REVIEW ARTICLE

When and How to Diagnose Fabry Disease in Clinical Pratice

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ABSTRACT

Fabry disease is a frequent lysosomal storage disorder secondary to the deficiency of alpha-galactosidase A enzyme. This X-linked genetic disease realizes progressive and systemic manifestations that affect both male and female. Fabry disease may present as "classical", as "late-onset" or "non-classical" forms. Symptoms and organ involvements of classical Fabry disease are acral pain crisis, cornea verticillata, hypertrophic cardiomyopathy, stroke and chronic kidney disease with proteinuria. Other common symptoms are often poorly recognized, such as gastrointestinal or ear involvements. In classical Fabry disease, symptoms first appear during childhood or during teenage years in males, but later in females. Patients with non-classical or late-onset Fabry disease have delayed manifestations or a single-organ involvement. Diagnosis is therefore difficult when classical organ involvements are missing, in paucisymptomatic patients or in late-onset forms. Recognition of Fabry disease is important because effective treatments are available. They have to be prescribed early. In male, diagnosis is made with alpha-galactosidase A enzyme activity dosage in leukocyte, that is very low or null in classical forms and under 30 percent in late-onset forms. Diagnosis is more challenging in females who may express normal residual enzyme activity. Other plasmatic biomarkers, such as lyso-globotriaosylceramide are interesting, especially in females. In this review, we aimed to summarize main clinical manifestations of Fabry disease to know when to evoke Fabry disease and propose a practical diagnosis algorithm to know how to diagnose.

Key Indexing Terms: Fabry disease; Hypertrophic cardiomyopathy; Alpha galactosidase a; Gla; Globotriaosylceramide..
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INTRODUCTION

Fabry disease (FD), also called Anderson-Fabry disease, is a frequent lysosomal storage disorder.[1] Deficiency of alpha-galactosidase A enzyme (α-Gal) leads to the involvement of the glycosphingolipid metabolic pathway. In this sphingolipidoses, clinical manifestations are secondary to the lysosomal accumulation of globotriaosylceramide (Gb3 *or* GL3). As seen in most rare diseases, diagnosis of FD is delayed by three years in average.[2,3] As a systemic disease, clinicians from several specialties (pediatricians, internist, cardiologist, neurologist, pain specialist, nephrologist, geneticist, *etc.*) can meet patients and suspect FD. Clinicians should know the main FD features and that females are not only carriers, but also affected.[2] Early diagnosis is important because effective treatments are available. They need to be prescribed early to prevent organ damage.[4] Depending on the genetic mutations, FD can present as its classical form that begins early with acroparesthesia, sweat involvement, angiokeratoma and cornea verticillata. Since the third decade, cardiac, renal and cerebrovascular involvements appear and inexorably evolve in the absence of early specific treatment. Other mutations are associated with late-onset diseases with more attenuated phenotypes, even if severe organ involvements may be present. Lastly, the heart may be the only affected organ, with isolated hypertrophic cardiomyopathy. Diagnosis is easy in males with classical FD, with a very low or null α-Gal enzyme activity measured in leukocytes. Diagnosis is more challenging in females in this X-linked disease and in late-onset forms.

We aim to summarize, in a practical topic, clinical manifestations and how to diagnose FD.

PATHOPHYSIOLOGY

FD is secondary to the deficiency of α-Gal enzyme. When enzyme activity is below 30 percent, deficient α-Gal is unable to metabolize Gb3 in the lysosomes. It leads to its accumulation and clinical manifestations.[5] Gb3 accumulates mostly in vascular endothelium and smooth muscle cells causing vascular occlusion and ischemia. It also accumulates within autonomic ganglia, renal tissue (glomerular, tubular and interstitial cells), cardiac muscle cells, endothelial cells of the cornea and skin. This sphingolipid accumulation is also associated with cytotoxic, proinflammatory and profibrotic effects.[6] Accumulation of Gb3 in cells and tissues is inversely correlated with residual alpha-Gal A activity.[7]

Galactosidase alpha (*GLA*) gene is located in the long arm of the X chromosome (Xq22.1 region.[8] As an X-linked disorder, males will pass the Fabry genetic disorder to their daughters only. Therefore, heterozygous females have half a chance to pass for the Fabry gene mutation to their daughters and sons. More than a thousand mutations have been described.[9-11] Patients with a very low (<3%) residual enzyme activity have more severe classical FD whereas patients with residual activity between 3 and 30 percent have more likely milder or late onset phenotypes.[9-12] Most of the pathogenic *GLA* variants are private and occur in a single or few families only.

Some mutations are known to be associated with classical FD and others (mostly missense mutations) are associated with milder late-onset phenotypes. Nevertheless, severity of phenotypes differs within families, probably by the influence of other genes.

Females are not only carriers but are also affected secondary to the inactivation of one X-chromosome in each cell in females. This phenomenon is called lyonization in reference to the geneticist Mary F Lyon.[13] The silenced inactive X chromosome is compacted to a small and dense structure called Barr body.[7,14] Inactivation is random, leading to different patterns of Gb3 accumulation depending on which X-chromosome is silenced.

EPIDEMIOLOGY

Prevalence may be underestimated if we consider that FD is underdiagnosed. At the contrary, newborn screening programs may overestimate prevalence of FD, finding non pathological variants, polymorphism and variants of unknown significance. Mutations associated with classical FD are present in 1:22,000 to 1:40,000 males, and atypical or late onset FD mutations are found from 1:1000 to 1:3000 males.[15-18] FD is present in all ethnic populations. Interestingly, in Taiwan, one cardiac variant (IVS4 +919G>*A*), is present with the extraordinary high prevalence of 1:1600 male newborns.[16]

TABLE 1. Natural history of symptoms and signs in classical Fabry disease.

Age of onset	Clinical manifestations
Childhood and teenage	Neuropathic pain Dyshydrosis (hypo and hyperhidrosis) Febrile crisis Ophthalmologic involvement (cornea verticillate, tortuous retinal vessels) Hearing loss Angiokeratoma Microalbuminuria Angiokeratomas Gastrointestinal symptoms
Second decade	Cardiomyopathy Strokes and transient ischemic attack Macroproteinuria and progressive GFR loss
From third decade	Worsening of organ involvement Organ failure Premature death

CLINICAL MANIFESTATIONS

FD may be suspected in patients with early systemic manifestations or in a single organ involvement. Severity ranges from the severe classic phenotype to paucisymptomatic. Age of onset is young in classic FD, but diagnosis can be made later in life, especially in patients with unexplained hypertrophic cardiomyopathy.

Major suggestive symptoms are indicated in Table 1. We propose to use of a semistructured medical history form can help clinicians to raise the suspicion of FD (Table 2).

Family history

Questioning family history and drawing a family tree are major points when suspecting FD. Clinicians have to define history of: stroke or transient ischemic attack (TIA), sudden death, premature death, cardiomyopathy (especially hypertrophic), renal involvement or dialysis, acral pain or unexplained gastrointestinal symptoms.

As females are not only carriers, family tree shows an X-linked or a pseudo-dominant pattern. Nevertheless, there is always a risk of *de novo* mutation, false paternity or mosaicism.[19] Drawing a family tree is also helpful to screen the entire pedigree.

Cutaneous involvement

When present, presence of angiokeratomas certifies that we are facing a classical FD and a very low enzyme activity. It is present in two-thirds of males and in one-third of females with classical FD.[20] Angiokeratoma are single in form or groups of superficial small reddish-purple skin lesions (Fig. 1). They increase in number and size with age. Classical locations are the umbilicus, hands, knees, elbows, and trunk spreading to the genital area during adolescence.[21]

Another classical feature of FD is sweating impairment (hypohidrosis or anhidrosis). It is secondary

TABLE 2. Semi-structured history form to question patient about Fabry disease symptoms.

Have you ever had ocular problems?	If yes : have you ever had : - Corneal verticillata - tortuous retinal vessels - conjunctival lymphangiectasia
Have you ever had heart problems?	If yes : have you ever had : - Unexplained hypertrophic cardiomyopathy?
Have you ever had skin problems?	If yes : have you ever had : - Reddish–purple skin rash in the bathing trunk area (angiokeratomas) - Decreased sweating (anhidrosis or hypohidrosis)
Have you ever had renal problems?	If yes : have you ever had : - chronic renal failure - proteinuria - parapelvic cysts
Have you ever had pain?	If yes : have you ever had : - Acroparesthesias : "burning" or "hot" pain in the hands and feet, particularly during fevers - Exercise, heat or cold intolerance
Have you ever had brain problems?	If yes : have you ever had : - unexplained stroke or transient ischemic attack (TIA) - white matters lesions on the MRI - vertebrobasilar dolichoectasia
Have you ever had hear problems?	If yes : have you ever had : - sudden or chronic hearing loss - tinnitus - vertigo
Have you ever had gastrointestinal problems?	If yes : have you ever had : - unexplained abdominal pain
Family history	Do you have family history of: - Fabry disease - Unexplained hypertrophic cardiomyopathy - Unexplained premature death - Unexplained renal involvement - Unexplained premature stroke/TIA - Exercise, heat or cold intolerance - Burning or hot pain in the hands or feet - Unexplained hearing loss

to clogging of sweat glands by glycosphingolipids deposits and sympathetic sudomotor fibres dysfunction (SFN).[22] Hyperhidrosis leads to unexplained hyperthermia and poor exercise tolerance. It is present in half of males and in a quarter of women.[20] At the opposite, cases of hyperhidrosis have been reported.[23]

Acroparesthesias and small fiber neuropathy

In FD, small unmyelinated and thinly myelinated nerve fibres are early affected, secondary to GB3 deposits that activate calcium-dependant voltage gate.[24] This realizes a small fiber neuropathy (SFN). Symptoms are chronic and acute pain, dysesthesias, deficits of thermal sensation, impaired sweating, gastrointestinal (GI) dysmotility, and hearing loss.[25,26] Acroparesthesia and pain affects from 60 to 80% of boys and girls with classical FD

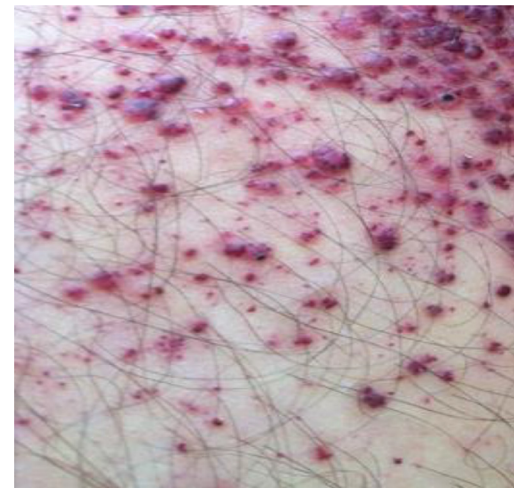

FIGURE 1. Angiokeratomas: groups of superficial reddish-purple skin lesions.

but occurs earlier in boys.[27,28] It decreases or even disappears with aging. Neuropathic pain has different clinical expressions: chronic and permanent pain, pain crisis that may be induced by fever or effort, evoked pain such as allodynia or hyperalgesia. Small fiber neuropathy can also be the only symptom of FD.[29] FabryScan is a 15-item questionnaire that may help clinicians to distinguish pain due to FD from other chronic neuropathic pain.[30]

Ophthalmologic involvement

Cornea verticillata, vessel tortuosity, cataracts and symptomatic conjunctival lymphangiectasia are ophthalmologic manifestations of FD.[31] Cornea verticillata is an important manifestation for diagnosis. It is asymptomatic and easily diagnosed with slit-lamp eye examination (Fig. 2). Prevalence in up to 70% in classical FD and 30% in late-onset Fabry disease.[31,32] Other complications can occur, such as posterior capsular cataracts, dry eye syndrome or conjunctival lymphangiectasia.[33]

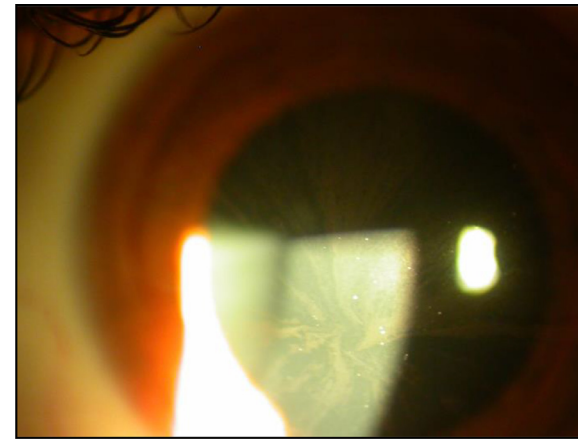

FIGURE 2. Cornea verticillata: corneal deposits forming a faint golden-brown whorl pattern.

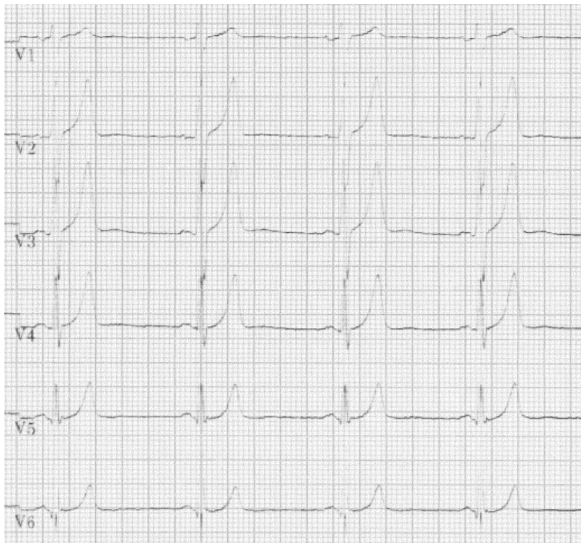

FIGURE 3. Electrocardiogram: left ventricular hypertrophy and short PR interval (120 ms).

Cardiac involvement

Cardiac involvement occurs in from 40 to 60% of FD patients.[34-40] Classical left ventricular hypertrophy (LVH) is present in 53% and 33% of untreated males and females' patients and increases with age.In patients with hypertrophic cardiomyopathy of unknown etiology, FD is found from 0.9 to 3.9% of cases.[41-44]

Electrocardiogram can showa short PR interval, that is helpful for FD diagnosis when present, and sinus bradycardia that is the most frequent rhythm abnormality (Fig. 3). Cardiomyopathy and myocardial fibrosis can lead to conduction abnormalities and sudden death. Other findings are chronotropic incompetence, supraventricular and ventricular tachyarrhythmias, valvular disease and microvascular dysfunction.[36,37] Cardiac involvement is similar in both classic and late-onset FD.

Echocardiography is a good way to diagnose LVH and evaluate cardiac dysfunction. Diastolic dysfunction may be present before LVH and is then important to diagnose. Magnetic resonance imaging (MRI) is needed to assess the infiltrative cardiomyopathy in late enhancement sequences. Classical distribution of abnormalities is infero-lateral, but every localization is possible. An MRI also evaluates the mass of the left ventricle and differentiates between scarring and fibrosis.[45] In females, cardiac fibrosis may precede LVH. Myocardial fibrosis is associated with a poor prognosis, increasing risks of arrhythmias and sudden death.[45-47]

Kidney involvement

Renal involvement is obviously associated with morbidity and mortality.[48] The key features of FD are proteinuria and alteration of renal function (reduced glomerular filtration rate). Natural history of kidney involvement begins with hyperfiltration with increasing glomerular filtration rate (GFR) above 120 ml/min. It is followed by podocyturia, increasing albuminuria, macroproteinuria, reduced GFR, and ultimately end-stage kidney disease.[49] High degree of proteinuria is associated with GFR decline.[50,51] Microscopic haematuria or nephrotic syndrome are relatively uncommon. Parapelvic cysts are frequently encountered in FD.

FD is found from 0.25 to 3.5% of males receiving haemodialysis.[52-54]

Cerebrovascular involvement

Cerebrovascular manifestations include strokes and transient ischaemic attacks (TIA) but also chronic cerebral white matter hyperintensities, basilar artery dolichoectasia, and cognitive impairment.[55] Strokes are observed in both sexes and at any age with an incidence from 7 to 32% of females and from 11 to 48% of males.[56] They are mostly ischaemic (87% of cases) but can also be haemorrhagic. FD is found in about 1% of patients facing stroke at young age.[57]

Atrial fibrillation is frequent in this population and increase risk of stroke. It has been shown that a specific Fabry score was superior to the usual CHA2DS2-VASc to identify risk of stroke in these patients. Predictors of stroke or transient ischemic attack are history of stroke or TIA, presence of angiokeratoma, renal dysfunction, LVH and global systolic dysfunction.[58]

White matter hyperintensities are present in about two-thirds of the patients.[59] They are secondary to the progressive microvascular involvement and it appears in the 4th decade, earlier than in the general population (Fig. 4).

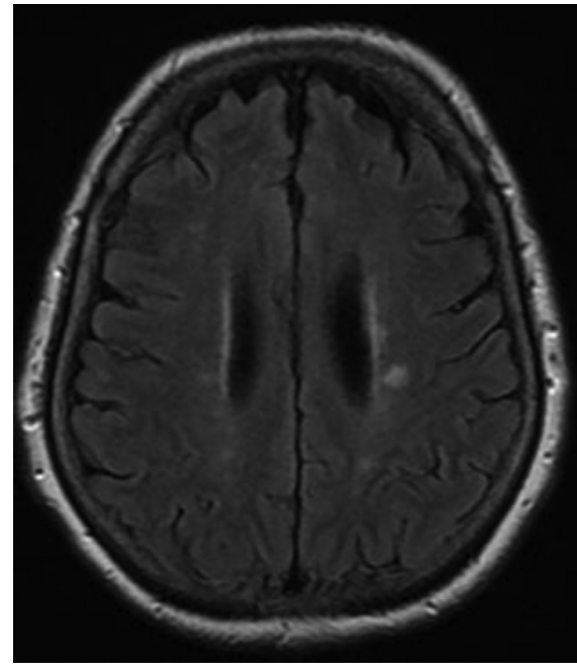

FIGURE 4. Cerebral MRI: T2-weighted-Fluid-Attenuated Inversion Recovery (FLAIR) MRI image showing white matter hyperintensities in a female with classical Fabry disease.

They can mimic multiple sclerosis.[60,61] This is particularly true in patients with atypical multiple sclerosis. In these patients, involvement of corpus callosum and the absence of infratentorial lesions should evoke FD.[62] In a population of well-defined multiple sclerosis, prevalence of GLA gene mutation was similar to the general population.[63]

Presence of vertebrobasilar dolichoectasia is also a marker of cerebrovascular disease with vessel remodeling.[64] Basilar artery is enlarged, elongated and tortuous but do not tend to rupt.

Cognitive impairment may be present in FD. Patients can face with reduced executive function performance.[64-66] These patients are also more likely to report symptoms of anxiety and depression.[66]

Depression is frequent, estimated at half of patients, and associated with presence of chronic pain.[66,67]

Otologic manifestations

Fabry disease can lead to progressive or sudden hearing loss (from 18 to 55% of patients).[68] It is secondary to involvement of cochlea, retrocochlea, acoustic vessel, brainstem, peripheral or central nervous system. Tinnitus is also frequent (from 17 to 53% of patients) and vertigo affects one third of patients.[69]

Gastrointestinal symptoms

GI symptoms are common, occurring from 50 to 60% of patients.[70] They are secondary to involvement of gut's autonomic function and vasculopathy. It may present as abdominal pain, bloating, diarrhea, constipation, nausea, vomiting, or pseudo-obstruction syndrome.[71] Denutrition has been described, secondary to malabsorption of nutrients due to glycosphingolipid deposits in intestinal villi.[72] Endoscopic explorations are usually normal, explaining delayed diagnosis in patients with predominant GI symptoms.

Bone manifestations

Fabry disease is an under recognized cause of premature osteopenia and osteoporosis with a prevalence from 50 to 87% of patients.[73,74]

Pulmonary manifestations

Patients frequently report pulmonary manifestations, such as shortness of breath during exercise, chronic cough, or wheezing. Plethysmography may be normal or objective anobstructive airway limitation.[75]

Quality of life

FD face a poor quality of life compared to the general population.[76] Factors associated with reduced quality of life are pain, gastrointestinal symptoms, hearing loss, asthenia and bimonthly intravenous therapy.

CLASSICAL, NON CLASSICAL AND LATE ONSET FABRY DISEASES

FD is classified as classical (i.e. severe) FD, nonclassical *or* late-onset FD with a later and milder phenotype and as cardiac variant of FD.[77]

Classical FD is associated with genetic variants leading to a very low (<3%) or null residual enzyme activity. These patients usually present with neuropathic pain, cornea verticillata, and angiokeratoma. They develop hypertrophic cardiomyopathy, cardiac rhythm disturbances, progressive renal failure, and stroke.

Nonclassical FD is characterized by a more variable disease course, in which patients are generally less severely affected or with disease manifestations limited to a single organ. In men, residual enzyme activity is under 30%. These patients are usually identified in screening populations with stroke, renal failure, or cardiomyopathy.[78,79] The cardiac variant of FD is the most common late-onset variant. Patients may be asymptomatic until cardiomyopathy is diagnosed from 50 years old.

Despite the X−linked inheritance pattern, females are often affected and may have severe involvements. They have usually milder phenotypes than males, but they may have severe organ involvement.[80] The skewed X inactivation may probably explain the variability of phenotypes in women.[9]

DIAGNOSIS

Management of FD must be performed or coordinated by a referral center of lysosomal storage diseases from diagnosis to the long term follow up. It needs to be a multidisciplinary team approach with a biochemist, pediatrician, neurologist, cardiologist, nephrologist, dermatologist, and geneticist.

Plasmatic tests

Measurement of α-Gal A activity is the first step of the diagnosis in both males and females. It is easily measured in leukocytes (gold standard), plasma or dried blood spot (DBS). Use of DBS testing is more practical and cost-efficient to transport. Measurements should be performed in referral laboratories for metabolic diseases.

Accumulated sphingolipids can also be measured. Initially, Gb3 was measured in urine, but measurement in plasma of its degradation product, globotriaosylsphingosine (Lyso-Gb3), has been shown to be more sensitive and specific.[81] In FD, Lyso-Gb3 is always elevated in males, but only from 40 to 60% of females.[82] Indeed in females, levels of Lyso-Gb3 increase with age and belong within normal ranges during childhood.[83] Nevertheless considering only adult females, both measurement of α-Gal A activity and plasmatic Lyso-Gb3 improves the diagnostic value for the detection of suspected symptomatic FD.[84-89]

Level of Gb3 or Lyso-Gb3 is usually correlated with FD severity.[90,91] Patients with late-onset FD have lower plasmatic levels Gb3 and lyso-Gb3 than patients with classical FD.[78]

Lastly, these markers are very useful during the follow up to evaluate response to therapy.

Tissue biopsy

Requirement for tissue biopsy is rare nowadays. It can show glycolipid deposits comforting the diagnosis of FD. It should still be discussed in patients with GLA variants of unknown significance and with inconclusive Lyso-Gb3 result to assess the diagnosis.[92] Skin biopsy is easily performed but cannot confirm the presence of significant deposits within the involved organs. Renal biopsy can suggest FD, showing on the light

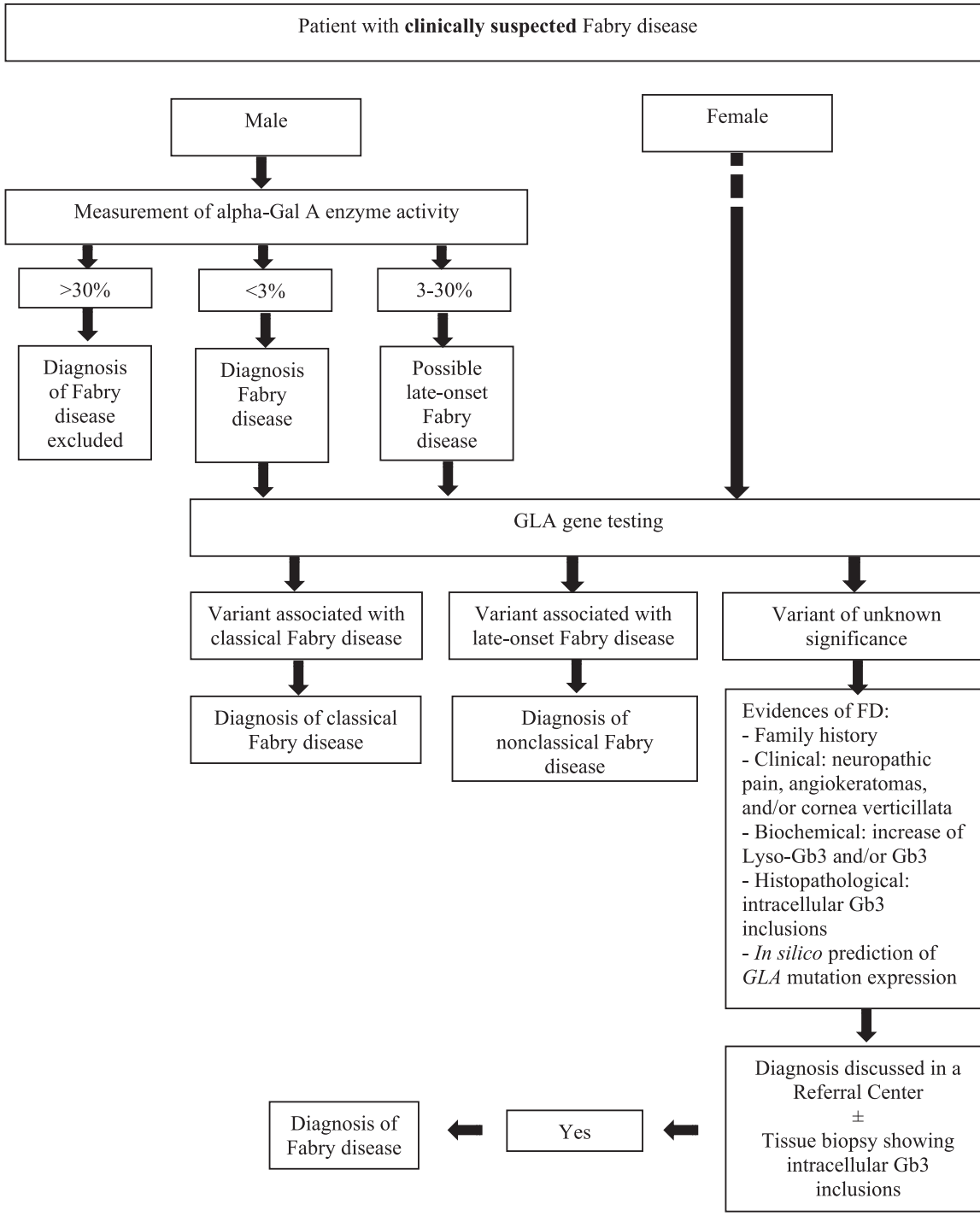

FIGURE 5. Diagnosis algorithm of Fabry disease.

microscopy vacuolation of podocytes, tubular, interstitial, glomerular and vascular Gb3 deposits and zebra bodies in the cytoplasm of podocytes.[93] Nevertheless, presence of suggestive storage inclusion is not sufficient to prove FD and need to be confronted with Gb3 measurement using spectrophotometry. Renal biopsy is also useful to evaluate irreversible damage (glomerulosclerosis, tubular atrophy, interstitial fibrosis, arterial sclerosis). Electron microscopy shows zebra bodies. Endomyocardial biopsy may be essential in cases of patients with cardiac variants or variants of unknown significance.

Genetic testing

Genetic testing for *GLA* gene mutation is always necessary to identify the causing mutation. A phenotypic variability with the same GLA variant is possible, but some variants are known to be associated with classical FD, others with late onset FD and others are polymorphism or of unknown significance.[79] Genetic testing is also needed to test family members and identify affected persons. It may be important for a therapeutic decision as migalastat, a pharmacologic chaperone, can only be prescribed in available mutations (40% of patients).[94] A patient with FD, a low enzyme activity, but no exonic mutation should lead to perform assessment of intronic mutations.[95,96]

Establishing diagnosis

A practical diagnosis algorithm is proposed in Fig. 5.

In males, a null or above 3% residual α-Gal A enzyme activity confirms classical FD. In males with late onset FD, enzyme activity varies from 3 to 30%. It is not sufficient to affirm the diagnosis. It needs to be confirmed by glycolipid deposits in the biopsy of an involved organ. Increased plasmatic Lyso-Gb3 concentration can also support the diagnosis.[84-89]

In females with classical or nonclassical FD, α-Gal A enzyme activity can be low or within normal ranges.[7] Demonstration of disease causing *GLA* mutation is needed. Recent studies suggest that systematic dosage of Lyso-Gb3 enhance diagnosis value in females.[84-89] It should however be within normal ranges in females with N215S cardiac.[97]

Pathogenicity of a variant of unknown significance is assessed by the presence of compatible FD clinical manifestation, low α-Gal A enzyme activity and highlighting of sphingolipid accumulation through high plasmatic Lyso-Gb3 concentration or histopathological evidence of FD. Testing family males of a suspected FD female with variant of unknown significance may be helpful (father and brothers).

Neuropathic pain, angiokeratomas, and/or cornea verticillata are major clinical characteristics for FD diagnosis in its classical form and may be absent in female with classical FD and with late-onset forms in both sexes.

In patients with *GLA* gene polymorphism, lyso-Gb3 is always normal.[98]

After diagnosis of FD in an index case, familial cascade screening needs to be rigorously performed in order to identify other affected persons. It is estimated that 5 family members are diagnosed around an index case. Genetic counselors can draw a complete family tree and identify at risk family members.[99] Another family consequence is the need of prenatal testing.

Specific treatments are licensed: enzyme replacement therapy and pharmacologic chaperone. They have to be discussed in referral centers.[100] Adjunctive therapy such as pain killers, anti-proteinuric agents and cardiologic drugs are also essential. Psychological, social supports and patient associations should be always proposed to patients.

CONCLUSIONS

FD is a rare but underdiagnosed condition. As a systemic disease, clinical manifestations of FD should be known and recognized by internal medicine physicians. This is a major issue as effective treatments change the natural course of FD when prescribed early.

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