-associated major events, including renal, cardiac, cerebrovascular complications and death, were found to be lower upon treatment [184]. In addition, a recent meta-analysis comprising 7 cohort

studies and 2 randomized controlled clinical trials involving 7513 participants; 1471 on ERT vs. 6042 on native treatment) showed that the stroke recurrence ratio in the ERT treatment group was 8.2% (95%CI: 3.8-12.6) and in the native-treatment group was 16.0% (95%CI: 10.2-21.7) [185]. Effect differences favored ERT treatment group over native treatment group ( $p = 0.03$ ) [185]. However, in both treatments, no obvious effect on brain lesions was noted, possibly due to the fact that these large molecules cannot cross the blood-brain barrier [186]. Treatment effect can be sufficiently monitored through lyso-Gb3 measurement in the plasma, further underscoring the utility of this biomarker in FD [18, 187].

Safety issues during enzyme replacement therapy mostly concern moderate infusion-related reactions, such as fever, flushing and rigors, which were present in 57% and 59% of the patients during the administration of agalsidase alfa and beta, respectively [169, 170]. In general, these reactions can be managed conservatively and may also be prevented by premedication with an antihistamine, paracetamol and/or dexamethasone, and by reducing the infusion rate [188].

Another significant concern is the formation of specific neutralizing antidrug antibodies against the enzymes in about 40% of all treated patients, which may attenuate the treatment efficacy [189, 190]. Plasma lyso-Gb3 have been found to be higher in patients with neutralizing antibodies [191], while increased left ventricular mass and progression of renal disease have been associated with the inhibition of enzyme replacement therapy [190]. The formation of the antibodies is typically observed within 3-6 months after initiating treatment [192]. The administered dose seems to be the most important trigger factor for neutralizing antibodies; this association also might explain the increased risk of antibody formation in patients receiving agalsidase beta compared to agalsidase alfa [193]. However, head-to-head comparisons have not been performed yet and future studies are warranted.

#### **Chaperone Therapy**

Chaperone therapy with migalastat has recently become available for FD patients aged  $\geq 16$  years with amenable mutations. In general, chemical chaperones are small molecules that assist the folding, maturation, binding or trafficking of the deficient enzymes and have been used in several inherited metabolic disorders, including lysosome storage disorders [194]. In the case of FD, migalastat is able to stabilize the endogenous  $\alpha$ -Gal A enzyme of the patients, facilitates its trafficking from the endoplasmic reticulum to the lysosomes, and increases the enzymatic function [195-197].

**Table 3.** Current and future treatment options in FD

Therapies	
<b>Available Therapies</b>	
Enzyme Replacement Therapy	Agalsidase alfa Agalsidase beta
Chaperone Therapy	Migalastat
<b>Developing Therapies</b>	
Enzyme Replacement Therapy	Pegunigalsidase alpha
Substrate Reduction Therapy	Lucerastat Venglustat
mRNA-based Therapy	Exogenous mRNA via lipid nanoparticles
Gene Therapy	Hematopoietic stem cells (ex-vivo) Recombinant adeno-associated virus vectors (in-vivo)

Migalastat is an oral treatment that is administered every other day at a dose of 123 mg. Despite the fact that patients with amenable mutations account for 37% to 60% of all the FD-patients in different cohorts [198, 199], its treatment efficacy is well established in this subset. Real-world data show that, indeed,  $\alpha$ -Gal A activity is significantly increased, while lyso-Gb3 levels are stabilized, and FD-specific manifestations and symptoms remain stable in patients under treatment [200, 201]. Additionally, a significant reduction in left ventricular mass has been noted in patients receiving this treatment [200, 201]. The efficacy regarding FD-associated neurological complications remains to be elucidated; however, it should be noted that migalastat, as a small molecule, is able to cross the blood-brain barrier.

In a phase III, randomized-controlled clinical trial, it has been shown that migalastat had a comparable efficacy to enzyme replacement therapy, underscoring that migalastat may be used as a viable alternative treatment option [202]. Furthermore, switching from enzyme replacement therapy to migalastat can be safely performed without requiring any special procedure, and may be considered in patients with amenable mutations, according to individualized criteria and patients' preferences [203, 204].

### Developing Disease Specific Therapies

Other forms of exogenous enzyme replacement therapies are being currently investigated, with the most promising being a pegylated form of  $\alpha$ -Gal A, named pegunigalsidase alpha. Pegunigalsidase alpha was found to have a much longer half-life compared to the available enzyme replacement therapies, with

preliminary clinical data suggesting efficacy in reducing peritubular capillary lyso-Gb3 as measured in kidney biopsies, while the drug was well tolerated with no significant adverse events [205].

Gene therapy, either ex vivo by transplanting hematopoietic stem cells that express  $\alpha$ -Gal A, or in vivo by infusing recombinant adeno-associated virus vectors are also under development [206]. Another approach concerns the administration of mRNA which directly codes wild-type  $\alpha$ -Gal A, with preclinical data providing promising results in the tested FD-models [207]. Whether the produced  $\alpha$ -Gal A enzyme will trigger the formation of neutralizing antibodies in these cases, remains to be determined [206].

Another therapeutic target in the metabolic pathway associated with FD is the substrate reduction therapy. Two molecules, lucerastat and venglustat, are currently under investigation in clinical trials. Lucerastat acts as a glucosylceramide synthase inhibitor, limiting the production of ceramide and, as a result, the accumulation of Gb3 [208]. Promising results regarding the efficacy in reducing plasma glycosphingolipids have emerged in one small trial evaluating treatment with lucerastat combined with available enzyme replacement therapies versus enzyme replacement therapies alone [209]. Venglustat has a similar action to lucerastat and has been shown to reduce skin capillary endothelial cell Gb3, plasma Gb3, plasma lyso-Gb3, and urine Gb3 in treatment-naïve FD-patients included in a phase II clinical trial [210]. Apart from the obvious metabolic controls, the patients were clinically stabilized, with no evidence for development of cardiovascular disease, stabilization of proteinuria and eGFR and overall lack of significant clinical progression [210]. Further data

from ongoing clinical trials are warranted; however, it seems that the treatment arsenal against FD is largely expanding and a variety of therapeutic options may be soon available for FD patients following a more individualized approach.

## Conclusions

FD is a progressive, multi-systemic disorder affecting both male and female patients, even from an early age. The potentially disabling manifestations, emanating from the nervous system, and the renal and cardiac implication, and the increased mortality warrant prompt and accurate diagnosis, followed by an appropriate treatment. Diagnosis can be achieved by metabolic and molecular testing in patients with high clinical suspicion, and supportive treatment should be administered according to FD manifestations. Since the early 2000's, FD-specific treatment became available for the patients and provided sufficient metabolic and clinical control. Apart from the enzyme replacement therapies, more recent drugs such as the already-approved migalastat and the under-investigation substrate reduction therapy and gene therapy expand the treatment options for FD patients, providing the opportunity for personalized medicine in FD.

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