Evaluation of Demographic, Clinical, and Etiological Data of Patients Admitted to Cardiology Clinics And Diagnosed with Left Ventricular Hypertrophy (LVH) on Electrocardiography And/Or Echocardiography: LVH-TR

Mehmet Kis (drmehmet.kis@hotmail.com)
Silopi State Hospital https://orcid.org/0000-0003-0775-8992
Yasemin Dogan
Kayseri City Education and Research Hospital: Kayseri Sehir Egitim ve Arastirma Hastanesi
Abdullah Yildirim
SBU Adana City Training and Research Hospital: SBU Adana Sehir Egitim ve Arastirma Hastanesi
Tuncay Guzel
Akhisar State Hospital
Lutfu Bekar
Hitit University Faculty of Medicine: T C Hitit Universitesi Tip Fakultesi
Onur Akhan
Bilecik State Hospital
Mustafa Dogdus
Usak University: Usak Universitesi
Hazar Harbalıoglu
Duzce Ataturk State Hospital
Dilay Karabulut
Istanbul Bakirkoy Dr Sadi Konuk Training and Research Hospital: Istanbul Bakirkoy Dr Sadi Konuk Egitim ve Arastirma Hastanesi
Elton Soydan
Ege University Faculty of Medicine: Ege Universitesi Tip Fakultesi
Selvi Oztas
Bursa City Hospital
Ahmet Oz
Istanbul Training and Research Hospital
Gulay Gok
Istanbul Medipol University: Istanbul Medipol Universitesi
Zeynep Kolak

Istanbul Dr Siyami Ersek Thoracic and Cardiovascular Surgery Training and Research Hospital: Istanbul Dr Siyami Ersek Gogus Kalp ve Damar Cerrahisi Egitim ve Arastirma Hastanesi

Ercan Aksit

Çanakkale Onsekiz Mart University Faculty of Medicine: Canakkale Onsekiz Mart Universitesi Tip Fakultesi

Suleyman Anil Sarica

Bayburt State Hospital: Bayburt Devlet Hastanesi

Murat Bayrak

Antalya Kepez State Hospital

Berkay Ekici

Lokman Hekim University: Lokman Hekim Universitesi

Oguzhan Birdal

Ataturk University Faculty of Medicine: Ataturk Universitesi Tip Fakultesi

Berat Uguz

Bursa City Hospital

Mesut Gitmez

Batman Training and Research Hospital

Nihan Caglar

Bakirkoy Dr Sadi Konuk Training and Research Hospital: Istanbul Bakirkoy Dr Sadi Konuk Egitim ve Arastirma Hastanesi

Gul Ilayda Berk

Antalya Atatürk State Hospital: Antalya Ataturk Devlet Hastanesi

Mustafa Oguz

Van Training and Research Hospital: Van Egitim ve Arastirma Hastanesi

Ali Nazmi Calik

Istanbul Dr Siyami Ersek Thoracic and Cardiovascular Surgery Training and Research Hospital: Istanbul Dr Siyami Ersek Gogus Kalp ve Damar Cerrahisi Egitim ve Arastirma Hastanesi

Salih Kilic

SBU Adana City Training and Research Hospital: SBU Adana Sehir Egitim ve Arastirma Hastanesi

Mehdi Zoghi

Ege University Faculty of Medicine: Ege Universitesi Tip Fakultesi

Asim Oktay Ergene

Dokuz Eylul University Faculty of Medicine: Dokuz Eylul Universitesi Tip Fakultesi

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Research Article

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Abstract

Purpose: Left ventricular hypertrophy (LVH) is a common condition in the population and potentially modifiable cardiovascular (CV) risk factor often overlooked in clinical practice. Early diagnosis and treatment-related regression of LVH reduces adverse CV events and improves survival. For this reason, we planned to LVH-TR trial to determine the etiological causes of LVH, the symptoms that patients present with, and the effects of demographic characteristics of patients on LVH.

Methods: Our study is a multicenter, national, observational study and included 886 patients who applied to the cardiology clinics in 23 centers between February 2020 and August 2021. In the initial evaluation, the Fabry and amyloidosis algorithm was followed in patients whose traditional etiologic cause(s) could not be identified (LVH of unknown origin).

Results: The mean age of the patients was 58.92 years, and 60.3% of them were male. More than 90% of the patients were NYHA class I & II patients. The most common etiological causes of LVH in our study were hypertension with a rate of 69.7%, heart valve disease with 10.2%, and hypertrophic cardiomyopathy with 9.2%. Athlete's heart was detected in 8 patients, LV non-compaction was detected in 4 patients.

The rate of LVH of unknown cause was 18.8%. Fabry disease was suspected in 143 patients, and Amilodose disease was suspected in 16 patients. There were 43 (4.85%) patients with low α-Galactosidase A enzyme levels in patients who requested enzyme testing. GLA gene mutation analysis was positive in 1.58% of all patients, and these patients were diagnosed with Fabry, and 15 (1.69%) patients were diagnosed with amyloidosis by endomyocardial biopsy method.

Conclusion: In the etiology of left ventricular hypertrophy, the rate of LVH of unknown cause was high. Fabry Disease and Amyloidosis should be considered primarily in this patient group. Early diagnosis of the disease by following the schemes leading to Fabry and Amyloidosis was essential in starting treatment before the progression of the disease.

Introduction

Left ventricular hypertrophy (LVH) is an abnormal increase in the mass of the left ventricular (LV) myocardium caused by the chronically increased workload on the heart (1).LVH is the most common result of the heart trying to pump blood against the high afterload, as in hypertension (HT) and aortic stenosis (AS) (2). Although HT is the most common cause of LVH, LVH can also be found in athletes and cardiomyopathies or storage disorders such as amyloidosis. In addition, genetic diseases also play an essential role in the pathogenesis of LVH (3, 4). Fabry disease (FD) is another disease that should be considered in patients with LVH (5).

FD is an X-linked lysosomal storage disorder due to α-galactosidase A (α-Gal A) enzyme deficiency resulting in progressive accumulation of globotriaosylceramide (Gb3) in various organ tissues (6). Most prevalence data for FD are based on systematic screening of high-risk populations such as hypertrophic

cardiomyopathy (HCM), cryptogenic stroke, or end-stage renal disease (7, 8). In patients with unexplained LVH, the prevalence of FD ranges from 0–12% in highly selected cohorts (6, 9, 10). Data on FD's frequency and clinical features in the LVH population are scarce. Affected individuals have a variety of clinical manifestations, including neurological, gastrointestinal, renal, and cardiac (11). In Fabry patients with cardiac involvement, echocardiography (ECHO) typically shows progressive increased LV wall thickness, especially concentric hypertrophy, AV valve thickness, papillary muscle thickness, and right ventricular free wall thickness (12–14). It has been reported that electrocardiographic (ECG) changes may be different from prolonged QRS duration to the increase in the Sokolow-Lyon index in FD (15, 16). Early diagnosis of FD is imperative, as evidence suggests that LVH can be prevented or regressed with early treatment with enzyme replacement therapy (ERT); moreover, the response to ERT is poor in advanced FD (17).

Cardiac amyloidosis (CA) is an infiltrative disease caused by the extracellular accumulation of insoluble amyloid proteins in the myocardium (18). Due to these infiltrations, progressive increase ventricular wall thickness and stiffness, and thus CA mimics LVH. Among all the characteristic ECHO findings of CA, the most common one is LVH (19). Therefore, ECHO is usually the first test to cast doubt on the diagnosis of CA (18, 19). A definitive diagnosis of CA requires confirmation of amyloid deposits in cardiomyocytes by endomyocardial biopsy, which can cause fatal complications (20). Bone scintigraphy, including technetium pyrophosphate (99mTc-PYP) scintigraphy and cardiac magnetic resonance imaging (CMRI), are helpful for noninvasive diagnosis of CA; however, they are costly and not available in all facilities (21). Therefore, CA should be screened appropriately in patients with LVH to identify those requiring further investigation (22). Of the etiologies leading to LVH and worse cardiac outcomes, cardiac amyloidosis is one of the most common factors (23). Amyloid infiltration of the heart typically leads to restrictive cardiomyopathy and progressive congestive heart failure (HF), and sudden death. In conclusion, early diagnosis and specific management are critical determinants in the prognosis of these patients (24).

LVH is a vital independent risk factor for cardiovascular morbidity and mortality (25). Early diagnosis and treatment-related regression of LVH reduces adverse cardiovascular events and improves survival (1, 2, 26). Therefore, we planned to perform an LVH-TR study to determine the etiologic causes of LVH, the symptoms presented by the patients, and the effects of patients' demographic characteristics on LVH.

Materials And Methods

Our study was a multicenter, national, and observational study. The number of centers participating in our study was 23. The study included 886 patients who applied to cardiology clinics between February 2020 and August 2021 and were diagnosed with LVH by ECG/ECHO. Signed voluntary consent forms were obtained from all patients. Our exclusion criteria can be listed as younger than 18 years, ECG and ECHO recordings not optimal for analysis. Demographic data, biochemical parameters, and imaging findings of the patients were recorded.

ECHO images were obtained in 4 standard views (parasternal long axis, parasternal short axis, apical two-chamber, and apical four-chamber) using the methods recommended by the American Society of Echocardiography guidelines (27).

Sokolov-Lyon criteria (S wave depth in V1 + longest R wave height in V5 - V6 > 35 mm) were used to diagnose LVH in ECG. Left ventricular mass index (LVMI) (0.8 × (1.04 × [(IVSd + LVIDd + PWTd) 3 − LVIDd3]) + 0.6 and normalized to body surface area) was used to diagnose LVH by ECHO. RWT (regional wall thickness) was calculated with the equation 2×LVPWd/LVDd.

Concentric LVH was defined as an RWT greater than 0.42, LVMI greater than 115 g/m^2 in men and 95 g/m^2 in women; eccentric LVH was defined as an RWT less than 0.42, LVMI greater than 115 g/m^2 in men, and greater than 95 g/m^2 in women; remodeling LVH was defined as an RWT greater than 0.42, LVMI less than 115 g/m^2 in men and less than 95 g/m^2 in women. LVH is defined as recommended in the 2018 ESH/ESC guidelines (28).

The Fabry and amyloidosis algorithm was followed in patients whose definitive etiologic cause(s) could not be identified (LVH of unknown cause) in the initial evaluation (figure 1 and 2) (29–34).

A dry blood sample was sent from male patients who suspected FD. α-Gal An enzyme level was checked, and genetic testing was performed on patients with low enzyme levels. Female patients with suspected FD were genetically tested with GLA Gene Mutation Analysis. Peripheral venous blood samples were taken from each patient. The blood was aspirated on dry blood sample paper and sent to an external laboratory to diagnose genetic diseases.

In patients suspected of CA, evaluation with MRI, tissue biopsy, bone scintigraphy with Tc-PYP, Tc-DPD, or Tc-MDP were performed within the possibilities of the centers participating in the study.

α-Gal A enzyme activity test

α-Gal An enzyme activity was based on a fluorimetric method's dry blood test. Substrate: 4-Methylumbelliferyl-α-D-galactopyranoside (TRC, M334475). Inhibitor: N-Acetyl-D-galactosamine (Sigma, A2795). Samples (3 mm DBS punch+inhibitor+substrate) were incubated for 17 hours at 37°C, and the reaction was stopped. Fluorescence was recorded at Ex: 366 nm Em: 442 nm in the fluorimeter. The calibration curve was created with 4-Methylumbelliferone (Sigma M1381), and the results were evaluated. The usual range of α-Gal A activity was defined as >2.50 nmol/mL/hr. This cut-off value was determined by the receiver operating characteristic test by the Duzen Laboratory group.

Mutation analysis

GLA gene sequence analysis was performed in terms of genotype analysis. The process performed in the Fabry genetic study is the sequencing process performed with the next generation sequencing (NGS) method. PCR products amplified by PCR from the DNA isolated in this procedure were sequenced and compared with the reference sequence (NCBI Genomic Reference Sequence: NG_007119.1,

NM_000169.2). Among the mutations detected here, those in the coding sequence were reported. In addition, the association of reported mutations with Fabry Disease was added from the "HGMD" database. For mutations not in the database, predictions of model analysis programs such as SIFT, Mutation t@ster, PolyPhen-2 have been added.

Ethics committee approval of our study was obtained from the Bakırköy Dr.Sadi Konuk Training and Research Hospital Clinical Research Ethics Committee on 20.01.2020 with the decision number 2020-02-21.

ClinicalTrials.gov application has been made for our study, and its identifier number was NCT04275882.

Statistical analysis

IBM SPSS Statistics 25.0 Program was used. "Kolmogorov-Smirnov" and "Shapiro-Wilk" tests were applied to determine whether the study data showed normal distribution. Descriptive statistics were prepared to include frequency (n), mean and standard deviation values. In addition, frequencies and percentages are given for categorical variables.

Results

The mean age of 886 patients included in the study was 58.92 (±14.05) years, and the male sex ratio was 60.3%. The mean body mass index (BMI) was 28.25 (± 4.65) kg/m^2. The patients' mean systolic and diastolic blood pressures were 138.56 (±21.85) mmHg and 82.45 (±12.84) mmHg, respectively. The patients' demographic data included in the study are summarized in Table 1.

Table 1
Demographic and clinical characteristics of the study population

Demographic feature	n=886
Age, years, mean±std	58.92±14.05
Male sex, n (%)	534 (60.3)
Body Mass Index, kg/m^2, mean±std	28.25±4.65
Systolic Blood Pressure, mean±std	138.56±21.85
Diastolic Blood Pressure, mean±std	82.45±12.84
Chest pain, n (%)	270 (30.5)
Palpitation, n (%)	249 (28.1)
Shortness of breath, n (%)	427 (48.2)
Syncope, n (%)	34 (3.8)
Smoking, n (%)	198 (22.3)
Anemia, n (%)	173 (19.5)
Atrial fibrilation, n (%)	97 (10.9)
CAD, CABG or PCI history, n (%)	299 (33.7)
Hipertansiyon, n (%)	642 (72.5)
Stroke/ TIA, n (%)	72 (8.1)
Hiperlipidemi, n (%)	225 (25,4)
Diyabetes mellitus, n (%)	240 (27.1)

The most common cause of etiology was HT, with a rate of 69.7%. Heart valve disease was the other most common cause with a rate of 10.2% and HCM with 9.2%. Athlete's heart was detected in 8 patients, LV non-compaction was detected in 4 patients. The rate of obesity alone in the etiology of LVH was 1.5%, chronic renal failure was 1.4%, and diabetes mellitus was 2.9%. Information on the etiological factors of LVH is summarized in figure 3.

Patients whose etiology could not be determined at the first stage were defined as LVH of unknown cause. Patients of unknown cause constituted 18.8% of the patients. Fabry disease was suspected in 143 patients, and Amilodose disease was suspected in 16 patients. There were 43 (4.85%) patients with low alpha-galactosidase A enzyme levels in patients who requested enzyme testing. GLA Gene Mutation Analysis was positive in 1.58% of the patients, and these patients were diagnosed with Fabry.

Stroke/transient ischemic attack was detected in 12.5% and chronic renal failure in 18.8% of Fabry patients. In ECG findings, 1 degree AV block was detected in 14.6%, S wave depth in V1 + the most extended R wave height in V5-V6 was over 35mm in 60.4%. Among the ECHO findings, a binary sign was 8.3%, AV valve thickness increase was 22.9%, papillary muscle hypertrophy was 25%. In Fabry patients with LVH, mean interventricular septal thickness was 16.59 mm, mean LVMI was 167.12 g/m^2, mean left atrial volume index was 34.09 ml/m^2, and mean RWT was 0.60.

In patients with amyloidosis, low QRS voltage was observed in 6 (40%) patients, and a pseudo-infarct pattern was observed in 4 (26.7%) patients. In ECHO, pericardial effusion was observed in 4 (26.7%) patients, and myocardial ground-glass opacity was observed in 5 (33.4%) patients. Bone scintigraphy in 10 (66.7%) patients and cardiac MRI in 5 (33.4%) patients were considered to have suspected amyloidosis, and cardiac biopsy was performed. Amyloidosis was diagnosed by the endomyocardial biopsy method in 15 (1.69%) patients. Parasternal long axis echocardiographic images of different LVH etiologies are given in figure 4.

Discussion

This study demonstrates that the rate of LVH etiology unknown cause was high (18.8%), apart from traditional etiological factors. Identifying the underlying etiology of LVH remains a challenging but crucial clinical problem, with significant therapeutic and prognostic implications. Contrary to popular belief, the frequency of Fabry and Amyloidosis was high in this patient group. By following the steps in the diagnostic scheme, the probability of making the diagnosis of Fabry and amyloidosis was increased. In this way, early diagnosis will increase the likelihood of patients benefiting more from treatment. Furthermore, our study showed that even patients with low α-Gal A enzyme levels may not have mutations in the GLA gene.

In our study, the most common etiological factors are compatible with the literature (31). In the study of Shu-Xia et al. conducted with 4270 hypertensive patients, LVH was detected in 42.7% of them by ECHO (30). The other most common causes of LVH in the general population are; valve diseases and HCM (25, 33–37). It is still controversial whether type 2 diabetes mellitus (T2DM) is associated with increased left ventricular (LV) mass regardless of body size. In a study that included 1932 patients (67.9±9.6 years; 769 males and 1163 females; 443 DM and 1489 non-DM) patients, LV mass (189±60 vs. 174±59g; $p<0.0001$) was found higher in the DM group than in the non-DM group. In addition, in multivariate analysis, Type 2 DM was independently associated with increased LV mass (P=0.03). The presence of type 2 DM was found to be associated with an increased risk of LV hypertrophy (adjusted odds ratio 1.46; 95% CI, 1.13–1.88, P=0.004) (38). DM was detected as an isolated etiological factor in 2.9% of LVH patients in our study.

HCM characterized by increased LV wall thickness is the most common non-ischemic cardiomyopathy with an estimated prevalence of 1 in 500 people (39). Over the past 10 to 20 years, investigators have been able to rapidly assemble large patient cohorts with ease, exceeding expectations based on earlier

perceptions of disease frequency. However, sometimes there may be difficulties distinguishing HCM from other conditions, such as athlete's heart and hypertensive heart disease. Especially a proportion of hypertensive patients may have more substantial hypertrophy (up to 16 mm) and fall into a "gray zone" in which ECG and ECHO features are indistinguishable from HCM.

Fabry disease should be considered in the differential diagnosis in patients with LVH. The FACSS study assessed the prevalence of Fabry disease in 100 male patients over 30 years of age with unexplained LVH. The prevalence of Fabry diagnosed with α-galactosidase A activity was 4% (9). In another study, 362 men and 178 women with LVH, who constitute the majority of hypertensive patients, mutations in the GLA gene were found in six patients (0.9%) (40). In a study examining plasma α-galactosidase A activity in 177 men with HCM, very low α-galactosidase A activity was found in two (1.1%) patients (41).In another study involving 34 consecutive female patients diagnosed with HCM, it was reported that Fabry disease might be responsible for up to 12% of late-onset HCM (10). Barman et al. reported that 2 (1.05%) patients were diagnosed with Fabry disease out of 190 patients with unexplained LVH (14). Inclusion of the specific patient group and/or only the wall thickness in the definition of LVH is seen as a disadvantage of these studies. However, in our study, not a specific patient group, all consecutively diagnosed patients with LVH were included. LVMI was used as LVH criteria, and Fabry and Amyloidosis algorithms (figure 2 and 3) were followed in patients with LVH of unknown cause. So, according to the results of our study, Fabry disease was detected in 1.59% of LVH patients.

Recent data suggest that may not be a rare condition. In a prospective study, nuclear scintigraphy scans showed that 13.3% of a patient aged ≥60 years with left ventricular hypertrophy (≥12mm) and hospitalized for HFpEF had wtTTR amyloidosis (18). In another study, the rate of cardiac amyloidosis was 17% in 109 patients with HFpEF and 5% in 131 control patients without HFpEF (42). In our study, cardiac amyloidosis was found at a rate of 1.69% in the LVH population. However, Beneyto et al. conducted etiological research in 591 patients with left ventricular hypertrophy. They found that CA led LVH etiologies (34.3%), followed by sarcomeric HCM (S-HCM, 32.1%), hypertensive cardiomyopathy (21.7%), unknown etiology (7.6%), and other (4.2%), including Anderson Fabry's disease (1.7%). The study excluded patients presenting with severe aortic valve stenosis, bioprosthetic aortic valve stenotic degeneration, and obstructive subaortic membranes. In the study, HT was present in 372 patients (62.9%), but HT was accepted as the etiology in 21% of the patients. Therefore, excluding other causes such as amyloidosis is necessary, especially in hypertensive patients with additional clinical findings (43).

LVH of unknown cause comprised 18.8% (167) of all LVH patients. Fabry and/or Amyloidosis tests could not be performed in eight of these patients. In patients with LVH of unknown cause, myocardial infiltration diseases such as amyloidosis, metabolic diseases such as Fabry, Pompe, and Danon, and mitochondrial myopathies should be suspected (29, 37–45).

Limitations

The main limitation of our study was that the TTE devices and techniques used in the 23 centers participating in the study were different. Although Fabry enzyme and genetic testing were performed in a single laboratory, each participant performed the analysis of electrocardiographic and echocardiographic findings himself/herself. Another limitation is that we could not investigate very rare storage diseases. We focused on Fabry and amyloidosis.

Conclusion

Although HT, valvular disease, and cardiomyopathies are responsible for most causes of LVH, it is essential to investigate patients with unexplained LVH as many causes are treatable. In the etiology of LVH, the rate of LVH of unknown cause was high. Therefore, FD and CA should be considered primarily in this patient group. By following the schemes leading to the diagnosis of FD and CA, early diagnosis of the disease was critical in starting treatment before disease progression. Low α-Gal A enzyme levels are not sufficient in diagnosing FD, and GLA gene mutation analysis should be performed for a definitive diagnosis.

Declarations

Conflict of Interest

The authors declare that there was no conflict of interest regarding this article.

Financial Resource

No financial resources have been used for this article.

Ethics committee

Ethics committee approval of our study was obtained from the Bakırköy Dr.Sadi Konuk Training and Research Hospital Clinical Research Ethics Committee on 20.01.2020 with the decision number 2020-02-21.

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Figures

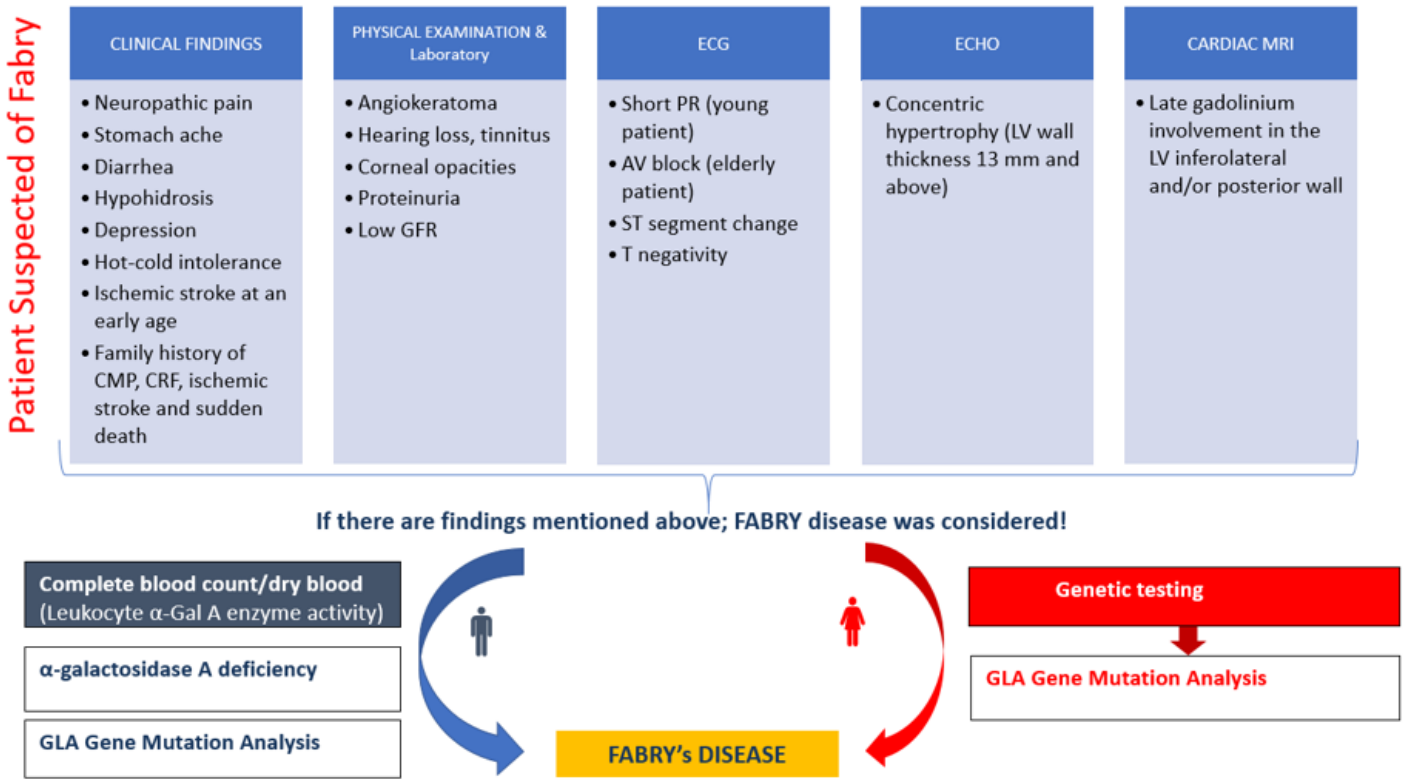

Figure 1

Fabry algorithm

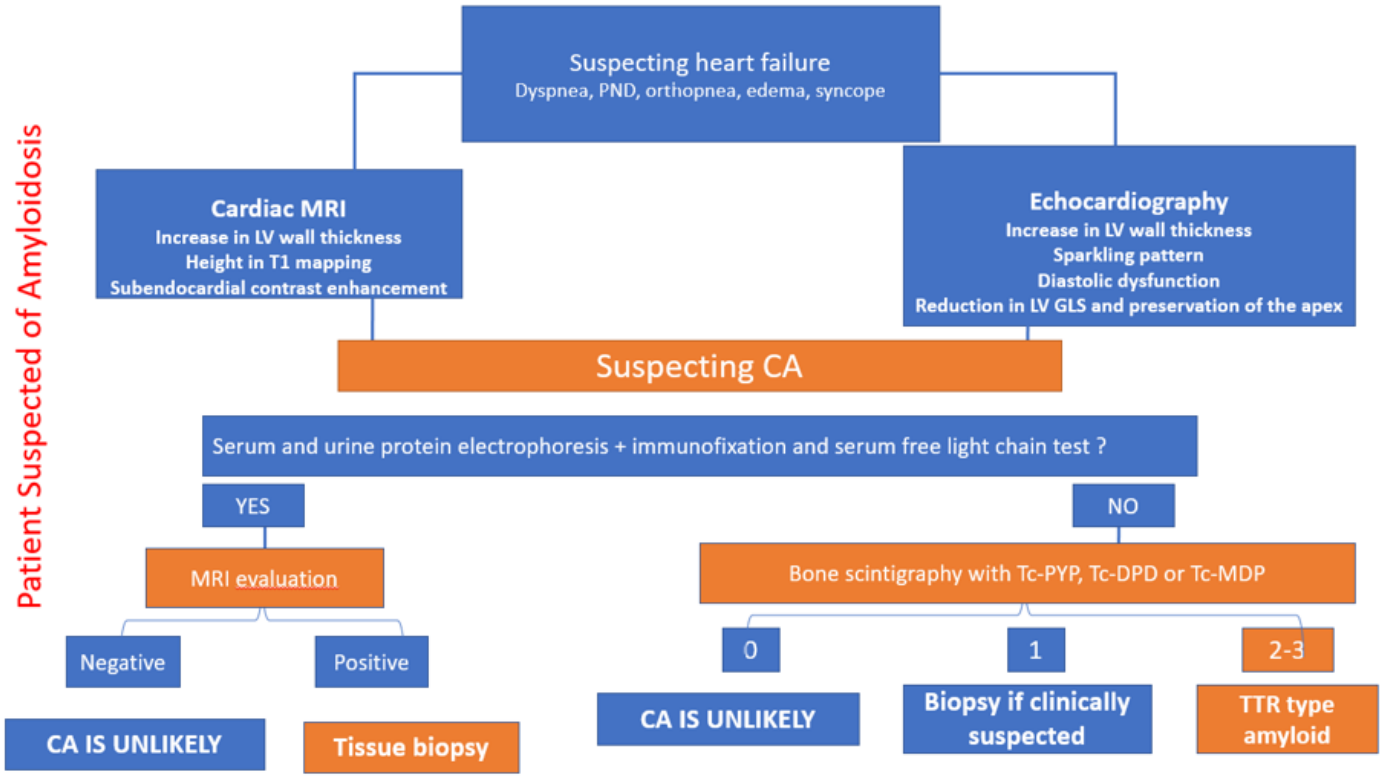

Figure 2

Amyloidosis algorithm

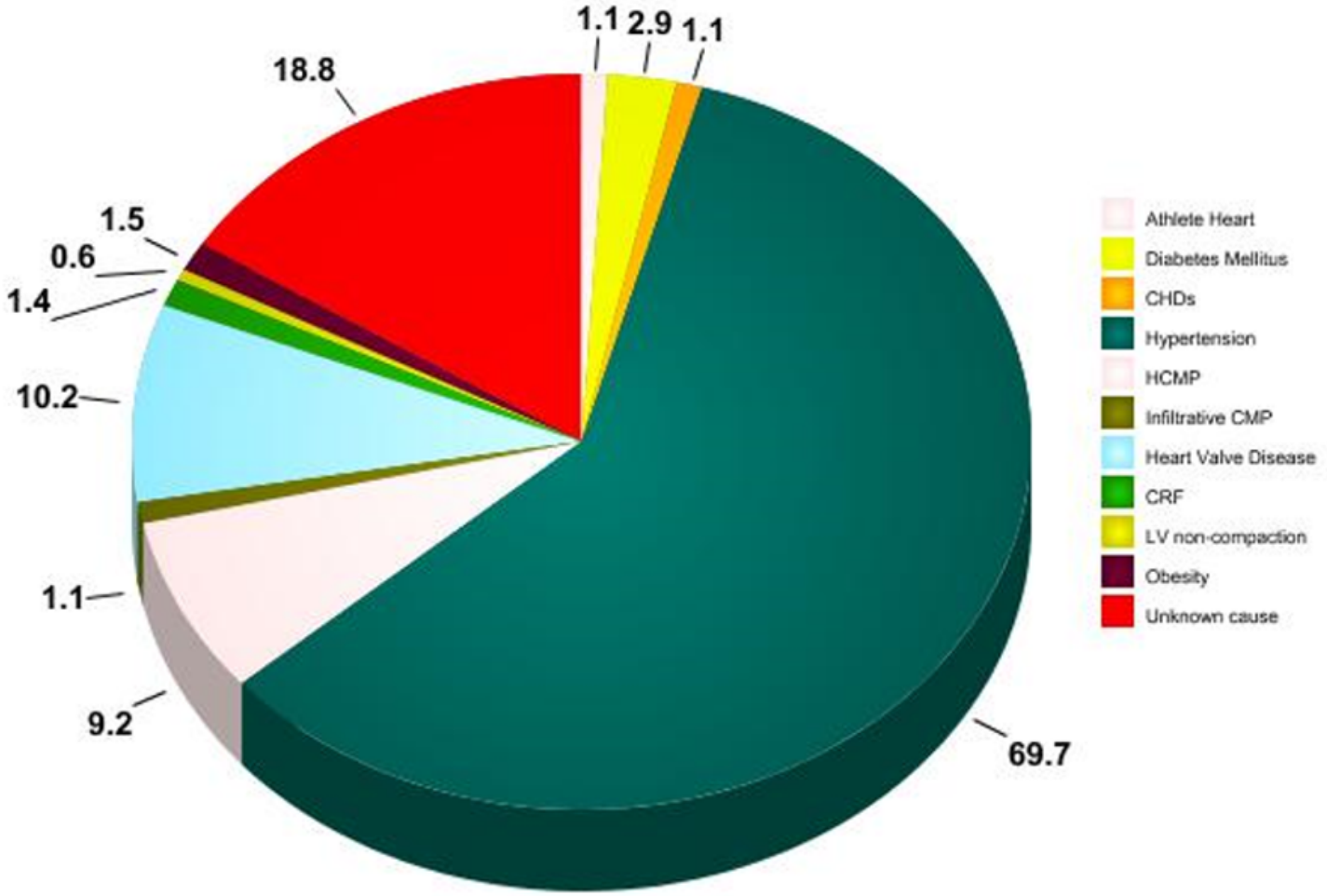

Figure 3

Etiology of LVH in Study Population

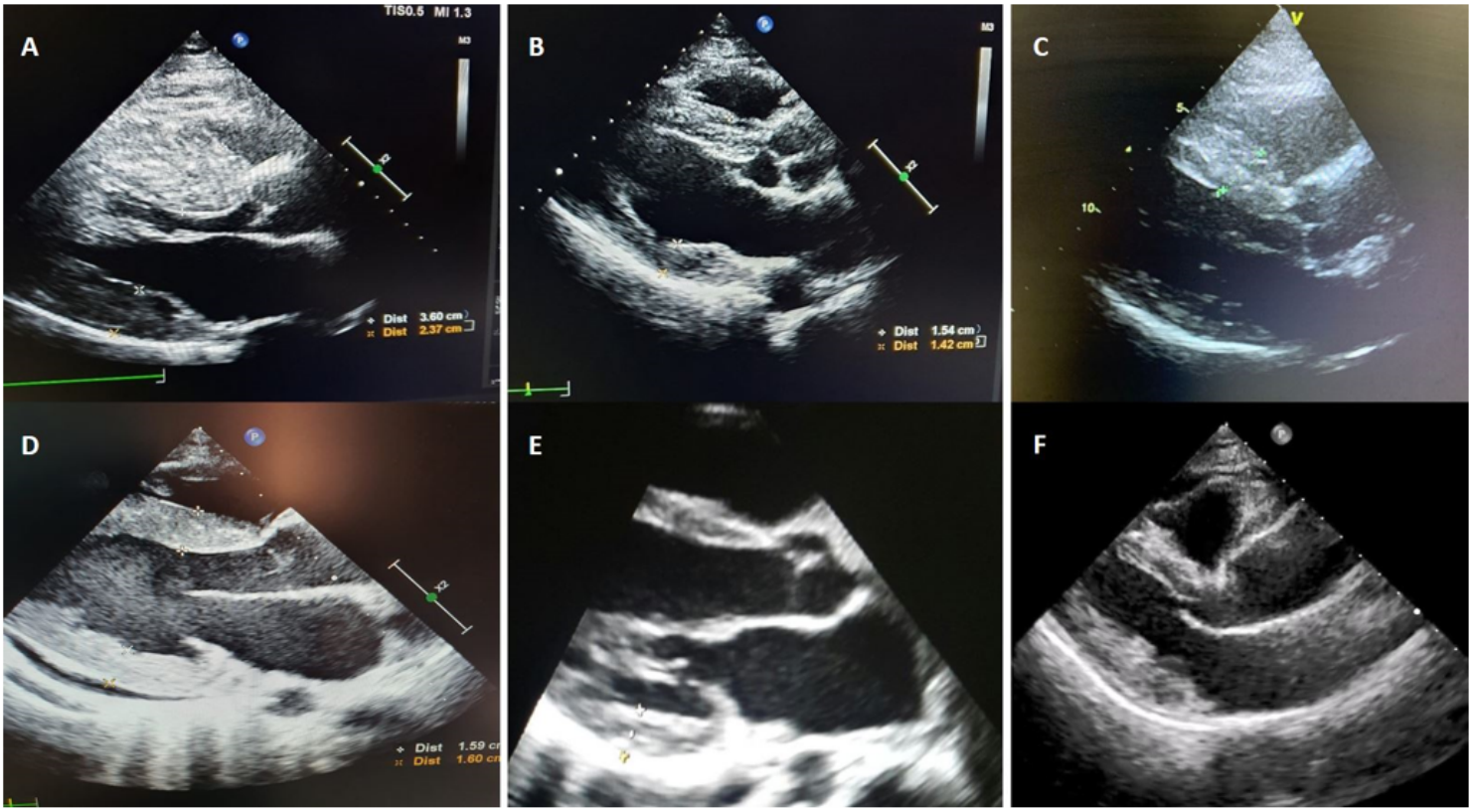

Figure 4

Echocardiographic images of different LVH etiologies. A: Fabry' s disease, B: Hypertension, C: Hypertrophic cardiomyopathy, D: Chronic renal failure, E: Athlete's heart, F: Amyloidosis.