Fabry disease (FD) /Anderson-Fabry disease (AFD)

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Other denominations

Angiokeratoma Corporis Diffusum, Anderson-Fabry Disease. Hereditary Dystopic, Lipidosis, Alpha-Galactosidase A Deficiency, Gla Deficiency and Ceramide Trihexosidase Deficiency

Introduction

Fabry disease (FD) OMIM # 301500; is an X-linked progressive multisystemic genetic sphingolipidosis caused by deficient activity of lysosomal enzyme α-galactosidase (α-Gal A) or (AGALA).[1] Gene mapped to the long arm (Xq22.1 region) of the X chromosome,[2] and subsequent cell and microvascular dysfunctions. More than 150 mutations have been reported, including missense, nonsense, splice site mutations, insertions/duplications and deletions. Enzyme Commission number 3.2.1.22. FD is an X-linked disorder, neither recessive nor dominant. The penetrance in females is quite high, with at least 70% of females showing clinical manifestations of the disease (26). FD is inherited in an X-linked manner, it refers to the location of the GLA gene (Fabry gene) mutation/defect on the X chromosome. The X and Y chromosomes, two of the 23 pairs of chromosomes in the body, among many other functions, determine the sex of an

individual. FD follows an X-linked inheritance pattern. In this type of inheritance pattern, if a man has FD he will pass the disease on to all of his daughters and none of his sons. If a woman has FD, each child born to her has a 50% chance of having the disease.

Main Chronological discoveries in Fabry Disease

First description: FD was first described by the famous Austrian dermatologist Johannes Fabry and surgeon William Anderson independently in 1898. It was recognized to be due to abnormal storage of lipids in 1952 In his first paper on this subject, Fabry et al (1898) called the skin lesions 'purpura papulosa haemorrhagica Hebrae', suggesting that they had previously been described by Hebra.[3] Anderson - Fabry Disease is a multisystemic disorder caused by the build-up - inside lysosomes - of globotriaosylceramide or Gb3, which is the accumulated lipid material discovered in 1963 by Sweeley e Klionsky.

Hashimoto et al, using electron microscopy, revealed the presence of bodies in endothelial cells, smooth muscle cells, fibrocytes and perivascular cells of patients with FD.[4] In the same year, Dempsey

et al observed that a sex-linked deficient gene with occasional penetrance in heterozygous females and constant penetrance in homozygous males was the cause.[5] Lyon et al, however, in 2002 showed that heterozygous females may be affected as severely as hemizygous males, due to the process of random inactivation of the normal X chromosome.[6]

Men aged >30 years and women aged >40 years most often present with unexplained left ventricular hypertrophy (LVH), usually concentric and non-obstructive, but sometimes mimicking sarcomere hypertrophic cardiomyopathy (HCM), particularly when isolated, as in the cardiac or late-onset variant of the disease. In HCM cohorts, up to 1% of patients have been diagnosed with FD. Frequent cardiac arrhythmias including chronotropic incompetence, severe conduction disturbances and others, cardiac heart failure (CHF) and sudden cardiac death (SCD), and cardiovascular complications are currently the leading cause of death at a mean age of 55 years in men and 66 years in women. Complementary to screening for extracardiac manifestations, the initial cardiac evaluation should include Holter recordings,

echocardiography and late gadolinium and T1 mapping cardiovascular magnetic resonance imaging (CMRI). Abnormalities of a non-hypertrophied inferolateral wall at the base of the left ventricle (thinning, decreased strain, midwall fibrosis) and low native T1 signal on CMRI are evocative. CMRI, native T1 is low in FD because of sphingolipid accumulation. Myocyte storage starts in childhood and accumulates faster in men before triggering two processes: a sex-independent scar/inflammation regional response (LGE) and, in men, apparent myocyte hypertrophy diluting the T1 lowering of sphingolipid.[7]

Aggressive cardiac management may include the control of cardiovascular risk factors, anticoagulation, permanent cardiac pacing and/or an implantable cardioverter defibrillator (ICD), while antiarrhythmic and β-blockers should be used with caution. Specific therapy should be initiated at the earliest stage, when the first structural or functional cardiac abnormalities are detected, and should include enzyme replacement therapy (available since 2001) or there are 2 drugs in this class: Agalsidase α (Replagal, Shire Human Genetic Therapies, Lexington, MA) is produced in a

lineage of human fibroblasts, and is given at a dose of 0.2 mg/kg as an i.v. infusion and dosed every 2 weeks; Agalsidase β (Fabrazyme, Sanofi Genzyme, Cambridge, MA) is produced in Chinese hamster ovary cells and is administered at a dose of 1 mg/kg as an intravenous infusion every 2 weeks.

Chaperone therapy (available since 2016) (the use of which is limited to patients with FD and an amenable α-galactosidase A gene mutation).[2]

Epidemiology

Prevalence: Estimated birth prevalence range between 1:40,000 and 110,000.[8-10] Prevalence in white male populations has been linked to FD in a wide range, approximately 1:17,000 to 1: 117,000. Classic FD mutations are seen in ≈1:22,000 to 1:40,000 males, and atypical presentations are associated with about 1:1000 to 1:3000 males and 1:6000 to 1:40,000 females.

Incidence: incidences ranging from as high as 1 in 40,000 live male births to 1 in 117,000 live male births.[8, 9]

Race: Although it is an under-diagnosed condition, the disease is seen in all racial and ethnic groups.

Sex: FD is an X-linked disease, affecting predominantly males, with females being carriers. Indeed, the clinical picture is far more pronounced in males, although females may show the phenotype, mostly characterized by neurological and cardiac symptoms. In males with a suggestive phenotype, the diagnosis is made by demonstrating low α-Gal A activity in leucocytes or plasma. In females, demonstration of a mutation in *GLA* is required to confirm the diagnosis. Females usually show less progression of hypertrophy than males, and it was recently suggested in an CMRI study that replacement fibrosis may be a valid screening tool in females as opposed to males in the early stages of Fabry's disease. Table 1 show the main sex differences in FD.

Table 1

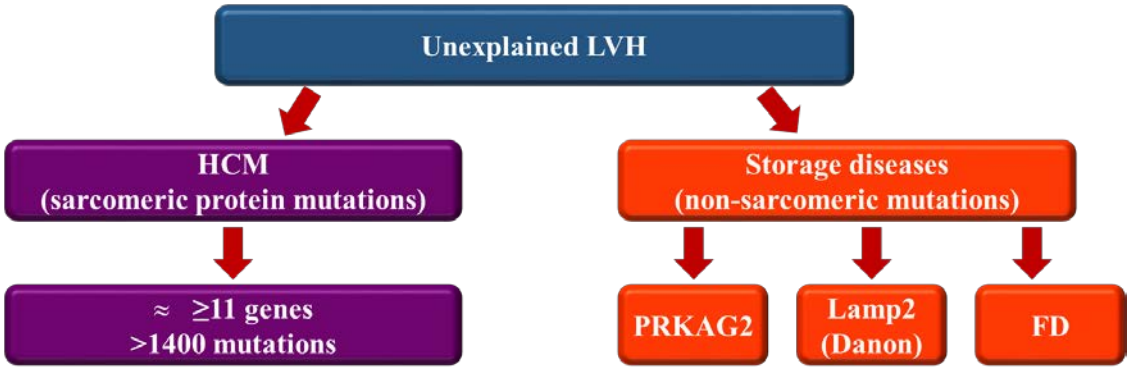
	Females	Males
Severity	Usually mild manifestation They are carriers	Primarily affected, more severe manifestation
Diagnosis	Demonstration of a mutation in GLA is required to confirm it.	It is made by demonstrating low α-Gal A activity in leucocytes or plasma
Atypical presentation	1:6,000 to 1:40,000 females	1:1,000 to 1:3,000
Unexplained LVH observation	Aged >40 years	Aged >30 years
FD mutations		≈1:22,000 to 1:40,000
Ventricular arrhythmias	20%	14%
Neurologic affectation[11]	61% of cases	75%
Cerebrovascular events	21%	25%
Mean age of death	64.4 years	51.8
QRS duration	Lower	Significantly higher
Right and left bundle branch block: infrequent	Unusual	Lesser unusual

Table 1. The sex-specific aspects of clinical disease expression and the potential modes of inheritance or the hereditary influences.

Sex characteristics and differences between cardiomyopathies

Figure 1 Sarcomere mutations responsible for HCM and its phenocopies or non-sarcomere with LVH.

Figure 1



***Modified from Eur Heart J*, Volume 33, Issue 5, March 2012, Pages 570–572, https://doi.org/10.1093/eurheartj/ehr438**

Note: HCM phenocopies include a variety of disorders such as glycogen storage disorders,[12, 13] lysosomal storage disorders such as Damon disease,[14] mitochondrial cytopathies involving the mitochondrial respiratory chain,[15] cardiac amyloidosis such as familial transthyretin-related amyloidosis (autosomal dominant).

With LVH[16] and of fatty-acid metabolism disorders (cardiac presentations were observed in 51% of patients: 67% patients presented with cardiomyopathy, mostly hypertrophic, and 47% of patients had heart beat disorders with various conduction abnormalities and arrhythmias responsible for collapse, near-miss and sudden unexpected death. All enzymatic blocks affecting FAO except CPT I and MCAD were found associated with cardiac signs).[17]

Electrocardiographic clues for the diagnosis of FD

The main electrocardiographic parameters found in FD are: bradycardia, shortening of the P-wave duration (PWD), shorter PR/PQ interval, PR/PQ interval minus P wave duration ≤40 ms in II lead, high voltage QRS complexes in the left precordial leads (voltage criteria),[18-21] prolonged QRS duration and bundle branch block, QT and QTc prolongation, prolonged Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratio, repolarization changes related to LVH and/or remodeling, and cardiac arrhythmias.

I) **Bradycardia**

SCD in FD is related to bradycardia. Symptomatic bradycardia leading to pacemaker implantation may be required in 5 to 10% of patients in long-term follow-up.[22] Sudden cardiac death in Fabry cardiomyopathy may be related to bradycardia.

II) **Shortening of the P-wave duration (PWD)**

It is one of the early signs of cardiac involvement.[23] ECG with short PWD duration has been demonstrated to be associated with higher risk of atrial fibrillation (AF). A short PWD is a marker of a higher rate of AF recurrences after pulmonary vein isolation procedure. A short P wave was reproduced in computer cardiac simulation pointing to the presence, most likely, of a so-far unknown condition that an increase in Na+ channel conductance shortens the PWD. This condition might be associated with lower responsiveness to class I antiarrhythmic for patients with paroxysmal and persistent AF but also for asymptomatic individuals who present the atrial phenotype.[24]

III) **Shorter PR/PQ interval without ventricular pre-excitation (delta wave) by the absence of accessory pathway**:

While both P-wave and PR-interval duration differ significantly from healthy subjects, short PR interval (it is considered a normal PR interval in adults between 120–200 ms) due to a short P wave duration as a result of accelerated conduction in the absence of accessory pathway), P-wave duration (PWD) yielded a higher diagnostic performance (92% sensitivity and 80% specificity).[7] Namdar et al suggested that PQ/PR interval could not be used solely as a diagnostic marker for FD.[25] From a universe of 150 genetically confirmed FD patients investigated by Nieman et al, "Fabry-specific" short PR interval was not relevant in this large population. Short PR interval showed 16 % of patients with shortened PR interval in both sex.[26]

IV) PR/PQ interval minus PWD ≤40 ms in II lead

This parameter had a Sensitivity: 82%, Specificity: 99%, Positive Predictive Value: 64%; Negative Predictive Value: 95%. Accuracy: 88% for the diagnosis of FD.[27] Without this electrocardiographic parameter it would be very difficult to distinguish FD from Ap-HCM. **Figure 2**

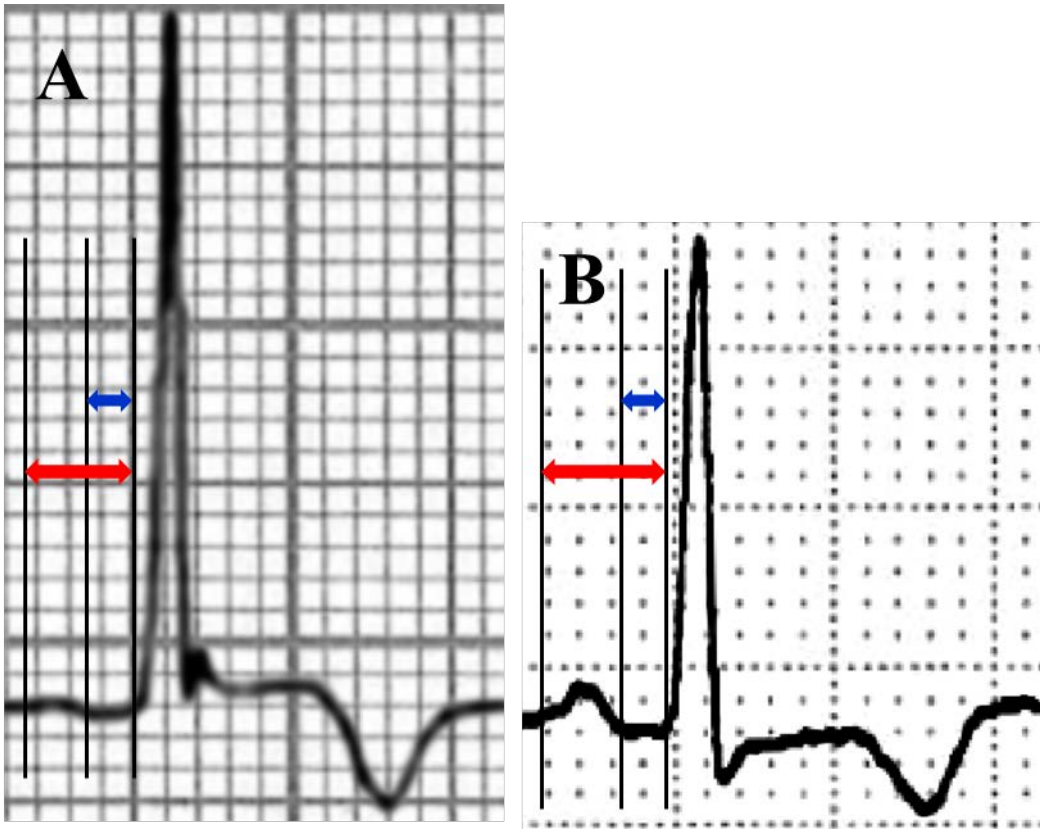


Figure 2. A) PR/PQ interval minus PWD ≤40 ms in II lead: Fabry Disease; B) PR/PQ interval minus PWD ≤40 ms in II lead: Ap-HCM.

V) High voltage QRS complexes in the left precordial leads (voltage criteria)

The presence of LVH was associated with a significantly higher frequency of cardiac symptoms, arrhythmias, and valvar disease.[19, 21] Additionally, both FD and amyloidosis are infiltrative heart disorders, and may to cause in cardiomyopathies. Frequently, the

transthoracic echocardiogram (TTE) reveals increased LV wall thickness in both disorders, with indistinguishable findings between both entities whit this methodology. Whereas, the ECG can help in differential diagnosis because the ECG abnormalities are different. In the patients with cardiac FD, the ECG shows high voltage QRS complexes in the left precordial leads frequently associated with strain pattern of repolarization. They are caused by an increase in LV mass, owing to cell size enlargement for the glycosphingolipids deposition in the myocytes' lysosomes. On the other hand, in cardiac amyloidosis, the ECG depicts QRS complexes with diffusely low voltages because the amyloid is present between myocytes and the cell size is normal.[28] example in the next **Figure 3**

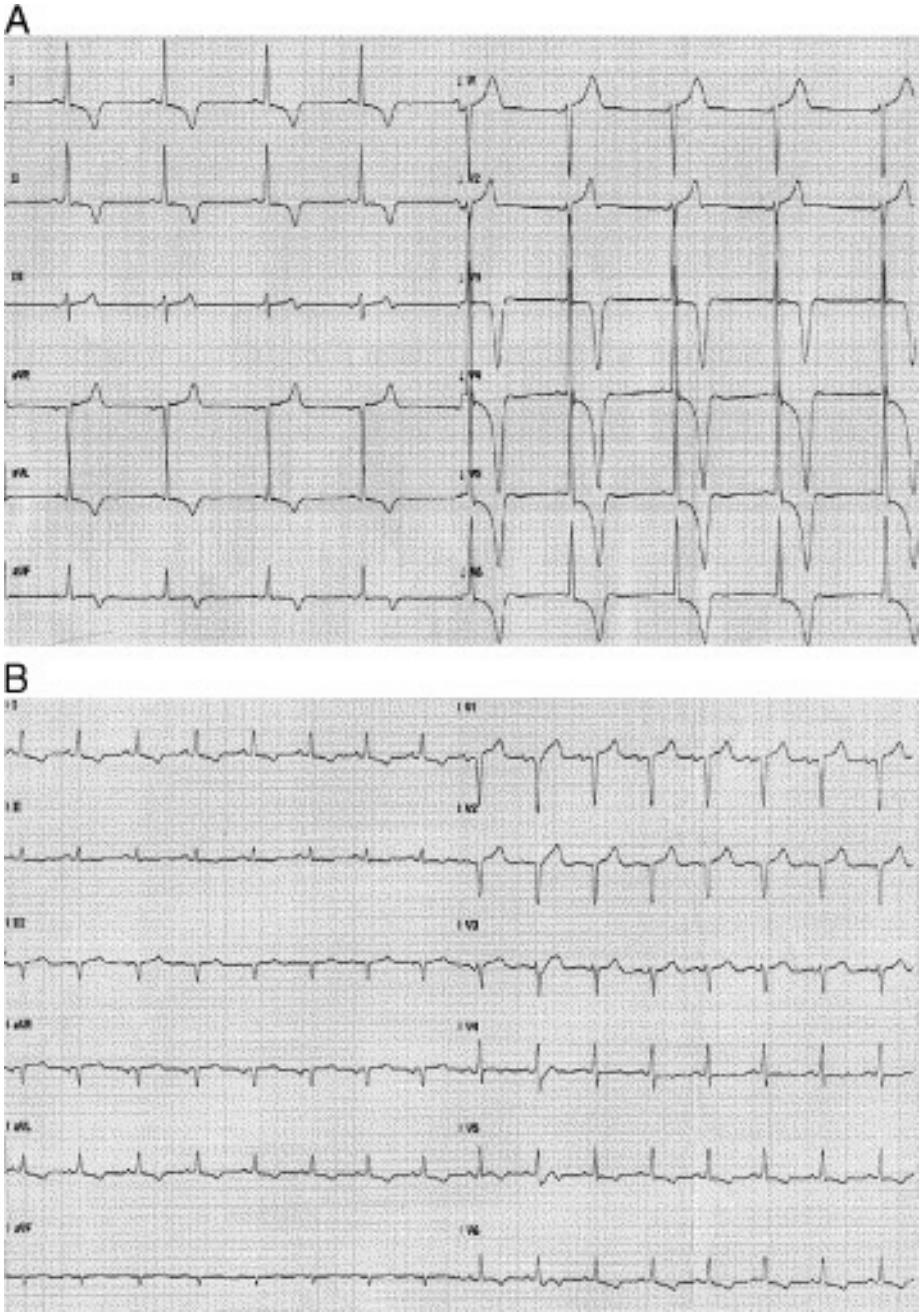


Figure 3 ECG showing complexes QRS with high voltages in FD. Positive Sokolow–Lyon index (adding the S wave in lead V1 or V2 (whichever was larger) and the R wave in lead V5 or V6 (whichever was larger), with a cutoff of 3.5 mV. (A) and low voltages in amyloidosis (B)

VI) **Prolonged QRS duration and bundle branch block**

It is eventually registered.[2] A normal QRS duration is defined as 70–110 ms in adult's hearts. To assess the diagnostic value of ECG scores for LVH and a combined ECG and TTE in FD.

Junqua et al, retrospectively reviewed the ECGs and TTEs of 61 adult patients with FD and LVH, and compared them with those from 59 patients with sarcomeric HCM.

Six ECG criteria for LVH were analyzed: Sokolow-Lyon voltage index;[29] Cornell voltage index,[30]; the Gubner-Ungerleider voltage (It is calculated as the sum of amplitude of the R wave in lead I and S wave in lead III ≥ 2.0 mV); Romhilt-Estes score; Sokolow-Lyon product (voltage index × QRS duration),[31] and Cornell product (voltage index × QRS duration).[32]

The authors observed RBBB was more frequent in patients with FD (54% vs. 22%; P=0.001), QRS duration, Gubner voltage and Sokolow-Lyon product were significantly higher in patients with FD. Maximal wall thickness was higher in patients with sarcomeric HCM. Indexed sinus of Valsalva diameter was larger in patients with FD. After multivariable analysis, RBBB, Sokolow-Lyon

product, maximal wall thickness and aortic diameter were independently associated with FD. The authors concluded that combining easy-to-assess ECG and TTE variables may be helpful in improving screening and reducing diagnosis delay in FD.[33]

QTc dispersion and Tpeak–Tend dispersion

The time interval from the peak to the end of the T wave (Tpeak to Tend), is used as an index of transmural dispersion of ventricular repolarization. Duration from the peak to the end of the T wave is measured in each precordial lead.

VII) The Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratio

This parameter was evaluated electrocardiographically in early stage of FD patients without ventricular hypertrophy), and compared to normal healthy individuals. Tp-e interval and Tp-e/QTc ratio were significantly higher in FD patients than the control group. The most significant finding was the positive correlation found between repolarization parameters and LV diastolic dysfunction. These results may be indicative of an early subclinical cardiac involvement in FD patients, considering the

diastolic dysfunction severity.[34] FD patients in early stage (without LVH) showed the relationship between these parameters and LV diastolic dysfunction.

VIII)Prolonged QT interval

The QT interval (normal 300–440 ms) It is measured from the beginning of the QRS complex to the end of the T wave, defined as the intersection of the tangent to the down slope of the T wave and the isoelectric line.

QTc prolongation and pronounced repolarization abnormalities are present before echocardiographic signs of LVH are detectable.[23] Corrected QT duration (normal <440 ms) is calculated by using the Bazett formula.

IX) Repolarization changes related to LVH and/or remodeling

ST-segment elevation is defined as the J-point elevation of ≥2 mm in the precordial leads and ≥1 mm in the limb leads.

ST-segment depression is defined as the J-point decline in ≥1.5 mm in the precordial leads and ≥1 mm in the limb leads.

T-wave inversions (TWI): Eventually diffuse, deep, asymmetric negative TWI.

Niemman et al in a large cohort of consecutive untreated FD patients covering a large spectrum of cardiomyopathy stages observed, in contrast with former assumptions, that ECG parameters are not suitable to stage FD cardiomyopathy. Most ECG parameters were normal in the complete cohort. However, the absence of ST or T alterations seems to make Late Gadolinium Enhancement (LGE) on CMRI very unlikely and might serve as a pretest, although one must keep in mind that there are a lot of patients with ST-/T-wave alterations and no LGE. All in all, the ECG T-wave and ST analysis seems a valuable amendment to TTE, especially when CMRI cannot be performed.[26]

When no ST or T alterations were observed, the presence of myocardial replacement fibrosis is very unlikely.

X) Cardiac arrhythmias

The substrate of cardiac arrhythmias in FD is consequence of an increased myocardial collagen content and regional fibrosis.[35] Bradycardia and conduction system abnormalities are related

initially to abnormal accumulation of glycolipids in the lysosomes of conduction tissues. Hypertrophy and eventual fibrosis provides a substrate for persistent conduction abnormalities and ventricular arrhythmias. SCD can be related to Brady arrhythmias or tachycardia's. Enzyme replacement therapy can improve cardiac function and clinical outcomes. Arrhythmias in FD can be treated with device or pharmacologic therapy. Pacemakers or ICD are important in the treatment of patients with FD disease who are at risk for arrhythmias. Sinus bradycardia frequently is not responsive to atropine.[36] AV conduction disturbances may be related to infiltration of the conduction system.[37] Deepak Acharya et al in a longitudinal study of 204 patients with FD showed that QRS duration and PR interval duration increased with age and were independent future predictors of need for pacemaker.[22] Patients who have pacemakers and defibrillators have high utilization of pacing in atria and ventricles.[38]

The ECG for differential diagnosis between FD and sarcomeric HCM

To evaluate the role of the ECG in the differential diagnosis between FD from sarcomeric HCM, Vitale et al in a multicenter retrospective, studied 111 FD patients with LVH were compared with 111 patients with HCM, matched for sex, age and maximal wall thickness by propensity score. Independent ECG predictors of FD were identified by multivariate analysis, and a multiparametric ECG score-based algorithm for differential diagnosis was developed. Short PR interval, prolonged QRS duration, RBBB, R voltage in aVL ≥1.1 mV and inferior ST depression independently predicted FD diagnosis, with a sensitivity 69%, specificity 84%, positive predictive value 82% and negative predictive value 72%. After bootstrap resampling, the mean optimism was 0.025, and the internal validated c-statistic for the score was 0.78.[39] Figure 4

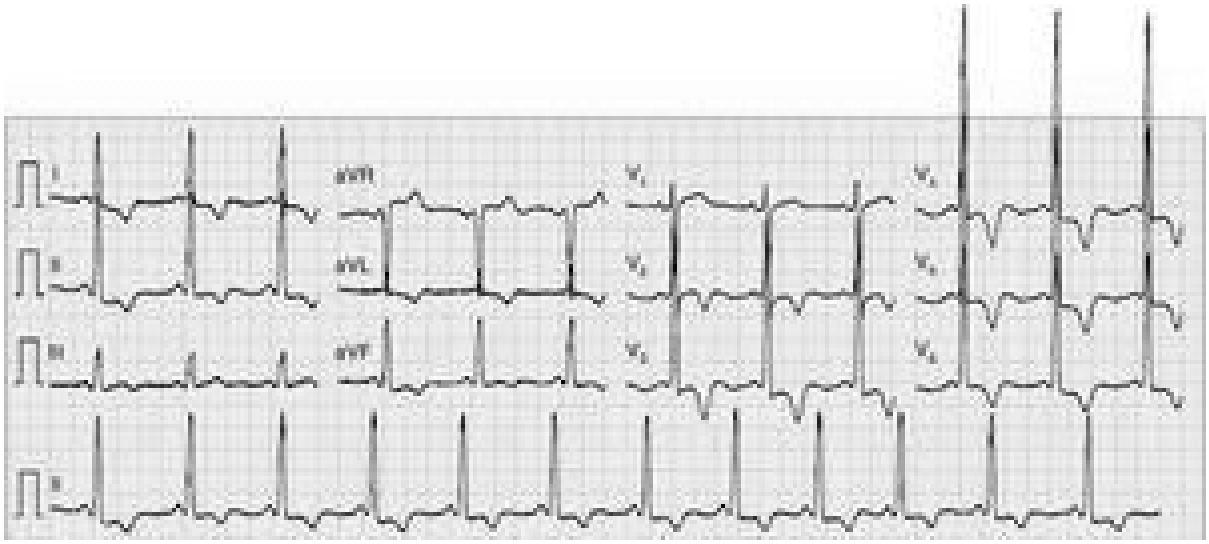


Figure 4 ECG showing sinus rhythm (66 bpm), short PR interval, increased QRS voltage and ST segment depression convex upward followed by diffuse, asymmetric negative T-wave inversion.

Other clinical manifestations and symptoms in FD[18]

- Acroparesthesia
- Heat/cold, exercise intolerance
- GI distress
- Hypohidrosis
- Neuropathic pain is reported to be a severe, disabling and common feature of FD in females. Most describe it as continuous, with exacerbations during illness and hot weather. Along with fatigue, neuropathic pain has a

significant impact on quality of life (QoL). Attacks of pain in the abdomen may have been misdiagnosed as appendicitis or other surgical emergencies.

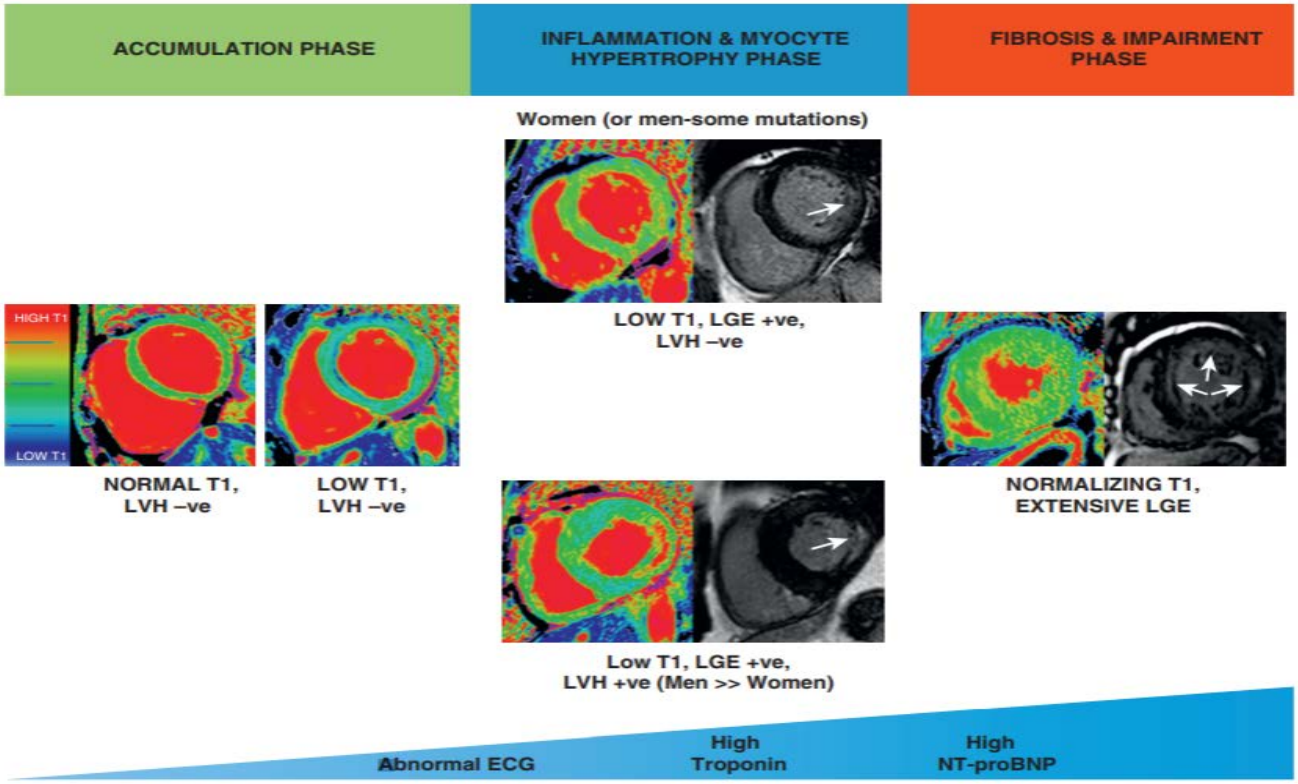
- Corneal whorling: IT is a telltale sign of this rare, debilitating and eventually fatal lysosomal storage disorder, FD causes lipids to accumulate in the various organs of the body.
- Corneal opacities — grey, brown, or yellowish streaks that appear on the cornea, the clear outer layer that covers the lens of the eye. Sometimes, they first appear as a haze or fog over the cornea, becoming more streak-like with time.
- Angiokeratoma corporis diffusum is the typical skin lesion
- Progressive renal disease with proteinuria: Progressive nephropathy is a main feature of FD. Although some clinical signs of FD nephropathy such as proteinuria, are already present in childhood (being noted in approximately 50% by 35 years old and 90% by 50 years old), patients are often diagnosed relatively late in the

course of the disease.[40] The prevalence of FD in dialysis populations has been examined in several studies, most of which report <1% of hemodialysis patients as having gene mutations.[41] Cardiac involvement, makes the management of dialysis therapy complicated. Renal failure was the usual cause of death.

- Early ischemic stroke: Young adults presenting with a cerebrovascular event in association with myocardial infarction and renal dysfunction should be considered for FD.[42]
- Progressive hearing loss and sudden deafness are frequent findings.[43]

Proposed Myocardial Phenotype Evolution in Fabry Disease.[7]

Figure 5



T1: non-contrast myocardial T1 mapping on cardiovascular magnetic resonance examination (CMR). Native T1 values are significantly lower in patients with FD by comparison with those with HCM and healthy volunteers.[44] LGE: Late Gadolinium Enhancement LGE-CMRI: ≈ 50% of patients with FD have cardiac involvement. LGE-CMRI is useful for the diagnosis of cardiac

involvement of FD by recognizing typical LGE patterns. LGE-CMR is valuable for differentiating FD from other diseases causing LVH. However, the use of gadolinium should be of particular concern in FD patients because they may have renal failure. FD patients commonly show LGE at the inferolateral basal or mid-basal segments of the LV lateral wall with a mid-cardinal distribution sparing the subendocardium. LGE represent areas of myocardial collagen scarring (fibrosis).[45] The end-stage of cardiac FD is characterized by intramural replacement fibrosis limited to the basal inferolateral wall of LV.[46]

The disease developmental model consists of an accumulation phase (silent myocyte storage and greater T1 lowering), a myocyte hypertrophy and inflammation phase, and a fibrosis and impairment (late) phase. Arrows refer to area of LGE. High Troponin: cardiac troponin I (cTNI) elevation. Continuous cTNI elevation seems to occur in a substantial proportion of patients with FD. The high accordance with LGE, reflecting cardiac dysfunction, suggests that cTNI-elevation can be a useful laboratory parameter for assessing myocardial damage in FD.[47] NT-proBNP: N-terminal

(NT)-pro hormone BNP (NT-proBNP) is a non-active prohormone that is released from the same molecule that produces BNP. Both BNP and NT-proBNP are released in response to changes in pressure inside the heart. These changes can be related to heart failure and other cardiac problems. A normal level of NT-proBNP, based on Cleveland Clinic's Reference Range is: < 125 pg/mL for patients aged 0-74 years and <450 pg/mL for patients aged 75-99 years **Figure 6**

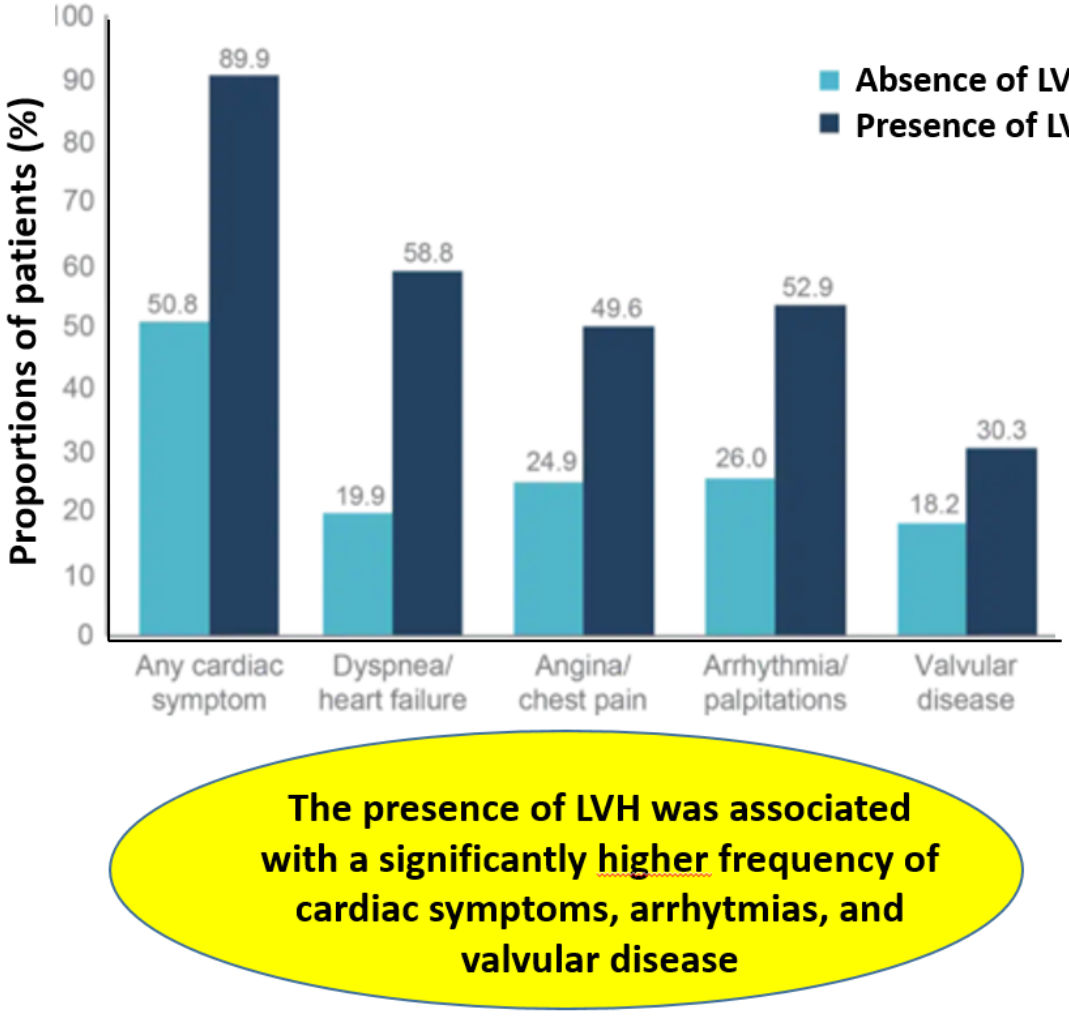
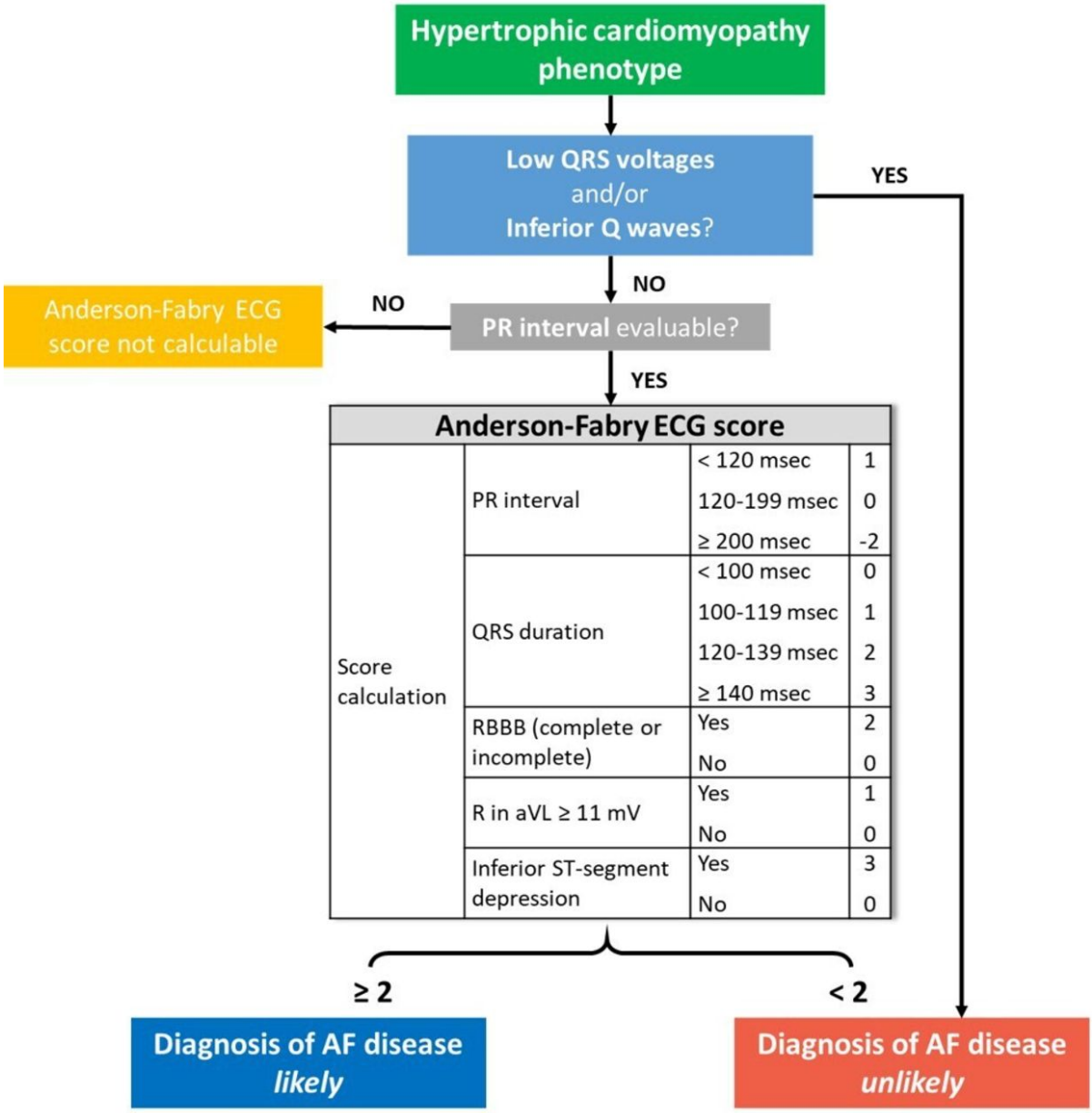


Figure 6



Flow diagram showing the proposed ECG score for differential diagnosis between Anderson-Fabry disease and hypertrophic cardiomyopathy. AF, Anderson-Fabry; RBBB, Right Bundle Branch Block.

Management

Specific therapy should be initiated at the earliest stage, when the first structural or functional cardiac abnormalities are detected, and should include enzyme replacement therapy (available since 2001) or chaperone therapy (available since 2016) (the use of which is limited to patients with FD and an amenable α-galactosidase A [GLA] gene mutation).[2] Treatment with migalastat or 1-Deoxygalactonojirimycin, an alpha-galactosidase A chaperone used for the treatment of FD in patients with an amenable galactosidase alpha gene (GLA) variant was generally safe and resulted in most patients in an amelioration of left ventricular mass. The most common adverse reactions reported with migalastat (≥ 10%) during the 6-month placebo-controlled, double-blind phase of its Study 1 clinical studies were headache, nasopharyngitis, urinary tract infection, nausea, and pyrexia However, due to the heterogeneity of FD phenotypes, it is advisable that the treating physician monitors the clinical response regularly.[48]

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