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Fabry Disease and Cerebrovascular Disease

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Abstract

Fabry Disease (FD) is a genetic pathology related to the X chromosome (manifested predominantly in carrying men and women) caused by deficit of alpha α-galactosidase A enzyme (also known as ceramide trihexoside), that catalyzes the hydrolytic cleavage of the terminal molecule of galactose from Gb3 (globotriaosylceramide). FD presents phenotypically with inadequate glycosphingolipids metabolism, which affects cell membranes leading to multisystemic clinical manifestations. In addition to cerebrovascular disease (CVD), that mainly affects young patients, other frequent complications are renal, cardiac and dermatological. Due to its low prevalence, chronic and non-specific evolution, with manifestations in young adult life, it is difficult to identify it. Its diagnostic confirmation requires measurement of the activity of the enzyme α-galactosidase A, accumulation of globotriaosylceramide (Gb3), and/or genetic determination by mutation of the GLA gene (gene for galactosidase Xq22.1). At the moment, there is no specific treatment for FD, only symptomatic treatment for the sequelae it generates on a systemic level. The objective of this study is to offer a general overview of the epidemiologic, fisiopathologic and clinic aspects of the FD, with special interest in its manifestation as cerebrovascular disease (CVD), for differential diagnosis consideration.

Keywords: *Fabry disease, cerebrovascular disease*

Background

Fabry Disease (FD) was initially recognized under the name of "hemorrhagic papular purpura",[1] when dermatologists Johannes Fabry and William Anderson first described angiokeratoma corporis diffusum in 1898.[2] Initially it was documented as a systemic vascular disease, and later on as a lipid storage disorder.[3,4] Accumulation of the glycolipids ceramide trihexoside (now called globotriaosylceramide (Gb3 or GL-3)) and galabiosylceramide in a variety of different cell types was identified in 1963;[5] several years later, the defect was established as insufficient activity of the ceramide trihexosidase enzyme, that catalyzes the hydrolytic cleavage of the terminal galactose molecule of Gb3.[6] The X-linked nature of the disease was first recognized in 1965.[7]

Definition

FD (OMIM #301500),[8] or *angiokeratoma corporis diffusum*, is a rare and highly debilitating inherited disorder of glycosphingolipid metabolism, associated with renal, cardiac, and cerebrovascular complications.[9]

Deficiency of agalactosidase, a lysosomal hydrolase, leads to progressive accumulation of glycosphingolipids (primarily ceramide trihexoside (GL-3 or Gb3)) in most visceral tissues, including vascular cells (endothelial and smooth muscle cells), heart cells (cardiomyocytes and valve cells), kidney cells (tubular and glomerular cells), nerve cells and mainly in the lysosomes of the vascular endothelium. The progressive accumulation of endothelial glycosphingolipids produces

tissue ischemia and infarction and leads to the principal clinical manifestations of the disease.[10]

Epidemiology

The prevalence of FD has been estimated to be around 1 in 40,000 males.[11] Another study found 12 of 37,104 consecutive male neonates with specific mutations in the α-galactosidase A gene (X-linked Xq22.1, as will be described in Physiopathology);[12] in turn, Clarke estimated in 2007 1 patient with FD for every 55,000 male births.[13]

Cerebrovascular manifestations are frequent both in the homozygous group and the symptomatic heterozygous. More importantly, these manifestations may be the first indication of the disease.[10] In a prospective study of 721 patients aged 18 to 55 years, 4.9% of male patients and 2.4% of female patients had biologically significant mutations in the GLA gene.[14]

In Mexico there are no studies on FD prevalence or its neurological manifestations, probably due to its low incidence and the diagnostic difficulty that it implied until a few years ago. In general, FD and its manifestation as Cerebrovascular Disease (CVD) are concealed under the classification of cryptogenic etiology, a common final diagnosis of CVD. In relation to this, it is worth mentioning the study by Barinagarrementeria et al., who collected a sample of 300 patients aged under 40 years with ischemic CVD in its different varieties, of which 32% were classified as cryptogenic, that is, without achieving the identification of the specific etiology;[15] it is likely that some of these cases could correspond to FD, however, this disease was not discarded.

In Argentina, a multicentric study carried out in 2017 collected data from 311 patients with CVD (80% infarctions, 9% transient ischemic attacks (TIAs) and 11% intracerebral hemorrhages), of which only 1 case presented evident FD with a pathogenic mutation: c.888G> A/p. Met296Ile/Exon 6, representing 0.3% of the sample and 1% of the patients with cryptogenic cerebral infarcts.[16]

In 2017, the Canadian Fabry Stroke Screening Initiative Study Group identified a single case with a genetic variant of uncertain significance (p.R118C) and no well-recognized pathogenic variants from a cohort of 365 patients with cerebral infarction and 32 with TIA, between 18 and 55 years of age. As a result, if such variant is considered pathogenic, FD prevalence would be of 0.3%.[17] This suggests that, in this population, more cost-effective methods for diagnosing FD should be applied instead of systematic genetic screening.

Pathophysiology

FD is considered an X-linked disorder (Xq22.1), mutating the GLA gene that encodes the α-galactosidase A protein (GLA, 300644),[8] with a high degree of penetrance in men, and intermediate in women: about 50-70% of women with mutations in the gene have manifestations of FD, while almost 100% of men have disease complications.[10] The α-galactosidase A gene is 12kb long, with seven exons and encodes a 429 amino acid precursor protein which is processed to a 370 amino acid glycoprotein that functions as a homodimer. There are 596 known mutations described for this gene, of which 416 are nonsense/stop mutations, 83 small deletions, 19 large deletions, 32 splice defects, three complex rearrangements, and one large insertion.[7]

The primary disease process begins in infancy, or even in fetal development stage, however, unlike many other lysosomal storage diseases, most patients remain clinically asymptomatic during the first years of life. In FD, lysosomal storage and deficient α-galactosidase A activity in plasma and leukocytes are thought to generate globotriaosylceramide accumulation and glycosphingolipids with cellular dysfunction, triggering a cascade of events that include cell death, compromised energy metabolism, small vessel injury, dysfunction of potassium-activated channels in endothelial cells, oxidative stress, impaired autophagosome maturation, and tissue ischemia, which can result in progressive organ dysfunction.[18]

Clinical manifestations (Table 1)

1.- Initial clinical manifestations

The most common initial symptoms of FD are episodic pain crisis that last from minutes to hours, primarily affecting the feet or hands, usually precipitated by exercise, fever, or heat, and modified by acetaminophen.[19] Mechanisms responsible for producing such crisis are not well known, but it is possible that glycophospholipids storage within the endothelial cells of the vasa nervorum, perineural cells, or dorsal root and autonomic ganglia, may cause altered vasomotor reactivity, resulting in a hypoxic state.[11]

Table 1. Clinical features in patients with Fabry disease. Modified from Germain D

System	Signs and symptoms
Sensory organs	– Ocular Cornea verticillata Posterior cataract Vasculopathy (retinal, conjunctival) – Auditory (vertigo/tinnitus) Sensorineural hearing loss
Central Nervous	– Cognitive impairment – Headache – Hemorrhagic or ischemic stroke with posterior circulation predominance – Psychiatric disorders
Peripheral Nervous	– Painful neuropathy (predominantly small fiber) – Neuropathic pain (Acroparesthesias) – Dysautonomia – Intolerance to heat or cold – Hypohidrosis or anhidrosis
Cardiovascular	– Arrhythmia – Unexplained ventricular hypertrophy – Conduction disorders on the electrocardiogram – Valvular heart disease
Respiratory	– Asthma – Dyspnea due to reduced exercise capacity
Digestive	– Postprandial abdominal pain – Nausea/vomiting – Episodic diarrhea – Early satiety
Nephron-urinary	– Microalbuminuria/proteinuria – Hematuria – Nephrotic syndrome – Kidney disease of undetermined etiology
Skin	– Angiokeratomas – Dyshidrosis (hypo/anhidrosis)

2.- Classic clinical manifestations

Patients with the classic form of the disease (no residual α-galactosidase A activity) have typical dysmorphic abnormalities, particularly on the face. These dysmorphisms include periorbital fullness, prominent supraorbital ridges, bushy eyebrows, receding forehead, prominent earlobes or ear rotation, pronounced nasal angle, large nose/bulbous nasal tip, prominent nasal bridge, wide alar base, full lips, coarse facial features, and prognathism.[7] During adolescence, skin lesions (angiokeratomas) appear, which are usually located at the periumbilical, genital and thigh root levels.[20] The accumulation of cytoplasmic material with a lipoid appearance causes epithelial deformation of the glomerular tufts, of the tubules, glomerular endocapillary cells, arteriolar muscle cells, that clinically manifest as proteinuria and renal failure.[8] The latter is the primary cause of death in patients with FD.[21]

3.- Manifestations of FD in the nervous system.

FD neurological complications are common and affect both the central nervous system (CNS) and the peripheral nervous system (PNS).[10] Data from the international Fabry Registry, a large cohort of 2,446 patients, indicate that CVD events are frequent in homozygotes and heterozygotes, occurring in 6.9% and 4.3%, respectively;[22] of which 87% were ischemic and 13% were hemorrhagic.[23] In Fabry Registry, the majority of patients experienced a first stroke between the ages of 20 and 50, and 22% had a first stroke before the age of 30.[24] CNS manifestations of FD include: cerebrovascular disease, hearing impairment with tinnitus, vertigo, psychiatric disorders, and cognitive impairment.[10]

3.1.- Clinical manifestations of FD as cerebrovascular disease

Homozygous men may present with dysarthria, diplopia, vertigo, nystagmus, nausea and/or vomiting, hemiparesis, ataxia, or hemibody sensory symptoms, related to the location and type of CVD that they develop. Headache is quite uncommon, reported in only 20% of patients. In most patients (58%), presentation is compatible with ischemia of vertebrobasilar territory, while anterior circulation was positively symptomatic in approximately 20% of patients.[25]

Vascular dementia due to penetrating small-vessel disease has also been described in patients with FD and should be considered in the evaluation of unexplained dementia, particularly in men younger than 65 years.[26,27]

Heterozygous females may also develop symptoms of neurological impairment, the most reported being cognitive impairment, vertigo, ataxia, hemiparesis, hemibody sensory

symptoms, and headache. In half of the patients, the clinical presentation was consistent with involvement within the vertebrobasilar territory, while the carotid territory was definitely affected in only 10% of cases.[25] Central retinal artery occlusions have also been reported[28] as well as central retinal vein occlusions.[29] In addition to dolichoectasia, white matter lesions and the "pulvinar sign", characterized by hyperintensity in the posterior region of the thalamus, can be observed in the T1 sequence of the MRI.[9]

Common features in the PNS include: peripheral neuropathy (particularly small-fiber neuropathy) with acroparesthesias, autonomic dysfunction characterized by hypohidrosis, intestinal dysmotility, and peripheral thermal and vasomotor dysregulation.[10]

3.2.- Pathological findings in the nervous system
Neuropathologic autopsy findings are consistent with prior events of cerebral ischemia and, rarely, intracerebral hemorrhage; extensive and superficial hemispheric infarcts, multiple small and deep infarcts and infarcts of the brainstem and/or cerebellum can also be observed, the latter being more frequent in symptomatic homozygotes and heterozygotes.[25]

The vessels of the circle of Willis often appear thickened. The narrowing of the lumen and intracellular deposits in arteries and arterioles are additional discoveries.[19] Dolichoectasia of the basilar and vertebral arteries, and less frequently of the carotid arteries, is a constant finding in both homozygotes and symptomatic heterozygotes.[25]

Ischemic and hemorrhagic CVD in FD seem to occur in a proportion similar to that observed in general population, however, at a younger age, TIAs seem to be a risk factor for CVD. Hypertension has been considered the most important risk factor for CVD in FD, and its effect is probably potentiated by underlying vascular degeneration secondary to glycosphingolipid deposits. In the Fabry Registry, patients with CVD were more likely to report a history of hypertension compared with FD patients without CVD, 52.9% *vs*. 20.5%, respectively.[9]

Various cerebral blood flow and intracranial vessel walls abnormalities have been identified, which may not be exclusive to the arterial system. Several mechanisms can contribute to FD vasculopathy, including: endothelial dysfunction, dysregulation of nitric oxide pathways, prothrombotic state, hyperhomocysteinemia, elevated levels of lipids and leukocyte adhesion molecules (Table 2).[19]

The dolichoectasia frequently found in FD, particularly in the large vessels of the posterior circulation, may be related to mechanical weakening of the vessel wall, caused by glycosphingolipid deposits and hypertension. Pathophysiologic mechanisms of CVD associated with dolichoectasia include embolus formation and occlusion of penetrating brainstem arteries. Cardiac involvement in FD can also predispose to CVD, mainly its association with arrhythmias.[9]

Table 2. Mechanisms of cerebral infarction in Fabry disease. Modified from Caplan, et al.

1. Intrinsic vascular pathology
a. Complete or partial thrombosis of main arterial trunks
b. Stretching, distortion and obstruction of tributary vessels
c. Artery-to-artery embolism
2.Glycosphingolipid deposition in the vessel wall with secondary occlusion
3. Cardioembolism
a. Septal motion abnormalities secondary to ischemic heart disease
b. Valvulopathies
c. Hypertrophic cardiomyopathy
4. Altered autonomic function
a. Arterial hypertension
b. Arterial hypotension
5. Prothrombotic states
a. Platelet activation
b. Activation of endothelial factors

Diagnosis (Figure 1)

In men, the diagnosis of FD is made by measuring the activity of the enzyme α-galactosidase A in plasma or peripheral leukocytes. On the contrary, women with suspected FD due to heterogocity may have normal levels of α-galactosidase A activity, so this measurement is not useful, and they must undergo GLA genotyping. Elevated levels of α-galactosidase A substrates in plasma and urine (Gb3 and lyso-Gb3) suggest FD diagnosis.[30]

The blood sample required for this diagnosis is 3ml of whole blood collected in a tube with ethylenediaminetetraacetic acid (EDTA). Currently there also exists enzymatic diagnosis in dried

blood spots collected on filter paper, this new methodology makes it possible to transport samples remotely for enzymatic analysis, retrospective diagnosis and population screening.[31]

GLA gene sequencing is the gold standard for diagnosing FD. Due to X-linked inheritance, there is no contribution of the mutated gene from the father to his offspring, while heterozygous females have a 50% risk of transmitting the mutated gene.[30]

Screening for Fabry disease in cerebrovascular disease

Screening for FD in high-risk populations became a major concern when enzyme replacement therapy (ERT), applied every 2 weeks, appeared in 2001. Regarding this, studies were carried out in different contexts that showed the severe complications of FD, including chronic kidney disease, left ventricular hypertrophy (LVH) and CVD. It is worth mentioning that screening may be biased towards patients with the most critical disease and classic phenotypes. In the Fabry Registry,[22] patients with CVD were diagnosed later than those without CVD, and most of them had not experienced renal or cardiac events prior to their first cerebral event, suggesting that the classic features of the disease may be absent or more subtle in these patients.

In recent times, atypical phenotypes have been reported with increasing frequency – some of which with CVD as a presenting feature –, in these cases, due to the fact that their clinical recognition requires a high index of suspicion, the diagnosis of FD is often delayed or is overlooked. Therefore, the accurate prevalence of FD in young patients with CVD is unknown.[9]

Regarding the Latin American population, there is only information from 333 patients included in the Fabry Registry,[32] mainly from Argentina, Chile, Colombia, Peru and, among them, some Mexicans. 167 Latin American women and 166 men are part of the registry, with an average age of 35.5 years for men and 37.9 years for women. Of these patients, 8 men (5%) and 3 women (2%) had CVD. Most of the Latin American patients in this registry come from nephrology and cardiology services. At the moment, there is no update of data by the Fabry Registry, whose recruitment is still open.[22]

Diagnosis and screening for FD has been a subject of study mostly in high-income countries, including neonatal screening programs. In countries such as Denmark, Australia and Japan, early detection programs — Dried blood spot testing (DBS) — have been implemented. This method uses dried blood spots on filter paper, generally obtained between 24 and 72 hours of extrauterine life, to measure enzyme α-galactosidase A activity or globotriaosylceramide accumulation.[33] These studies have managed to determine a sensitivity of 100% for the detection of newborns with FD, but with variable specificity when compared with the gold standard that is genetic sequencing (with a positive predictive value of 33 to 42%).[34] In the case of women, enzyme activity testing in blood has low sensitivity.

Treatment

In 2001, two recombinant enzymes were approved for use in Fabry disease: agalsidase alfa (Replagal®, Shire/Takeda) and agalsidase beta (Fabrazyme®, Sanofi Genzyme), called enzyme replacement therapy (ERT).[35] This therapy demonstrated a reduction in the production of LVH and in the progression of kidney disease when the clearance was less than 60ml/min/1.73m2, possibly attributed to their antiproteinuric therapy, which could lower the incidence of CVD in the long term by reducing the risk factors that promote it in both men and women. Another treatment option, Migalastat (1-deoxygalactonojirimycin; Galafold, Amicus Therapeutics) was approved in Europe in May 2016, in Canada in September 2017, in Japan in March 2018, and in the US in August of the same year, for long-term treatment of FD in adults (≥18 years of age in the United States and Canada, ≥16 years of age in other countries), with a susceptible mutation and an estimated glomerular filtration rate (eGFR) ≥30 mL/min/1.73 m2. Orally administered, Migalastat is a small chaperone that stabilizes the endogenous α-galactosidase A enzyme and supports proper protein folding in the endoplasmic reticulum, leading to increased protein enzyme activity and stability in lysosomes of susceptible mutation carriers.[36] In a multicentric study of the use of Migalastat for 12 months (FAMOUS study), a reduction in the mass of the left ventricle was demonstrated, although it was not possible to reduce the progression of kidney disease, possibly due to the intervention of other triggering factors.[37]

In the management of FD patients with acute cerebral infarction, intravenous thrombolysis[38] or an endovascular approach can be considered; experience with the use of either in this setting is limited to non-existent, although there are no specific reasons to discard such treatments.[10]

In secondary prevention, treatment is far from satisfactory, since there is no specific therapy for cerebrovascular complications of FD. Administration of antiplatelet agents may help prevent

the atherosclerotic and thromboembolic effects of vascular endothelial damage, but experience with this approach is limited.[10] Similarly, anticoagulant agents should be considered to help prevent stroke recurrence when the implicated cause is cardiac embolism.[19]

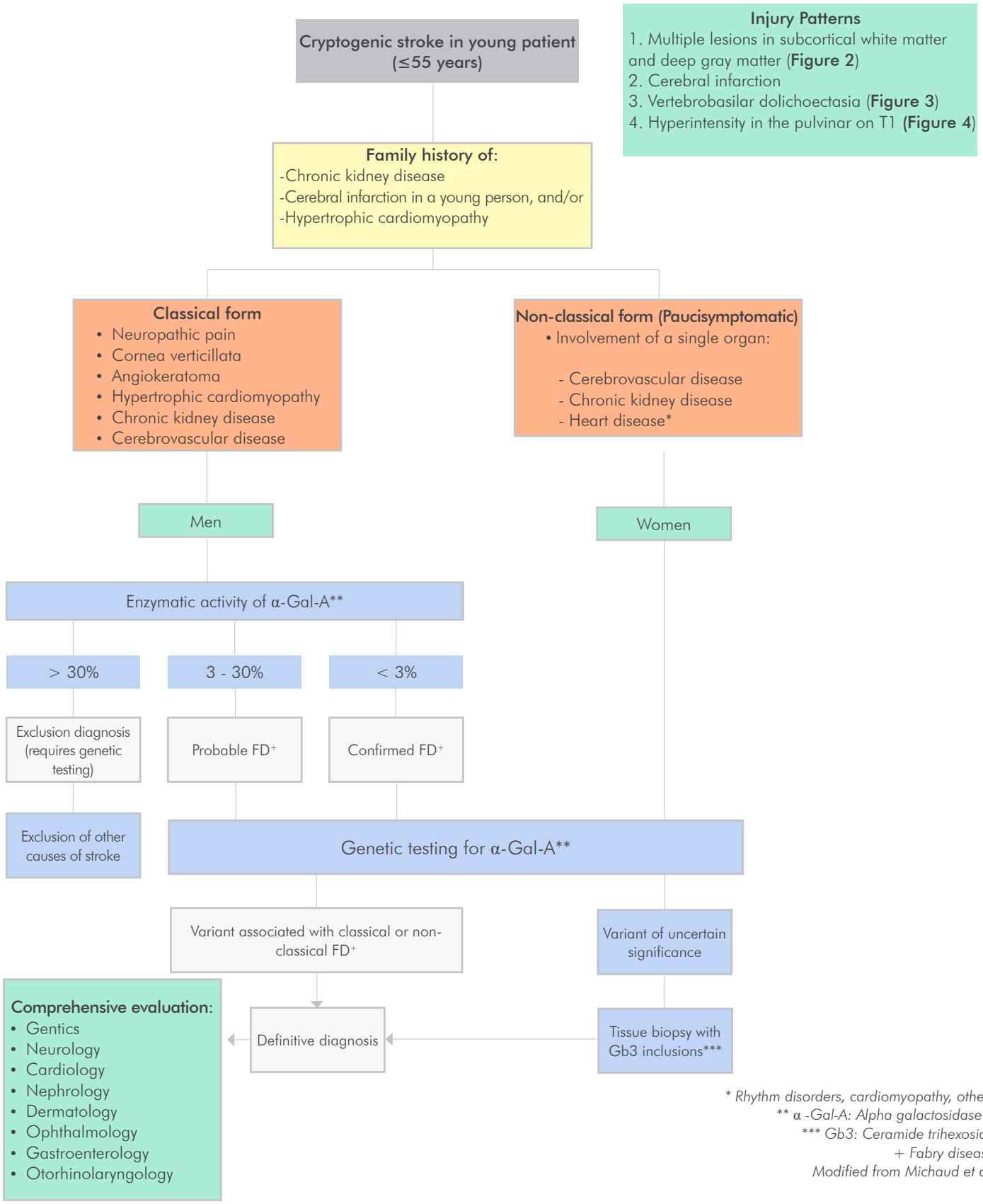
Forecast

FD is a progressive pathology with reduced life expectancy; the median survival age for men is 50-55 years, and 70 years for women. Quality of life is affected in all patients, not only due to target organ damage, but also as a result of other symptoms including gastrointestinal problems, acroparesthesias, depression, and intolerance to certain temperatures. Since its introduction in 2001, enzyme replacement therapy has been shown to be effective in relieving several of these symptoms, as well as delaying and even reversing disease progression.[7,39]

Conclusion

It is recommended that all young patients (<55 years) with a history of one or more events of ischemic or hemorrhagic CVD of undetermined etiology (cryptogenic), primarily those with systemic diseases (dermatological, cardiac or renal), undergo screening for Fabry disease, whether by determination of α-galactosidase A activity or sequencing of the GLA gene. CVD treatment in these patients is similar to that established in clinical guidelines for the general population, since there is no specific treatment for this pathology, but it requires a multidisciplinary approach[40] and follow-up (see Figure 1 on the next page).

Figure 1. Fabry Disease diagnostic algorithm



** Rhythm disorders, cardiomyopathy, others*
*** α -Gal-A: Alpha galactosidase A*
**** Gb3: Ceramide trihexoside*
+ Fabry disease
Modified from Michaud et al.

Figure 2. Axial T2-FLAIR MRI. Multiple hyperintense lesions in subcortical white matter and bilateral deep gray matter

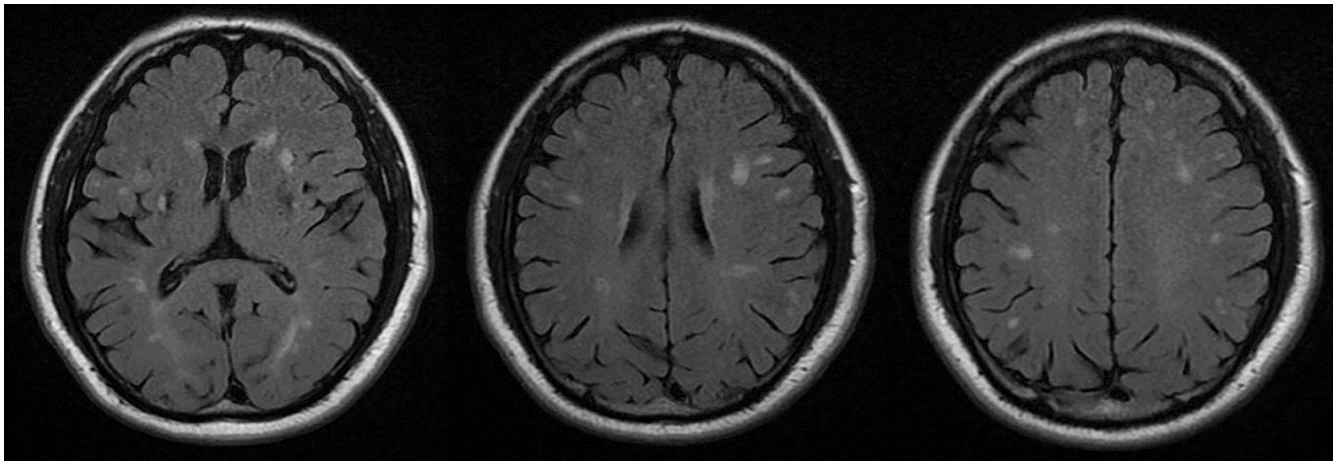


Figure 3. Coronal 3DTOF MRI. Vertebrobasilar dolichoectasia

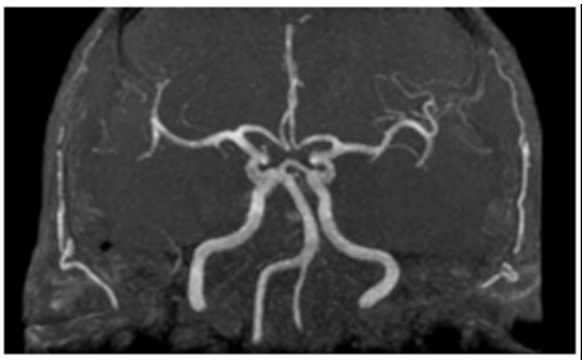
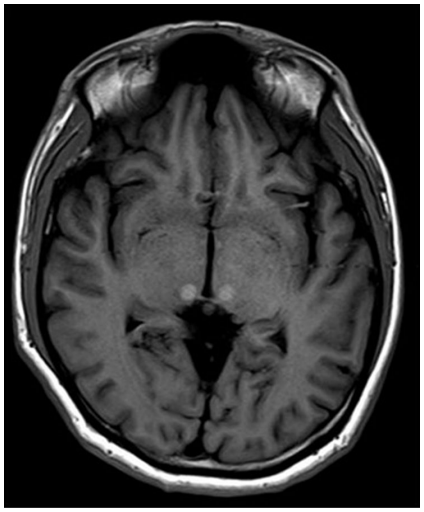


Figure 4. Axial T1 NMR. Hyperintensities in the pulvinar nuclei of the bilateral thalamus in a patient with Fabry disease. (Pathognomonic).



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