



OPEN ACCESS

Review article

Storage diseases with hypertrophic cardiomyopathy phenotype

Luis Ruiz-Guerrero¹, Roberto Barriales-Villa^{2,3*}

ABSTRACT

Never judge a book by its cover, nor assume hypertrophic cardiomyopathy (HCM) as sarcomeric, as appearances can deceive. HCM phenocopies account for a 5–10% of the cases, mainly represented by storage diseases, flagged by the increasing prevalence of senile cardiac amyloid in developing countries. Multisystemic and heterogeneous presentation of these entities is a challenge for clinicians, and time delay in diagnosis is a major concern. Promising drugs and gene-specific tailored therapies are under development, therefore, more than ever, appropriate understanding of these conditions is mandatory for adequate early treatment and counselling.

In this review, storage disorders will be classified as extracellular and intracellular deposit storage diseases, focusing our attention on the most prevalent conditions from the cardiologist's perspective.

¹ Cardiology Service, Hospital Universitario Marqués de Valdecilla, Instituto de Investigación Marqués de Valdecilla (IDIVAL), Santander, Spain

² Inherited Cardiovascular Diseases Unit, Cardiology Service, Complejo Hospitalario Universitario de A Coruña, Instituto de Investigación Biomédica de A Coruña (INIBIC), Servizo Galego de Saúde (SERGAS), Universidade da Coruña, A Coruña, Spain

³ Centro de Investigación Biomédica en Red. Enfermedades Cardiovasculares (CIBERCV), Madrid, Spain

*Email: rbarrialesv@gmail.com

<https://doi.org/10.21542/gcsp.2018.28>

Received: 11 May 2018

Accepted: 15 June 2018

© 2018 The Author(s), licensee Magdi Yacoub Institute. This is an open access article distributed under the terms of the Creative Commons Attribution license CC BY-4.0, which permits unrestricted use, distribution and reproduction in any medium, provided the original work is properly cited.

Cite this article as: Ruiz-Guerrero L, Barriales-Villa R. Storage diseases with hypertrophic cardiomyopathy phenotype, *Global Cardiology Science and Practice* 2018;28
<https://doi.org/10.21542/gcsp.2018.28>

1 EXTRACELLULAR DEPOSIT STORAGE

1.1 Cardiac amyloidosis (CA)

1.1.1 Introduction and epidemiology

In the heart, amyloidosis can mimic hypertrophic cardiomyopathy and lead to systolic and diastolic dysfunction, as a result of the stiffness and poor compliance of the myocardium, the small ventricle cavity and the reduced diastolic contribution of infiltrated atriums. The hallmark of amyloidosis is the disruption of vital organ function through the deposition of extracellular fibrils, conformed by aggregate of proteins with unstable tertiary structures, misfolded and/or misassembled. Other particular aspects of this fibrils are that they are rigid, non-branching, linear, width of about 75 nm and indefinite in length. The component is also defined as insoluble or poorly soluble, resistant to proteolytic degradation.

There are multiple sources of amyloid fibrils (see Table 1). The most prevalent protein components of the fibril in CA are immunoglobulin light chains (AL) and amyloid transthyretin (ATTR). The latter can either be familial (ATTRv-CA) because of an inherited pathogenic variant of transthyretin (*TTR*) gene or non familial (ATTRwt-CA), caused by a wild type abnormal form of transthyretin, also known as senile cardiac amyloidosis. The other component of the fibrils are chaperone proteins of which the pentraxin serum amyloid P (SAP) is the most commonly represented.

It has been postulated that the main form of CA is the ATTRwt, though its real prevalence is not well established. More prevalent in men than in women (80% vs 20%) and with an age of onset that can be as early as mid sixties², it is usually under-recognized as it can sometimes mimic other cardiac conditions that are found in the elderly population. Several data support overrepresentation of ATTRwt-CA. Series of autopsies have identified the deposit of TTR amyloid fibrils in up to 25% of postmortem hearts from individuals older than 80 years-old³. Recent studies also described a prevalence of 16% of patients with severe aortic stenosis undergoing transaortic valve replacement, condition which was associated with the low-flow low-gradient phenotype and mild reduced ejection fraction⁴. A French pilot study estimated that the prevalence of

Table 1 Classification of most common amyloid types with cardiac involvement.

Fibril Protein	Precursor Protein	Features	Other Target Organs
AL	Immunoglobulin light chain	S, L, A, H	All organs, usually except CNS
AH	Immunoglobulin heavy chain	S, L, A	All organs except CNS
AA	(Apo) Serum amyloid A	S, A	All organs except CNS
ATTRwt	Transthyretin, wild type	S, A	Heart mainly in males, ligaments, tenosynovium
ATTRv	Transthyretin, variants	S, H	PNS, ANS, heart, eye, leptomeninges
Ab2Mwt	b2-Microglobulin, wild type	S, A, HD	Musculoskeletal system
Ab2Mv	b2-Microglobulin, variants	S, H	ANS
AApoAI	Apolipoprotein AI variants	S, H	Liver, kidney, PNS, testis, larynx (C-terminal variants), skin
AANF	Atrial natriuretic factor	L, A	Cardiac atria

Notes.

S, Systemic; L, Localized; A, Acquired; H, Hereditary; HD, Hemodialysis Associated; CNS, Central Nervous System; PNS, Peripheral Nervous System; ANS, Autonomic Nervous System.

Modified from Sipe et al, Amyloid J 2016.¹

ATTRwt could be as high as about one third of patients with heart failure and preserved ejection fraction⁵. In spite of the recent increasing data suggesting the high prevalence of senile cardiac amyloidosis, this fact is not new, as it had been already reported by Pomerance in 1965, concluding that “*senile cardiac amyloid would appear to be the commonest existing form of amyloid, and likely to continue increasing with the increasing age of the population*”⁶.

The inherited form is less prevalent than the ATTRwt. The median age at diagnosis ranges from 60–70 years-old, depending on the gene variant. Over a 100 *TTR* gene pathogenic variants have been described, some endemic and ethnic-group mutations identified, with autosomal dominant pattern of inheritance. For instance, the p.Val122Ile pathogenic variant has been reported in African or Afro-Caribbean descent with an estimated population prevalence of 3% to 4%⁷. However, ATTRv-CA is not always found with isolated cardiac involvement, as it is mainly considered a neurologic disease, causing familial amyloidotic polyneuropathy.

From what respects to AL-CA, about 8-12 cases per million of prevalence is estimated. It results from any monoclonal gammopathy of hematologic disorders such as multiple myeloma (main cause), monoclonal gammopathy of uncertain significance or B cell dyscrasias. Among 30 to 50% of patients with AL amyloidosis have cardiac involvement⁸. The AL-CA mean age of presentation is 65 years-old, predominantly in female gender⁹.

There are other forms of cardiac amyloidosis, such as the secondary or reactive systemic amyloidosis, in which a chronic inflammatory state leads to an overproduction of the serum amyloid A (SAA) protein, a major acute-phase protein, that will eventually form the amyloid fibrils. Albeit, cardiac involvement is extremely rare and renal involvement dominates the clinical course in this patients¹⁰.

A particular and rare form of amyloidosis is the dialysis related amyloidosis, formed by the wild type deposit of Beta 2-microglobulin, a complication of long-term renal replacement therapy. Severe forms appear to manifest after 15 years of dialysis¹¹.

1.1.2 Etiopathogenesis

The predominant mechanisms of amyloid fibrils formations and the affinity for the tissue deposition differ depending on the amyloidosis syndrome. Even the causative effect of the organ dysfunction, although not well understood, may vary depending on the amyloid composition. For instance, in the heart, the deposition causes thickening of both ventricles, with subendocardial and diffuse distribution in the AL-CA whereas in ATTR can be a patchy or transmural involvement. It is also possible to find fibrils in the small intramural coronary arteries. The atrium, the conduction system, the valves and the pericardium can all be affected¹².

TTR is an homotetrameric protein that carries the thyroid hormone thyroxine (T₄) and retinol-binding protein bound to retinol. It is mainly produced by the liver and in less quantity by the choroid plexus and retinal pigment epithelium. The dissociation of the protein into monomers, which is the rate-limiting step for amyloid formation, is the first point of discordance. Familial point mutations, usually missense variants that lead a change in protein amino acids, are known to destabilize the tetramer. Depending on the TTR mutation (Figure 1), the phenotype may change, from isolated neurological involvement to predominant cardiac features¹³. The explanation of the differential involvement is unknown. Val30Met (p.Val50Met renamed according to the updated nomenclature) is the most common mutation worldwide. It is endemic in some areas of Portugal, Japan, Sweden and Spain¹⁴. This variant has a bimodal presentation with

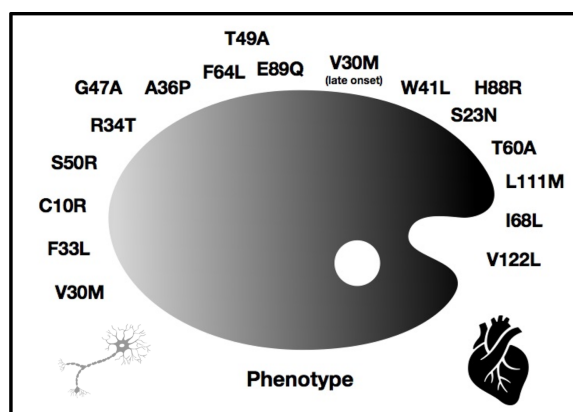


Figure 1. Spectrum of association genotype-phenotype in familial ATTR, proposed by Rapezzi et al. From isolated peripheral neuropathy (V30M) to predominant cardiac phenotype (V122L) (modified from 13).

an early onset disease in the third-to-fourth decade of life characterized by peripheral neuropathy and a onset leading to cardiac involvement¹⁵.

In the wild type syndrome, the gene is unaltered and the protein is then produced normally. The instability and dissociation of the tetramer has been hypothesized to be caused by alterations in chaperone proteins¹⁶. The other fact that is required for amyloid fibrils formation is the aggregation of the monomers. The possibility of releasing aggregation-driving segment that were blocked in the tetrameric form is one plausible cause for the constitution of the cross- β -pleated sheet¹⁷.

In AL-CA, the free light chains (LC) produced by the clonal cells are less kinetically stable and more susceptible to unfolding. A faster unfolding of full-length chains activates the aberrant processing by endoproteases and interferes in the extracellular refolding, cutting the LC into segments that form aggregates for amyloid fibrils¹⁸. Similarly to what occurs with ATTRm, there is no explanation for the tissue tropism and the type of LC, but it has been described that regions IGLV1-44, IGLV2-14 and IGLV3-1 in the germline genes are related to AL-CA more often. This would support a genetic basis also in AL-CA¹⁹.

The mechanism of AA is the excess of production of SAA but, for unknown reasons, only a small proportion of patients with chronic inflammatory states develop amyloidosis¹⁰.

Eventually in all types, the amyloid fibrils act as cellular chemical stressors, producing reactive oxygen species, damaging the cells by mechanisms that are incompletely understood²⁰. Myocyte dysfunction and apoptosis can also be induced by amyloidogenic light chains, directly and independent of independent of cardiac fibril formation through non-canonical activation of p38 MAPK signalling²¹.

1.1.3 Diagnostic work-up

The diagnosis of CA can be challenging. The diffuse deposition and organ involvement, together with the nonspecific signs and symptoms, makes the diagnostic work-up complex and the need for the clinician to be aware of the right clues, to reach diagnosis without time delay. Usually, patients may be visiting more than one physician before diagnosis is reached²².

The diagnostic work-up should be initially based on clinical features, electrocardiogram and echocardiogram. Then, if the suspicious of CA is high,

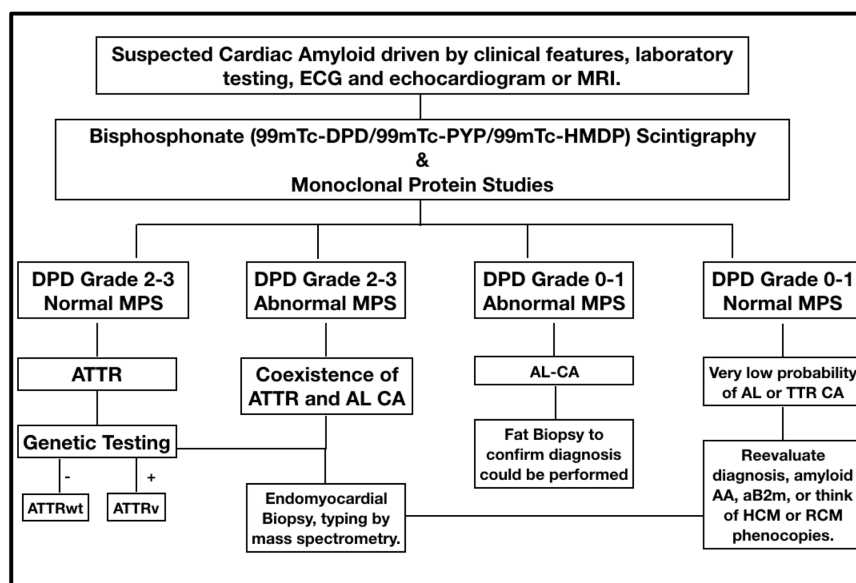


Figure 2. Diagnostic work-up algorithm. (DPD, (99m)Tc-3,3-diphosphono-1,2-propanodicarboxylic acid ((99m)Tc-DPD); MPS, monoclonal protein studies)²³.

complementary tests will be performed, if feasible, starting from the non-invasive ones (Figure 2).

1.1.3.1 Clinical features and family history. Fatigue is the main clinical symptom due to diastolic dysfunction. Hypertrophic cardiomyopathy or hypertensive cardiomyopathy can rise as an erroneous diagnosis in these patients. Palpitations related to the novo atrial fibrillation are another referral reason. Congestive heart failure or low cardiac output state, associated with asthenia, cardiac cachexia and orthostatic hypotension, are end-stage disease manifestations. Usually, renal failure exacerbates the clinical picture and the refractoriness to heart failure therapy (Table 2).

Particularly in AL amyloidosis, it is rare to have the diagnosis before symptoms appear and, when this happens, the patients may already have advanced organ damage. Typical findings include neuropathy, nephrotic syndrome, hepatomegaly, peri-orbital bleeding and macroglossia. Some of these findings are also shared with ATTR-CA, i.e., neuropathy or hepatomegaly caused by congestive heart failure or chronic kidney disease²⁴.

Table 2 Clinical Red Flags for CA syndromes.

- Spinal stenosis (ATTRv-CA)
- Symmetric sensorimotor peripheral neuropathy in lower extremity (ATTRv-CA)
- Postural hypotension and orthostatic syncope.
- Gastric emptying disorder, pseudo-obstruction.
- Chronic diarrhea and weight loss.
- Erectile dysfunction.
- Macroglossia and periorbital purpura (pathognomonic in AL-CA)
- Easy bruising without anticoagulation.
- “Popeye” sign or deformity of the biceps muscle, after tendon non traumatic rupture (Figure 3).
- Vitreous opacities, cotton wool type (ATTR)
- Bilateral Carpal tunnel syndrome (ATTR)



Figure 3. See the disproportionate prominence of contracted biceps, a result of distal biceps tendon non-traumatic rupture.

Table 3 Electrocardiographic findings from refs 9,26–28.

-
- Low-voltage criteria: QRS amplitude less than 5 mm in limb leads or less than 10 mm in precordial leads. (About half of AL-CA patients and about 30% of ATTR-CA.)
 - Pseudoinfarct pattern (About 30% to 60% of the patients).
 - Atrial fibrillation (varies according to etiology with a mean value of 15% to a prevalence of 40% in ATTRwt amyloidosis).
 - QRS duration (ms) in ATTR-CA is higher than in AL-CA (122.3 ± 34.9 vs 103.4 ± 25.6). In about 30% of the patients the QRS duration is over 120 ms.
 - Any degree of AV-block is found in about 15% to 30% of patients.
-

1.1.3.2 Electrocardiogram (ECG). There are almost always pathologic findings in the ECG (Table 3). Some registries report less than 2% patients with normal ECG. The most reliable electrocardiographic characteristic to support CA diagnosis is the relation between the left ventricular wall thickness and the QRS voltage, first described by Carroll in 1982²⁵. A simpler index was latter proposed by Quarta et al., considering the division of total QRS score (the arithmetic sum of the QRS complexes in peripheral and precordial leads) by LV wall thickness²⁶.

The study of syncope is particularly complex in these patients as there is a tendency to hypotension resulting from both dysautonomic disorders, low output and diuretics and bradyarrhythmias. About 20% of ATTRwt patients need a pacemaker and it has been suggested that prophylactic pacemakers should be implanted in some scenarios²⁹.

1.1.3.3 Laboratory Tests.

1.1.3.3.1 Monoclonal Protein Studies (MPS)

MPS is mandatory to rule-out AL-CA. Blood serum electrophoresis is less accurate than immunofixation (IFE) of serum and urine to demonstrate a monoclonal band and, quantification of serum free light chains (sFLC), is used to obtain the kappa/lambda ratio, which is abnormal in >90% of patients with untreated AL amyloidosis. The definition of abnormal FLC ratio is <0.26 or >1.65 (slightly variations depending on laboratory assays)³⁰. The combination of serum and urine IFE and quantification of serum free light chains (sFLC) have a 99% sensitivity for identifying AL-CA substrate. However, two caveats in this studies merit discussion. The first, is the high prevalence of monoclonal

gammopathy of uncertain significance (MGUS) in patients older than 75 years-old, which makes difficulties in distinguishing between ATTRwt-CA and AL-CA in this population. A moderate increase in circulating free light chains is not necessarily pathological in this subgroup³¹. The second is the changes in clearance of the FLC depending on renal function, where the reference range switches from 0.26 to 1.65 (normal renal function) to 0.37 to 3.1 (renal failure)³².

1.1.3.3.2 NT-pro-BNP, Troponin and Proteinuria

Troponin and natriuretic peptides levels are usually high in CA due to LV dysfunction and the direct toxicity of amyloid fibrils and precursors. This is particularly important in AL-CA³³. Proteinuria with or without impaired glomerular filtration rate should raise suspicion as well.

1.1.3.4 Echocardiography. An increase in left ventricle thickness is the most obvious imaging sign of CA (Figure 5). Restrictive physiology (Figure 8) may not be present early in the disease and ejection fraction is usually in the low range of normality, although the ventricle function is abnormal (Figures 4–9) (Table 4).

1.1.3.5 Bisphosphonate (^{99m}Tc-DPD/^{99m}Tc-PYP/^{99m}Tc-HMDP) scintigraphy.

Bone scintigraphy using (^{99m}Tc)-3,3-diphosphono-1,2-propanodicarboxylic acid ((^{99m}Tc)-DPD) or similar has become the gold standard for the diagnosis of TTR related cardiac amyloidosis with a specificity and positive predictive value of 100% when grade 2 or 3 myocardial radiotracer uptake on bone scintigraphy was found, in absence of a monoclonal protein in serum or urine²³. The semiquantitative visual score of cardiac retention, graded from 0 to 3, compares the uptake of the heart with the bone, being heart grade 2 uptake equal to bone (Figure 10).

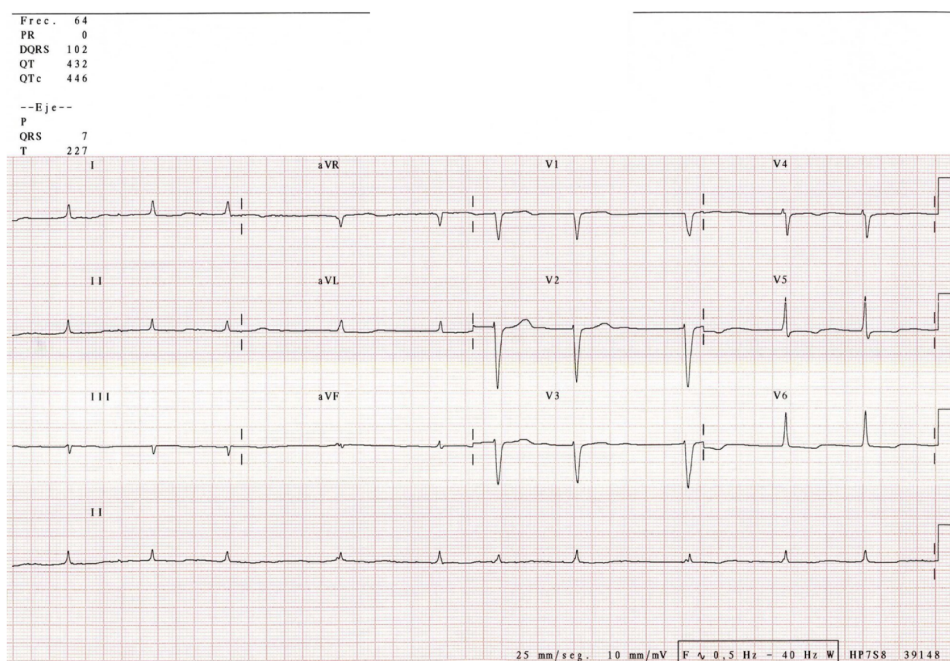


Figure 4. Typical electrocardiographic findings, showing atrial fibrillation, low voltages and pseudoinfarct pattern. Male patient, 86 years-old.

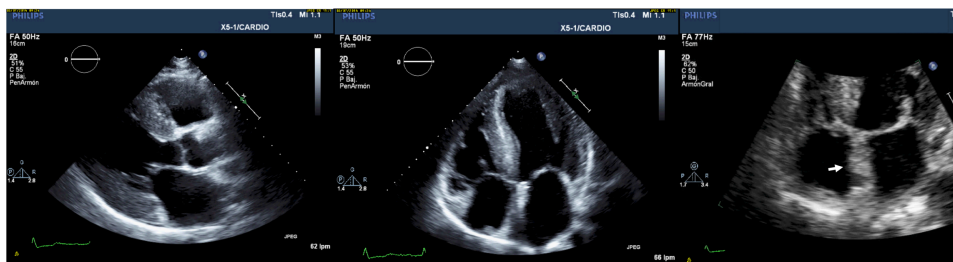


Figure 5. 2-dimensional echocardiographic images of a patient with ATTR-CA. Concentric LVH is visible in the first on the left and in the image in the middle. Ground glass appearance of the myocardium is also apparent. In the image on the right hand side we can appreciate interventricular septum thickening (white arrow) and valve thickening.

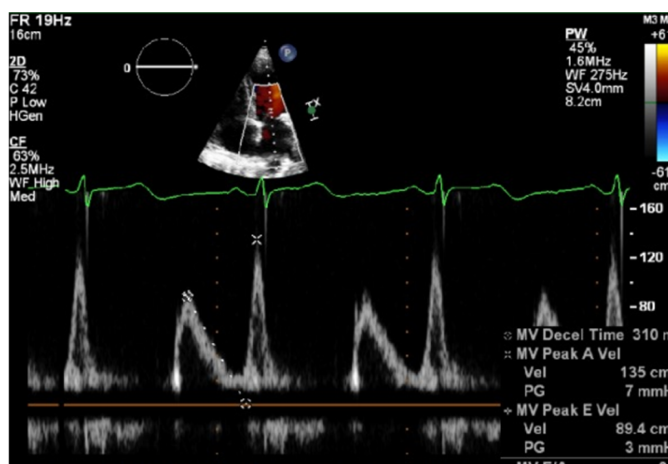


Figure 6. Diastolic dysfunction in early stages, shown by E/A relation <1 in Doppler wave mitral inflow velocities.

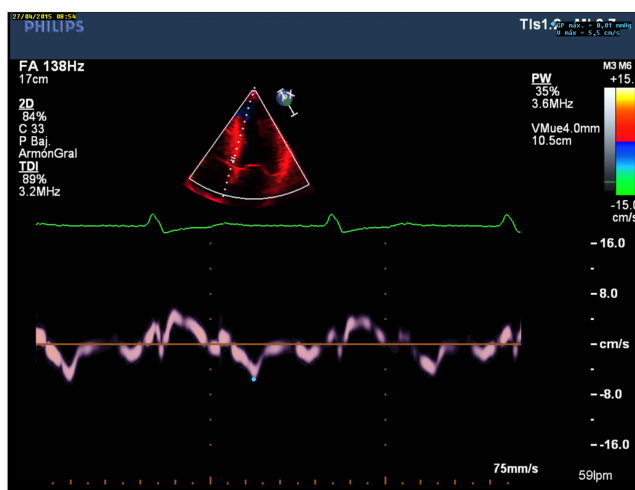


Figure 7. Low velocities in tissue Doppler imaging of the mitral annulus (under 8 cm/s) can be seen in early stages.

1.1.3.6 Cardiac Magnetic Resonance Imaging (CMRI). Cine CMRI imaging permits quantification of ventricular ejection fraction and chamber volumes, with great accuracy to measure and characterize ventricular hypertrophy and its distribution. In

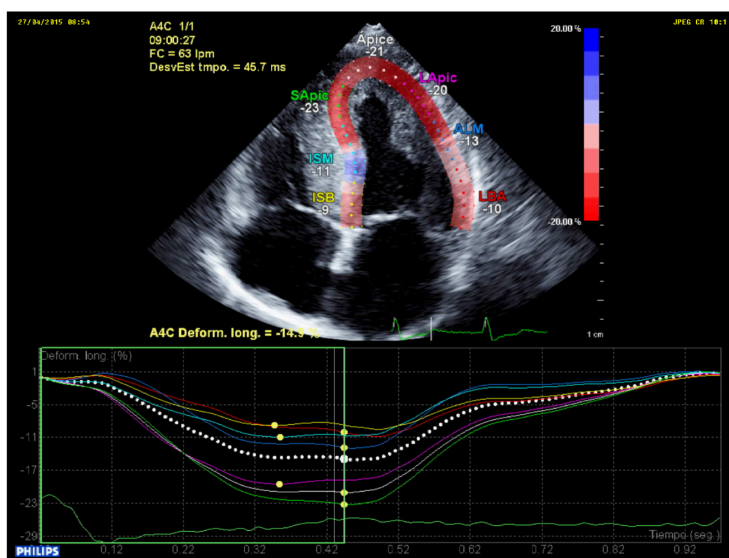


Figure 8. Abnormal ventricular strain and strain rate, typically with apical sparing. Apical Strain/ Basal Strain >2.1 .

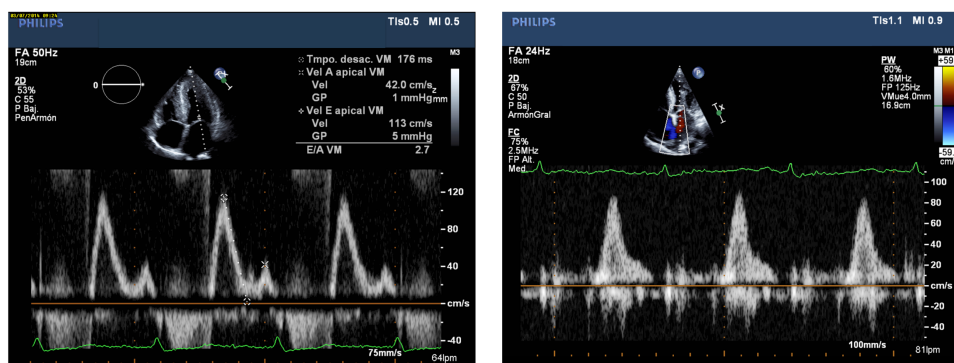


Figure 9. Restrictive physiology. In the image on the left, E wave high velocities measured in the mitral inflow with very low A wave velocities with abnormal deceleration time, indicates high left atrial pressure and poor compliant left ventricle. On the right hand side, the pulmonary vein Doppler velocities show absence of systolic inflow wave and high diastolic velocities, consistent with restrictive physiology as well.

Table 4 Echocardiographic clues in HCM phenocopies (storage disorders)³⁴.

- Increased interatrial septum thickness (Amyloidosis)
- Increased atrioventricular valve thickness (Amyloidosis; Anderson–Fabry disease)
- Abnormal ventricular strain and strain rate, typically with apical sparing (Amyloidosis) (Figure 7).
- Increased RV free wall thickness (Amyloidosis, Anderson–Fabry disease)
- Mild–moderate pericardial effusion (Amyloidosis)
- Ground-glass appearance of ventricular myocardium (Amyloidosis)
- Concentric LVH (Amyloidosis, Glycogenosis, Anderson–Fabry disease)
- Extreme concentric (LVH Danon disease, Pompe disease)
- Global hypokinesia (with/without LV dilatation) Anderson–Fabry; mitochondrial disease; TTR-related amyloidosis; PRKAG2 mutations; Danon disease)

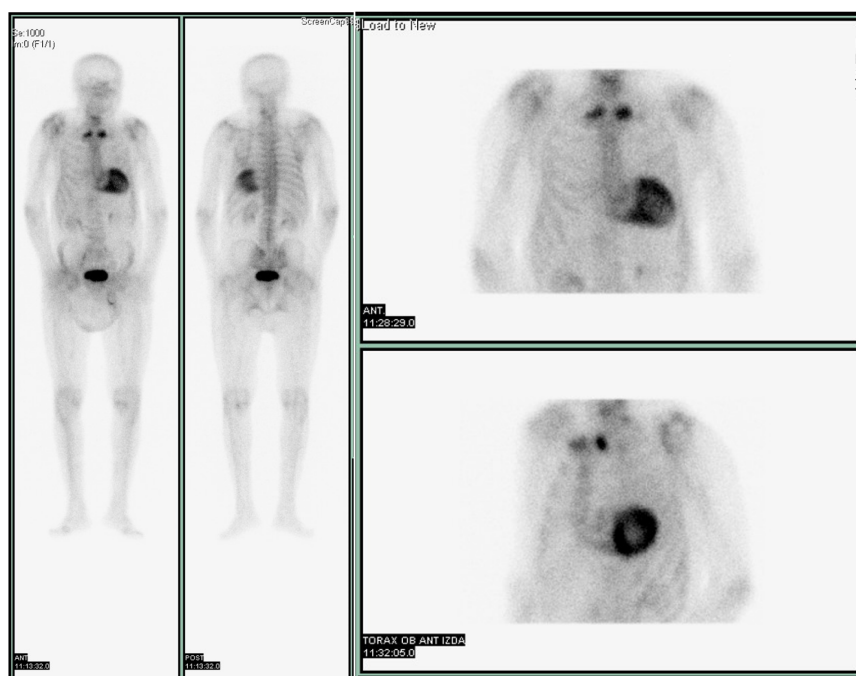


Figure 10. Bisphosphonate scintigraphy. Grade 3 uptake score in a patient with ATTR-CA.

this line, asymmetrical LVH was described recently to be the commonest pattern among ATTRwt-CA³⁵ based on MRI studies. The LGE distribution pattern in the LV can be variable and corresponds to underlying fibrosis and amyloid deposition. LGE can be global subendocardial (the typical one), transmural, localized or patchy. Right ventricular and left atrial LGE often appear. One particular distinction in cardiac amyloidosis assessment by CMRI is that achieving good quality acquisitions and interpretation of the LGE is really challenging due to the difficulties in the election of the optimal inversion recovery time. This is a source of false negative results that might be reduced with the implementation of automatic tools like the PSIR (phase sensitive inversion recovery) sequence. Assessment of the myocardial T1 relaxation times with T1 mapping can overcome this problem³⁵.

1.1.3.7 Biopsy. Endomyocardial biopsy (EMB) is considered the gold standard for diagnosis of storage diseases³⁶. However, the variable distribution of amyloid in the heart leads to false negative biopsies, as some parts of the myocardium do not contain the deposits. Peri-cellular and nodular interstitial involvement are the most common patterns although less frequently, deposits in the arterial wall are also seen. In systemic amyloidosis biopsies can be taken from abdominal fat, rectal mucosa, oral cavity mucosa or minor labial gland. Congo red and Sirius red, are the histological staining used, showing apple-green birefringence when viewed with cross-polarising filters in a light microscope. Electron microscopy visualises the form (non-branching) and size of the fibrils (7–10 nm in diameter). Typing the amyloid fibril is also possible by using immunohistochemical examination (IHC) or mass spectrometry-based (MS) methods.

1.1.3.8 Genetic testing. Genetic testing, whenever possible, is recommended for differentiating ATTRwt from the familial form of ATTR, with the corresponding genetic counseling for the family members³⁴.

1.1.4 Staging and prognosis

1.1.4.1 ATTR-CA. In 2017, Gillmore et al. proposed a new staging system for ATTR-CA with the NT-proBNP peptide and the estimated glomerular filtration rate. Stage I was defined as NT-proBNP ≤ 3000 ng/L and eGFR ≥ 45 ml/min, Stage III was defined as NT-proBNP >3000 ng/L and eGFR <45 ml/min, and Stage II, the remainder. Among the cohort that they used to validate the system, the median survival for stage I, II and III was 69.2 months, 46.7 months and 24.1 months respectively³⁷. A recent study reported that lower baseline serum TTR concentration levels is independently associated with poor outcomes in this patients in patients with ATTRwt³⁸.

1.1.4.2 AL-CA. The staging system for AL-CA proposed in 2012 by Kumar et al. (Mayo Clinic, Rochester, MN) is based on FLC-diff (difference between involved and uninvolved light chain), cTnT (cardiac troponin T biomarker), and NT-ProBNP. Patients were assigned a score of 1 for each of FLC-diff >18 mg/dL, cTnT >0.025 ng/mL, and NT-ProBNP $>1,800$ pg/mL. Stages I to IV were created and the median overall survival from diagnosis was 94.1, 40.3, 14, and 5.8 months, respectively³⁹.

1.1.5 Treatment

The severity of the disease at diagnosis determines the response to the treatment. Central to new treatments in CA is the reduction of precursor proteins that form amyloid fibrils.

1.1.5.1 Amyloid non-specific therapy. Maintenance of fluid and electrolyte balance is crucial for heart failure management. The usual drug therapy for heart failure not only has not demonstrated benefits in CA but has also be seen to be harmful. In particular, vasodilators can exacerbate orthostatic hypotension and syncope and Beta-blockers can cause severe bradycardia. There is a high risk of toxicity with digoxin and nondihydropyridine calcium channel blockers caused by their high avidity to amyloid fibrils⁴⁰.

Heart transplant for very selected patients can be done, but is controversial. Restrictive selection of recipients and adequate management of underlying disease in AL-CA or ATTRv with modern therapies may improve outcomes⁴¹. Inflow cannula “suck-down” events, arrhythmias and septum displacement causing impaired right ventricle function are potential problems with ventricular assist devices⁴².

1.1.5.2 Amyloid specific therapy. Diflunisal, a nonsteroidal anti-inflammatory, has been shown to improve neurological symptoms and Tafamidis has been demonstrated to delay disease progression⁴³ in familiar peripheral neuropathy caused by TTRv. Ongoing trials are evaluating the effect on the heart of Tafamidis⁴⁴. Only liver transplant for ATTRv-CA and treatment of hematologic monoclonal disorder, in AL-CA, is currently approved. Albeit, there are promising molecules coming in the near future (Table 5). In example, antibody therapies such as the one targeting residues from 115–124 of the Met30Val variant has been tested with encouraging results⁴⁵.

1.2 Cardiac oxalosis (CO)

CO is an extremely rare cause for LVH, consisting of extracellular deposit of oxalate, due to an overproduction caused by a deficiency of the alanine-glyoxylate aminotransferase liver enzyme. The underlying diseases are named primary hyperoxalurias, rare autosomal recessive disorders of oxalate metabolism. Heart failure as a result of systolic dysfunction and restrictive cardiomyopathy, with LVH in one third

Table 5 Potential therapies in Cardiac Amyloidosis.

-
- Synthesis suppression:
 - Eliminate the clonal plasma cells and stem cell transplantation (AL-CA)
 - Liver transplant (ATTRv)
 - Epigallocatechin gallate (Green Tea). (ATTR)
 - Patisiran (small interfering RNA, reduces transcription of TTR)
 - Ionis (interference with the splicing of TTR)
 - Stabilizers (prevent the homotetramer of TTR from dissociation into monomers):
 - Diflunisal (ATTRv)
 - Tafamidis (ATTRv)
 - Doxyciclina (ATTR)
 - Tolcapone (ATTR)
 - AG-10 (selective to ATTRwt and ATTRv- *V122I*)
 - Deposit removal (clearance):
 - The antiamyloid 11-1F4 monoclonal antibodies
 - Pyrrolidine-2-carboxylic acid + IgG anti-SAP antibodies (ATTR, AL)
 - Antiamyloid monoclonal NEO001
-

of the patients, together with rhythm disorders, are the cardiac features found in this entity. Urolithiasis, nephrocalcinosis and progressive renal failure, complete the rest of this syndrome's picture⁴⁶.

2 INTRACELLULAR DEPOSIT STORAGE DISEASES

There are more than 50 lysosomal storage disorders described⁴⁷. Those most commonly associated with hypertrophic cardiomyopathy phenotype are Fabry disease, Pompe disease and Danon disease. Although previously associated to lysosomal disease, because increased deposits of glycogen and amylopectin occurs in the lysosome, PRKAG2 syndrome's etiopathogenesis cornerstone is the AMP kinase dysregulation, a non-lysosomal-associated enzyme. Mucopolysaccharidoses (MPS) type IH and II and the classical glycogen storage diseases that produce hypertrophy in the heart (types II, IIa, III and IV) will also be discussed below.

In the initial evaluation of a patient with the suspicion of a metabolic disorder, some general investigations should be performed (Table 6). It is important to rule out growing-up disorders in the infants, by plotting growth centiles. Dismorphic appearance or skin abnormalities should be assessed and a neuro-ophthalmological examination is mandatory. Respiratory or liver involvement of the disease is also part of the work-up. Clinicians should be aware of the complexity of some specialized biochemical tests that may require special collection methodology. Storage of DNA for pathogenic variants analysis is particularly useful, in addition to the study of family history. In some cases might be of utility to take a skin biopsy for cell culture in order to perform enzyme tests.

In the differential diagnosis of LVH, the ECG is an essential test and there are hints that suggest a possible metabolic disorder. For example, ventricular pre-excitation may be seen in PRKAG2 syndrome, Danon disease, Pompe disease as well as other non storage disorders like MELAS syndrome, Leigh syndrome, MERRF syndrome or oncocytic cardiomyopathy.

Table 6 Useful laboratory tests⁴⁸.

General tests:	Glucose, Urea, Electrolytes, Creatinine, Liver function tests. Urine ketones. Blood gases, ammonia, lactate, anion gap. Full blood count.
Specific tests	Carnitine, acylcarnitine profile, CSF lactate and amino acids. Urine organic acids, urine amino acids, plasma amino acids, uric acid

2.1 Mucopolysaccharidoses (MPS)

Hurler syndrome (MPS type IH, autosomal recessive) and Hunter syndrome (MPS type II, X-linked) are the two MPS that may provoke myocardial thickening. Other cardiovascular abnormalities associated are valvular disease, coronary artery narrowing or pulmonary and systemic hypertension.

2.2 Anderson–Fabry disease

2.2.1 Introduction

Fabry disease (Anderson–Fabry Disease (AFD) or *angiokeratoma corporis diffusum*) is a rare disorder of the metabolism of the α -galactosidase A, a lysosomal enzyme that degrades neutral glycosphingolipids, mainly globotriaosylceramide (Gb3), resulting in progressive intracellular accumulation.

2.2.2 Pathogenesis

GLA is the gene that encodes α -galactosidase A and maps to Xq22.1. Variants in this gene can affect enzyme synthesis, folding, degradation, trafficking or activity, leading to inability to degrade Gb3. Males have low or absent enzyme activity, but as a result of the lyonization process (transcriptional inactivation of one of the X chromosomes in some cells during embryogenesis) may present with atypical forms and a wide spectrum of signs and symptoms (Figure 12), depending on enzyme's activity preservation or absence among the different organs and tissues⁴⁹.

2.2.3 Diagnostic work-up

2.2.3.1 Clinical presentation

2.2.3.1.1 Cardiovascular manifestations

Heart disease is present in all forms of AFD, with concentric LVH as the hallmark. The proportion of patients with Fabry disease among those previously diagnosed of HCM, ranges from 0.5% to 12% depending on the reported series⁵⁰.

The electrocardiogram in AFD is a very useful tool as a diagnostic red flag (LVH criteria and short PR interval) and for risk stratification, as atrial fibrillation and conduction system disease, mainly complete atrioventricular block (Figure 14). Short PR interval (Figure 11), which can be present in children under 10 years-old⁵², is seen in about 40% of the patients⁵³. Interestingly, it is not due to an accessory pathway but to an accelerated conduction of the atrioventricular node (AVN). Some studies report 17% incidence of AF on ambulatory monitoring. Also ventricular arrhythmias driven by fibrosis and conduction abnormalities can be present in 8% of cases⁵⁴.

Sudden cardiac death, though rare, can be the first presentation, due to ventricular arrhythmias or complete AV block. Heart valves can be affected in about 15% of the patients, with thickening, fibrosis and calcification, but usually does not result in significant impairment⁵¹.

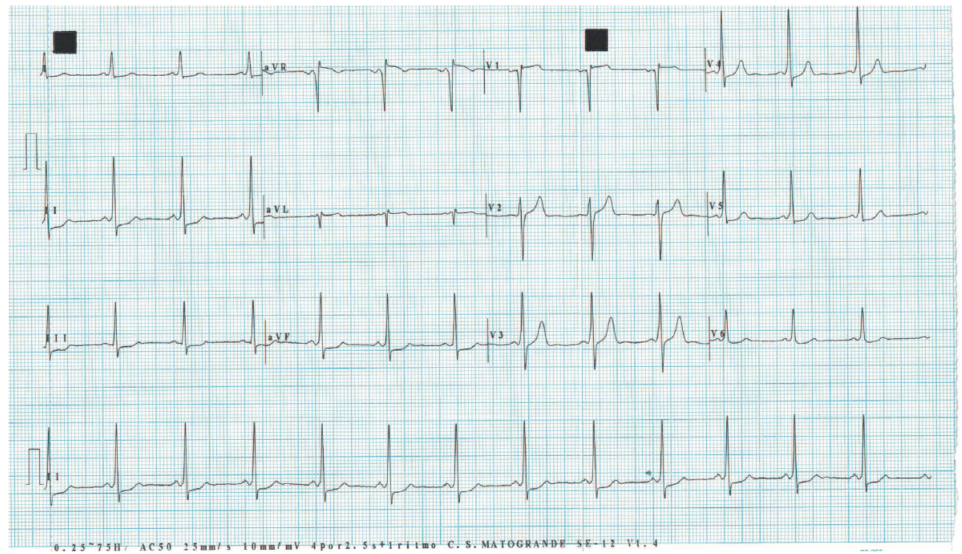


Figure 11. Electrocardiogram of a 20 year-old male patient with classic form of AFD. Sinus rhythm and short PR interval is patent. Repolarization abnormalities with T wave inversion in V3 to V6 and I an aVL is also present.

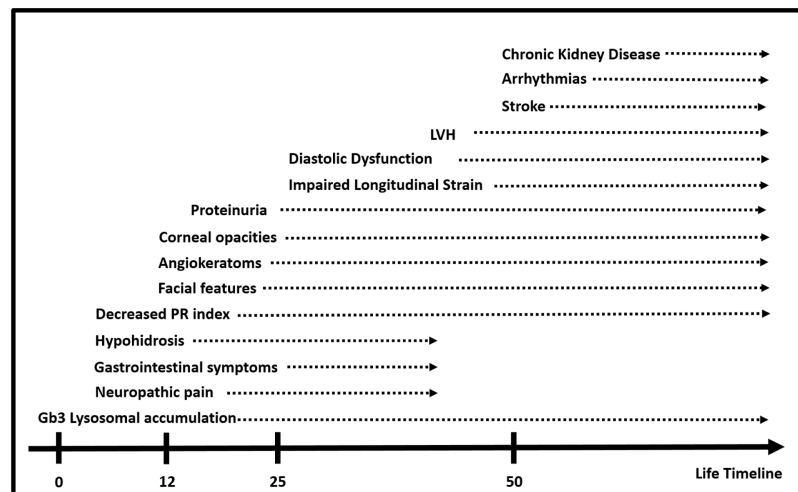


Figure 12. Red Flags and life-time relation. The chart shows the approximate onset of the symptoms and duration. Hypohidrosis, gastrointestinal symptoms and neuropathic pain, in some patients may disappear with age.

Some AFD patients complain of angina. This is more commonly seen in combination with LVH and might be due to increased oxygen demand for similar reason to what occurs in HCM, but also in response to diffuse arteriopathy associated to cellular damage of the arterial walls. The prevalence of aortic dilatation (AD) increases with age and it is more prevalent in male and usually affects the sinus of Valsalva and the ascending aorta⁵⁵. It was reported a AD prevalence of 9,6% in males by Barbey et al.⁵⁶.

Hypertension is also overrepresented (about 50%), contributing to increase cardiovascular risk and ventricular hypertrophy.

Echocardiography is essential in the diagnostic work-up, staging and follow-up. Table 7 describes some of the typical findings.

Table 7 Summary of echocardiographic findings⁵⁷.

Left Ventricle	Increased wall thickness: concentric (not exclusively but most common). Mean age: 42.0 ± 14.5 years in men and 50.1 ± 12.0 years in women
	Binary sign, hyperechogenic endocardial border adjacent to a hypoechogenic subendocardial layer. Sensitivity 15.4% - to 28% and a Specificity of 73.3% to 80%.
	Thickening and hyperechogenicity of papillary muscle
	Ejection fraction (EF) of LV generally preserved in early stages. Diastolic function often impaired. Reduced systolic longitudinal strain in basal and posterolateral segments. Loss of base-to-apex circumferential strain gradient.
Right ventricle	RVH. EF and Function behaviours similar to LV.
Atria	Mild to moderate enlargement
Valves	Mitral valve prolapse and leaflet thickening (also aortic) and redundancy.
Aorta	Sinus of Valsalva and ascending aorta dilatation (not the descending)

Significant LVOT obstruction has been described in very few cases, although Calcagnino et al. reported in 2011 a series of 14 symptomatic patients, of which 6 had provoked LVOT significant gradient⁵⁸.

LV ejection fraction is generally preserved but in advanced disease it can be reduced, terminating in end stage heart failure. Diastolic function is impaired but restrictive physiology is rare, unlike other infiltrative disorders like CA. For both diastolic and systolic function, some studies have seen that impairment begins with the increased wall thickness or fibrosis⁵⁹. Fibrosis is assessed in the MRI with LGE, being the typical finding the localized enhancement of the basal posterior left ventricle wall, which can be accompanied by wall thinning in late stages. Notwithstanding, more sensitive techniques like strain or MRI have shown markers of disease earlier than the ordinary echocardiographic findings. Global systolic longitudinal strain is lowered in patients with Fabry disease without LVH. Based on this statement, and to facilitate natural history description and variations with potential treatments, Yeung et al. have proposed a revised (from Weidemann et al.) stage classification as in Table 8:

Since the advent of new techniques in MRI such as T1 mapping (shortened in AFD patients in early stages), new studies are in progress and will definitely help to better understanding of disease history and treatment response⁶⁰. Focal 18F-FDG uptake has been demonstrated in some patients and is associated with impaired left ventricular longitudinal function⁶¹.

Table 8 Stages in Fabry diseases based on MRI and echo-strain⁵⁷.

Stage	LGE	LVH	Longitudinal Function	Radial Function
0	No	No	Normal	Normal
I	No	No	Reduced	Normal
II	No	Yes	Severely reduced	Reduced
	Yes	No	Severely reduced	Reduced
III	Yes	Yes	Severely reduced	Severely reduced

2.2.3.1.2 Kidney disease

Renal impairment is preceded and caused by the deposit of Gb3 in podocytes, endothelial, epithelial, and tubular cells. Proteinuria is the first manifestation, leading to end-stage renal failure without treatment in the fifth decade of life. It has been reported that podocyturia might be an earlier marker of disease than proteinuria, although microalbuminuria/proteinuria is the most commonly used method for kidney function assessment in early stages (first or second decade of life)⁶². Novel procedures to differentiate female AFD patients are proteomic analysis or urinary Gb3 or lyso-Gb3 determination⁶³.

2.2.3.1.3 Neurological disease

Peripheral neuropathy often manifests as pain crisis more than as acroparesthesias. Hearing loss is common and it is progressive. Hypohidrosis happens in 53% of males and 28% of females, and the age at onset is 23 ± 17 years in males and 26 ± 20 years in females, according to the FOS (Fabry Outcome Survey, Orteu et al. 2007). Both neuropathic pain and hypohidrosis are associated with heat intolerance. Ischemic stroke, weather due to vasculopathy or to atrial arrhythmias, may present in the fifth decade of life. Recent research suggests that there may be an increased risk of developing Parkinson Disease in individuals with *GLA* mutations⁶⁴.

2.2.3.1.4 Gastrointestinal

Autonomic nervous system dysfunction, vasculopathy and tissue inflammation are the main proposed mechanisms of the etiopathogenesis of gastrointestinal disturbances in AFD. All this may translate into abdominal pain, intestinal and stomach motility disorders, malabsorption, etc. In children it impacts on quality of life, academics and plotting growth centiles. The psychological stress is also a feedback to bolster gastrointestinal symptoms⁶⁵.

2.2.3.1.5 Dermatological

The most common finding are the angiokeratomas, reported in 66% of males and 36% of females, though is not specific of AFD. Whereas in men are usually located in what it is called the “bathing trunk” area, in women it is more likely to find them on the proximal limbs and the trunk. The other cutaneous symptom related are telangiectasias on face, lips, mucosa and areas exposed to the sun like the V of the neck⁶⁶. Lower limb oedema and lymphoedema may be also patent. Typical facial features in the classic form can be in up to 50% of the patients, showing prominent earlobes, lips and nasolabial pledges or heavy hairy eyebrows⁶⁷.

2.2.3.1.6 Ophthalmological

Visual impairment is an uncommon but slit-lamp evaluation will show the cornea verticillata (CV), which respond to golden brown or gray deposits in the inferior interpalpebral portion of the cornea in a clockwise fashion, is the most common finding. Amiodarone, chloroquine or indomethacin can also cause CV. CV can be present in females as a milder form. Another site of deposits is the posterior capsule, causing the Fabry cataract. Some patients also exhibit aneurysmal dilatation and tortuosity of conjunctival and retinal vessels, sign that has been proposed to be a new sensitive prognostic marker⁶⁸.

2.2.3.1.7 Others

Pulmonary involvement (chronic bronchitis, wheezing, or dyspnea), skeletal (osteopenia and osteoporosis) and lymphatic (limb lymphedema and pitting edema) has also been described in some patients.

2.2.3.2 Diagnostic Tests

2.2.3.2.1 Enzyme assay

Alpha-galactosidase (α -GLA) activity assay alone is diagnostic when it is absent or very low in men, although genetic testing to look for pathogenic variants is highly recommended, because in some cases benign polymorphisms can cause reduced levels of the enzyme. The easiest way to look for the enzyme activity is to go for the dried blood spots test. Leukocyte enzyme can also be tested and it is useful in atypical forms of AFD. In women, as they can still have some activity, a disease-causing mutation should be the target for making the diagnosis. For uncertain significance variants, if available, in vitro GLA mutation expression assays would be the definite test. Albeit, since is not widely used, a consistent co-segregation study would fulfil the criteria requirements for diagnosis establishment. In some cases, mostly atypical variants, biopsy can make the diagnosis (Figure 13). Although renal biopsy's yield is higher, starting from a skin biopsy could be less invasive.

Apart from testing the α -GLA activity, it is also possible to get classic form of AFD diagnosis if the urine Gb3 determination is in the high range and for those with atypical form of AFD, determination of lyso-Gb3 in urine is also a diagnostic useful tool^{69,70}.

2.2.3.2.2 Genetic testing

The majority of the causal pathogenic variants in AFD exhibit a predilection to nonsense insertion/deletion or premature truncation mutations because of a frameshift. Whereas missense mutations appear to be less prone to cause disease, it has also been suggested that some missense variants can be cause of late onset forms or in some cases are associated with particular phenotypes. This is the case of the p.N215S



Figure 13. Renal biopsy under electron microscopy showing the typical zebra body, formed by Gb3 deposit in the lysosome (white arrow).

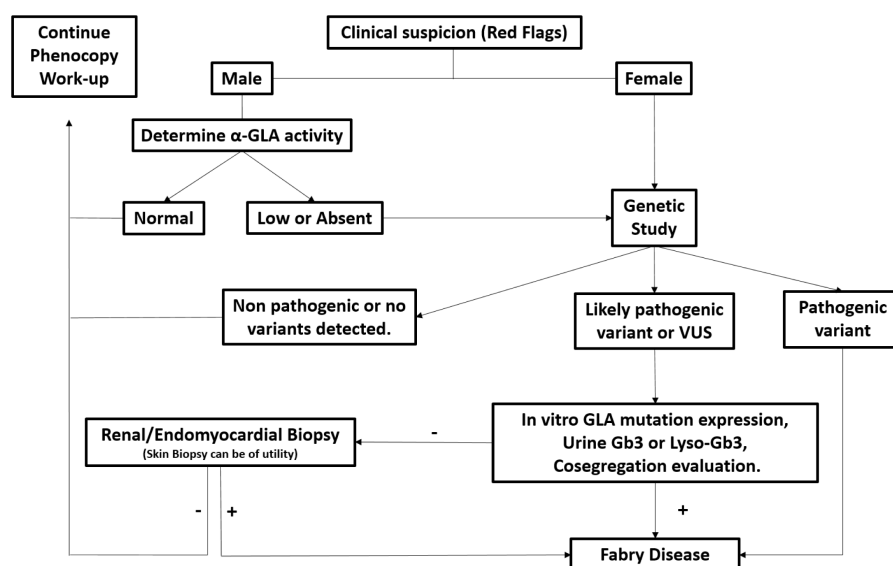


Figure 14. Algorithm for diagnostic work-up.

pathogenic variant, which presents with cardiomyopathy in the absence of renal involvement⁷¹. Disease expression may vary among members of the same family, even between males, which makes treatment decisions and counselling more difficult.

Implications of genetic study not only have to do with diagnosis or counselling but also with treatment, since some specific treatments are solely effective against certain pathogenic variants. Variants of uncertain significance should be cautiously evaluated, and an upgrade in pathogenicity degree ought to be carefully proved by functional studies or a consistent co-segregation analysis, following guidelines consensus^{72,73}. Urine Gb₃ or lyso-Gb₃ can be useful in this scenario.

2.2.4 Life expectancy and cause of death

According to data from the Fabry Registry, life expectancy in USA for men was 58.2 years (74.7 years in men population) and 75.4 years for women (80.0 years in women population). The main cause of death varied in the registry, being renal failure for deaths before 2001 and cardiac disease for the patients who died after that period. These may be biased by the effect of ERT, although it has not been proved. Also dialysis and ACEI/ARB adjunctive therapies are related to improved outcomes.

All this is general AFD data population and each individual can have a different surveillance scenario, mostly depending on the genetic GLA variant and expressivity.

2.2.5 Management

Non-specific treatment includes angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) to maintain a urine protein to creatinine ratio less than 0,5 g/g. Some evidence also support the potential use of medications such as amiloride as podocyte stabilizer and antiproteinuric or paricalcitol⁶³.

Active investigation for atrial fibrillation is recommended and anticoagulation should be initiated independently of CHADSVASC score. No stroke primary prevention strategy with antiplatelet therapy or lipid-lowering agents has shown any current evidence, although individualized decision is reasonable.

Pain release is a mayor issue to solve, and neuroleptics drugs are an option for neuropathic pain (gabapentin, carbamazepine). For pain crisis, opioids can be used.

Heart or renal transplant is feasible at end-stage organ burden, considering that the α -GLA activity is normal in the donor and the receptor will be free from Gb3 deposit in the transplanted organ.

2.2.5.1 Enzyme replacement therapy (ERT). There are two available ERT, intravenously administered. The agalsidase beta, with a posology of 1 mg/kg every 2 weeks (European Medical Agency (EMA) and US Food and Drug Administration (FDA) approved) and agalsidase alfa, with posology of 0.2 mg/kg every 2 weeks (EMA approved).

There is not a complete consensus for ERT initiation indications, and symptoms or organ manifestations criteria may vary among the different guidelines. Also the level of evidence is often driven by expert consensus or small RCT. Following the recommendations of USA Expert Panel 2016, ERT should be started in the classic form of AFD in symptomatic children at any age and in asymptomatic males with classical mutations by age of 8–10 years. For asymptomatic females, decision should be made considering family history of females. This patients should be followed closely to reassess therapy initiation⁷⁴. In adult patients, starting ERT should be considered at the time of diagnosis, although in end-stages it may not be effective⁷⁵. In patients with late onset form o atypical form of AFD, organ damage (laboratory biomarkers, biopsy or echocardiogram) evidence is required to support the initiation of the ERT.

2.2.5.2 Non-ERT approaches. Recently, the European and Canadian Medical Agencies have approved migalastat, an oral medication consisting of a molecular chaperone. Chaperones are proteins that assist the covalent folding or unfolding and the assembly or disassembly of other macromolecular structures. For this reason, migalastat is only useful for certain pathogenic variants of GLA.

2.2.6 Screening recommendations

First-degree relatives should be evaluated, for early diagnosis purposes, co-segregation analysis and counselling. Concerning newborn screening, it is not currently included in most of the government's screening programs, although some centers have started doing it. Newborn screening is challenging, as it is the management and counselling of possible AFD detected cases. The phenotype and prognostic heterogeneity of the disease, together with the unknown significance of many rare variants, can make newborn screening a double-edged sword.

2.3 Glycogen storage diseases

The classical glycogen storage diseases that produce hypertrophy in the heart are types II, IIa, III and IV, and will be discussed below.

2.3.1 Glycogen storage disease type II (Pompe disease/acid alpha-glucosidase deficiency/acid maltase deficiency)

The first identified lysosomal storage disorder was Pompe disease (PD). PD is characterized by an abnormal deposit of glycogen in the lysosomes, in which acid alpha-glucosidase (GAA) enzyme is deficient or absent. It is an autosomal recessive disorder and has two forms of presentation: the early infantile-onset Pompe disease (IOPD), and the late-onset Pompe disease (LOPD). The former is distinguished by developing heart disease with high risk of tachyarrhythmia and SCD usually before the first year of life, whereas the later has very rarely been found to present cardiac involvement.

It is a rare disorder with an estimated prevalence in the general population of 1:40,000⁷⁶, with higher prevalence in certain countries such as Taiwan and Austria, in which newborn screening is active^{77,78}.

The severity, tissue manifestations and age of onset, correlate with the nature of the pathogenic variant and degree of residual enzyme activity⁷⁹.

There are three initial pathogenic mechanisms encountered in PD. The most commonly known is the abnormal deposit of glycogen in the lysosomes. The second one is disruption of the normal process of macroautophagy that is needed for the recycling and degradation in the cell, leading to accumulation of toxic materials, as well as oxidative stress. The last one is the resulting damage of the mitochondria, playing an important role in myocardial and skeletal muscle impairment⁸⁰.

In the IOPD form, left ventricular hypertrophy by definition is present before age 12 month and can be as early as in utero. Enzyme replacement therapy (ERT) with alglucosidase alfa treatment should be started as soon as possible, as it has shown to improve cardiomyopathy, ventilation free-survival and overall survival. Without ERT, surveillance is estimated in around two years⁸¹. Associated with the cardiac condition, life impairment is affected by respiratory and ventilation problems, hypotonia, muscle weakness, feeding difficulties and low growth centiles.

Left ventricular hypertrophy, short PR and LVOT obstruction are the main characteristics. While LVH progresses, the obstruction may worsen and lead to heart failure and respiratory insufficiency, being the most common cause of death⁸².

Among laboratory test performed, serum creatine kinase (CK) as well as urinary oligosaccharides, can raise suspicion about a glycogen storage disorder.

For the diagnosis, determination of GAA deficiency can be made by dry blood spot, but should be confirmed by molecular analysis and genetic testing, in which biallelic pathogenic variants of *GAA* gene must be present.

2.3.2 Danon disease (LAMP2 deficiency)

Danon disease (DD) is a rare HCM phenocopy (1% of HCM⁸³), with an X-linked dominant inherit pattern, caused by an inborn disorder in the final step of the autophagic process in the cell, which involves a deficient function of the lysosome-associated membrane protein 2 (LAMP2)⁸⁴.

LAMP2 is located in the lysosome membrane and acts in the process of autophagosome maturation by facilitating the fusion with endosomes. Mutations affecting the *LAMP2* gene that alter the isoform LAMP-2B are responsible for DD. The resulting impaired autophagy will lead to glycogen and non-degraded substance deposit, promoting organ changes and damages. In a similar way to what happened in PD, mitochondrial disturbances play an important role in the pathogenesis of the disease.

2.3.2.1 Diagnostic work-up

2.3.2.1.1 Clinical manifestations

This is a multisystemic disorder, where the extracardiac manifestations of patients with LVH should call clinicians attention to reach the correct diagnosis. Due to the haplo-insufficiency, the characteristic presentation occurs in boys and young males gathering massive increase in cardiac mass, skeletal myopathy and cognitive and psychiatric comorbidities. However, females are also affected but later in age and with different clinical course, as a result of lyonization process. Difference in presentation is synthesized in [Table 9](#). Determining levels of serum creatine kinase or liver function tests can also be of utility.

2.3.2.1.2 Cardiac assessment

Concentric massive left ventricular hypertrophy in a boy or a young male, with a pre-excitation pattern in the ECG, is the typical presentation of DD. On the contrary, dilated

Table 9 Difference in clinical course between sexes. (Note that not many data registries are available and some rates are based on small sample series.)

	Males	Females
Age of onset	13.3 ± 8.0 ⁸⁵	28.9 ± 4.2 ⁸⁵
LVH	88–100% ⁸⁶	(33%) ^{86,87}
DCM	10–12% (late progression) ^{86,87}	(28%) ^{86,87}
Pre-excitation	69% ⁸⁶	27% ⁸⁶
Atrial Fibrillation		75–85% ^{90,91}
Heart transplant	20.8 ± 6.7 ⁸⁶	32.3 ± 14.5 ⁸⁶
Defibrillator	41% ⁸⁶	31% ⁸⁶
Death	20.1 ± 5.2 ⁸⁶	40.2 ± 12.6 ⁸⁶
Skeletal myopathy	80–90% ^{86,87}	33–50% ^{86,87}
Gastrointestinal disease	77% ⁸⁶	50% ⁸⁶
Respiratory disease	50% ⁸⁶	16,7% ⁸⁶
CK elevation	All ⁸⁷	50% ⁸⁸
Cognitive impairment		Mild cognitive deficits in most of the patients ⁸⁹
Psychiatric disorder (PD)	69.2% (at least one PD)	mood and anxiety the most common ⁸⁹
Retinal problems	69% ⁸⁶	64% ⁸⁶

cardiomyopathy is more commonly seen in females. There is a high incidence of atrial fibrillation and ventricular arrhythmias, and the surveillance rate without ICD or heart transplant is really poor in this patients.

Very few reports have been made of MRI characterization of DD. Almost all the cases describe extended LGE, involving different parts of the left ventricle but usually sparing the interventricular septum⁹².

For the definite diagnosis, *LAMP2* gene pathogenic variant is required. Most of the described disease-causing variants are nonsense or frameshift mutations, leading to absence of protein synthesis.

Biopsy of affected tissue, although not obligatory for diagnostic purposes, will show autophagic vacuole accumulation.

2.3.2.2 Treatment. A close follow up is highly recommended since the diagnosis is done, knowing the poor prognosis and high incidence of life threatening events. Primary prevention of SCD should be assessed based on family history, symptoms, arrhythmias and fibrosis in the MRI, as there are no current specific guidelines in this sense.

Exercise promotion and psychological therapies as well as ophthalmological evaluation ought to be offered to these patients. As in all monogenic disorders, genetic counselling must be offer.

2.3.3 Glycogen storage disease type III (Cori disease, Forbes disease or glycogen debrancher deficiency)

GSD III is a rare autosomal recessive storage disorder, caused by the deficient activity of glycogen debranching enzyme. The LVH is usually found in the IIIa form of GSD type III disease, whereas the IIIb type symptoms are related to the liver. Despite of ventricular hypertrophy, derived cardiac symptoms are not frequently reported. However, there is lack of longitudinal studies evaluating these patients.

Other related features are hepatomegaly, hypoglycemia, hyperlipidemia, variable forms of myopathy and growth retardation⁹³.

2.3.4 Glycogen storage disease type IV (Anderson disease, brancher deficiency or amylopectinosis)

It is a rare autosomal recessive metabolic disorder and ventricular hypertrophy as cardiac involvement, caused by a deficiency in glycogen-branching enzyme. There are several forms with different ages of presentation, being the childhood the age of presentation with LVH and myopathy⁹⁴.

2.4 PRKAG2 syndrome

2.4.1 Introduction

PRKAG2 syndrome (PS) is a rare autosomal dominant inherited disease, with an early onset, caused by a mutation in *PRKAG2*, the gene encoding for the $\gamma 2$ regulatory subunit of the 5' Adenosine Monophosphate-Activated Protein Kinase (AMPK), which is located in chromosome 7. The pathogenic variants known to cause PS are almost in all cases missense variants.

The main characteristic of PS is its manifestation as a hypertrophic cardiomyopathy phenocopy and a pre-excitation pattern in the surface electrocardiogram. Extracardiac involvement is very rare but severe forms with skeletal myopathy with high levels of creatine kinase (CK) are reported in the literature⁹⁵. Hypertension in the adolescence may be considered an extracardiac expression of the syndrome.

AMPK is regulator of cell metabolism and its activation leads to ATP production by increasing the glucose uptake and fatty acid oxidation and to an inhibition of lipids and proteins synthesis process. In the absence of energy deficit, AMPK should not be activated. In PS, the disorder in the $\gamma 2$ regulatory subunit, which acts as a sensor, entails an aberrant increase of kinase activity.

On the contrary to what initially was thought, only up to 4% of the cardiac mass is due glycogen deposits. In fact, the effect of *PRKAG2* in the cardiac growth might be independent from the deposits. A proposed via responsible for myocyte hypertrophy is the increased insulin sensitivity and hyperactivity of Akt, that results in activation of mammalian target of rapamycin (mTOR) and inactivation of forkhead box O transcription factor–signaling pathways⁹⁶. AMPK activation also increases Ca²⁺ sensitivity of contractile regulation, similarly to what occurs in sarcomeric HCM, sharing common pathophysiological pathways⁹⁷.

2.4.2 Diagnostic work-up

PS is usually diagnosed between the third and fourth decade of life, but severe forms of specific pathogenic variants can manifest as early as the first months of life. There is a high penetrance and one quarter of patients present asymptomatic. There is poor information in natural history of PS reported to date. The few studies available report a high risk of cardiac complications⁹⁸.

Ventricular pre-excitation is a hallmark that must put the clinician on the track to diagnose PS (Figure 15). A 12% prevalence of patients with storage diseases has been reported among subjects diagnosed with hypertrophic cardiomyopathy and ventricular preexcitation⁹⁹. In PS, the accessory pathways (decremental AV connections or fasciculoventricular pathways) are thought to be a consequence of abnormal atrioventricular septation favoured by the accumulation of glycogen and amylopectin^{96,100}.

The detection of a pathogenic variant in *PRKAG2* gene is the gold standard for the diagnosis of PS¹⁰¹. Endomyocardial biopsy can show vacuoles PAS stain (Periodic Acid-Schiff) positive and disarray is an uncommon finding.

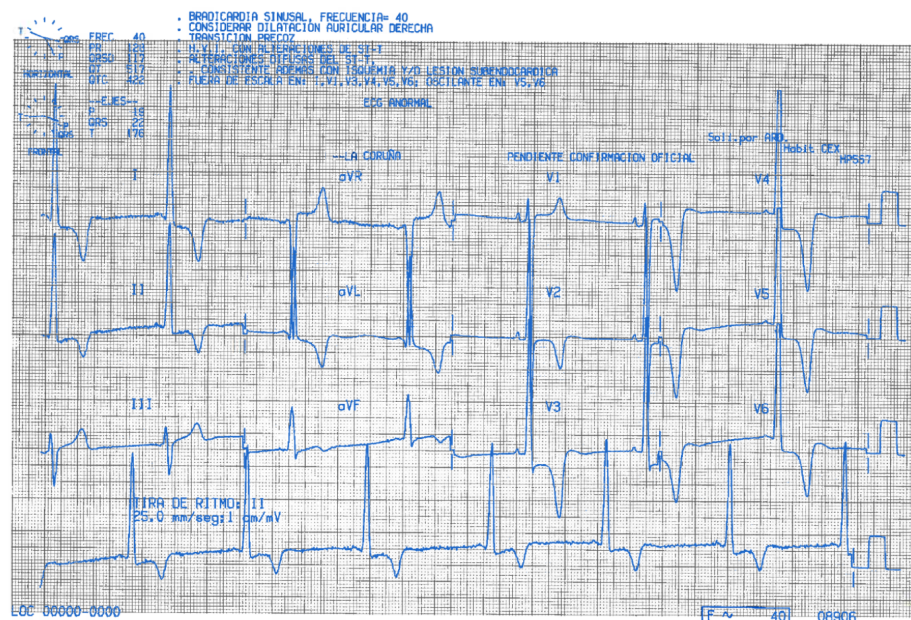


Figure 15. ECG showing pre-excitation pattern and high voltages with T-wave inversion.

Concentric left ventricular hypertrophy is present in two thirds of the patients, usually with impaired diastolic function and some with restrictive pattern. Ejection fraction is generally preserved, occasionally with LVOT obstruction. It is also reported the progression to dilated cardiomyopathy. Supraventricular arrhythmias are frequent (38%) mainly atrial flutter and atrial fibrillation. In two thirds of cases there is a form of bradyarrhythmia (AVB or sinus dysfunction) that may need pacemaker implantation. Sudden cardiac death, although rare, can be a form of presentation in a range of 12 to 20% of the patients⁹⁸.

The MRI is very useful for early characterization myocardium even in the absence of LVH, when there is no LGE but T1 mapping values may be reduced. In the initial phases of fibrosis development, focal mid inferolateral pattern is the common location, whereas a more diffuse pattern but focused on interventricular septum is present in advance stages. Likewise, as fibrosis increases, T1 mapping values will raise as well¹⁰².

2.4.3 Management

There are no current specific guidelines for the management of PS, neither for treatment recommendations nor for risk stratification of SCD.

Clinical follow-up is recommended with periodical echocardiogram to look for heart failure (HF) sign and symptoms of disease progression and to establish HF optimal treatment. Early detection of atrial fibrillation or flutter for primary prevention of stroke should be assessed with ECG monitoring, at the time that ventricular arrhythmias or bradyarrhythmias are screened.

It appears to be reasonable to stratify risk of the accessory pathways and undergo ablation on an individualized basis, due to the high incidence of atrial arrhythmias and VF degeneration. Family screening and counselling should always be offered.

There is no treatment currently available for PS, although ongoing research is being developing in the field of genome editing in experimental models with the CRISPR¹⁰³. Interestingly, it is also under research the effect of the novel sodium/glucose cotransporter 1 (SGLT) inhibitors used for diabetes mellitus treatment¹⁰⁴, as AMPK is a modulator for the SGLT activity.

2.5 Chloroquine-induced cardiomyopathy

Extended therapies with chloroquine, an antimalarial drug used for lupus treatment, can cause a vacuolar myopathy-like disease, presenting with biventricular hypertrophy and LGE usually in the septum. Mitral, aortic, and tricuspid valve thickening, as well as atrioventricular conduction delay or block, may complete the cardiac phenotype. Retinopathy, myopathy or peripheral neuropathy, can be also part of the syndrome.

These similarities with LSD might be explained by the fact that chloroquine interferes with lysosomal enzyme activity and mitochondrial oxidative metabolism, conducting to glycogen and phospholipids deposit in the same way that occurs in the inborn metabolism disorders reviewed above. Luckily, it might be a reversible condition after drug withdrawal¹⁰⁵.

3 CONCLUSION

A comprehensive anamnesis is the critical diagnostic tool for facing a patient with left ventricular hypertrophy. Being familiar with the different signs and extracardiac symptoms that characterize the phenocopies is necessary to reach a definite diagnosis (Table 10). The implications of identifying an inborn metabolic disorder or a familiar condition is crucial for the patient's safety and wellbeing, as well as for family planning¹⁰⁶.

Apart from the previously summarized (Table 10), some fatty acid and carnitine disorders can also present with hypertrophy, although these are very rare conditions.

Table 10 Summary of storage disease that can mimic Hypertrophic Cardiomyopathy phenotype.

Cardiomyopathy	Pathogenesis	Substance	Gene & Inheritance Pattern
Extracellular Deposit			
Familiar CA	Amyloid fibril formation.	TTR	<i>TTR</i> (AD)
Non Familiar CA	Amyloid fibril formation.	TTR, LC, SAA	–
Cardiac Oxalosis	Glyoxylate metabolism	Calcium oxalate	<i>AGXT, GRHPR, HOGA1</i> (AR)
Intracellular Deposit			
Fabry Disease	Alpha-Galactosidase. Lysosomal storage.	Globotriaosylceramide	<i>GLA</i> (X-Link)
Hurler Syndrome	Glycosaminoglycan-degrading enzymes. Lysosomal storage.	Glycosaminoglycans	<i>IDUA</i> (AR)
Hunter Syndrome	Glycosaminoglycan-degrading enzymes. Lysosomal storage.	Glycosaminoglycans	<i>IDS</i> (X-Link)
Pompe Disease	Defective autophagy lead to Lysosomal storage.	Glycogen	<i>GAA</i> (AR)
Cori Disease	Glycogen debrancher deficiency. Lysosomal storage.	Glycogen	<i>AGL</i> (AR)
Anderson Disease	Glycogen brancher deficiency. Lysosomal storage.	Amylopectin-like glycogen.	<i>GBE1</i> (AR)
Danon Disease	Defective autophagy	Autophagic vacuoles	<i>LAMP2</i> (X-Link)
PRKAG2 Syndrome	Dysregulation of AMPK	Glycogen	<i>PRKAG2</i> (AD)
Chloroquine-induced myopathy	Drug-induced Lysosomal disorder.	Glycogen	–

Notes.

CA, Cardiac Amyloidosis; TTR, Transthyretin; LC, Light Chains; SAA, Serum Amyloid A; AR, Autosomal Dominant; AR, Autosomal Recessive.

Friedreich ataxia, in which abnormal iron regulation and deposition is involved, is explained in other section of this compendium (see *Neuromuscular with HCM*).

Likewise, the differential diagnosis HCM phenocopy should always include other cardiomyopathies such as mitochondrial cytopathies, hypertensive cardiomyopathy, athlete's heart, infant of diabetic mother's HCM and rasopathies (Noonan, Costello, Leopard and Cardiofaciocutaneous syndrome).

REFERENCES

- [1] Sipe JD, Benson MD, Buxbaum JN, Ikeda SI, Merlini G, Saraiva MJ, Westermark P. Amyloid fibril proteins and amyloidosis: chemical identification and clinical classification International Society of Amyloidosis 2016 Nomenclature Guidelines. *Amyloid*. 2016;23(4):209–213.
- [2] González-López E, Gagliardi C, Dominguez F, Quarta CC, de Haro-Del Moral FJ, Milandri A, Salas C, Cinelli M, Cobo-Marcos M, Lorenzini M, Lara-Pezzi E, Foffi S, Alonso-Pulpon L, Rapezzi C, Garcia-Pavia P. Clinical characteristics of wild-type transthyretin cardiac amyloidosis: disproving myths. *Eur Heart J*. 2017;38(24):1895–1904.
- [3] Dharmarajan K, Maurer MS. Transthyretin cardiac amyloidosis in older North Americans. *J Am Geriatr Soc*. 2012;60:765–774.
- [4] Castaño A, Narotsky DL, Hamid N, Khalique OK, Morgenstern R, DeLuca A, Rubin J, Chiuhan C, Nazif T, Vahl T, George I, Kodali S, Leon MB, Hahn R, Bokhari S, Maurer MS. Unveiling transthyretin cardiac amyloidosis and its predictors among elderly patients with severe aortic stenosis undergoing transcatheter aortic valve replacement. *Eur Heart J*. 2017;38(38):2879–2887.
- [5] Bennani Smires Y, Victor G, Ribes D, Berry M, Cognet T, Méjean S, et al. Pilot study for left ventricular imaging phenotype of patients over 65 years old with heart failure and preserved ejection fraction: the high prevalence of amyloid cardiomyopathy. *Int J Card Imaging*. 2016;32:1403–13.
- [6] Pomerance A. Senile cardiac amyloidosis. *Br Heart J*. 1965;27(5):711–8.
- [7] Jacobson DR, Alexander AA, Tagoe C, Buxbaum JN. Prevalence of the amyloidogenic transthyretin (TTR) V122I allele in 14 333 African-Americans. *Amyloid*. 2015;22:171–174.
- [8] Pinney JH, Smith CJ, Taube JB, Lachmann HJ, Venner CP, Gibbs SD, Dunga J, Banyersad SM, Wechalekar AD, Whelan CJ, Hawkins PN, Gillmore JD. Systemic amyloidosis in England: an epidemiological study. *Br J Haematol*. 2013;161:525–532.
- [9] Sperry BW, Vranian MN, Hachamovitch R, et al. Subtype-Specific Interactions and Prognosis in cardiac Amyloidosis. *J Am Heart Assoc*. 2016;5:e002877.
- [10] Lachmann HJ, Goodman HJ, Gilbertson JA, Gallimore JR, Sabin CA, Gillmore JD, Hawkins PN. Natural history and outcome in systemic AA amyloidosis. *N Engl J Med*. 2007;356(23):2361–71.
- [11] Takayama F1, Miyazaki S, Morita T, Hirasawa Y, Niwa T. Dialysis-related amyloidosis of the heart in long-term hemodialysis patients. *Kidney Int Suppl*. 2001;78:S172–6.
- [12] Maleszewski JJ. Cardiac amyloidosis: pathology, nomenclature, and typing. *Cardiovasc Pathol*. 2015;24:343–350.
- [13] Rapezzi C, Quarta CC, Obici L, Perfetto F, Longhi S, Salvi F, Biagini E, Lorenzini M, Grigioni F, Leone O, Cappelli F, Palladini G, Rimessi P, Ferlini A, Arpesella G, Pinna AD, Merlini G, Perlini S. Disease profile and differential diagnosis of hereditary transthyretin-related amyloidosis with exclusively cardiac phenotype: an Italian perspective. *Eur Heart J*. 2013;34(7):520–8.
- [14] Ripoll-Vera T, et al. Daño cardíaco en una cohorte de pacientes con amiloidosis por transtiretina por la mutación Val30Met. *Rev Esp Cardiol*. 2017. <http://dx.doi.org/10.1016/j.recresp.2017.09.006>.
- [15] Suhr OB, Lindqvist P, Olofsson BO, et al. Myocardial hypertrophy and function are related to age at onset in familial amyloidotic polyneuropathy. *Amyloid*. 2006;13:154–9.
- [16] Buxbaum JN, Tagoe C, Gallo G, Walker JR, Kurian S, Salomon DR. Why are some amyloidosis systemic? Does hepatic “chaperoning at a distance” prevent cardiac deposition in a transgenic model of human senile systemic (transthyretin) amyloidosis? *FASEB J*. 2012; epub Feb 23.
- [17] Saelices L, Johnson LM, Liang WY, Sawaya MR, Cascio D, Ruchala P, Whitelegge J, Jiang L, Riek R, Eisenberg DS. Uncovering the mechanism of aggregation of human transthyretin. *J Biol Chem*. 2015;290(48):28932–43.
- [18] Morgan GJ, Usher GA, Kelly JW. Incomplete refolding of antibody light chains to non-native protease-sensitive conformations leads to aggregation: A mechanism of amyloidogenesis in patients? *Biochemistry*. 2017;56(50):6597–6614.
- [19] Perfetti V, Palladini G, Casarini S, et al. The repertoire of λ light chains causing predominant amyloid heart involvement and identification of a preferentially involved germline gene, IGLV1-44. *Blood*. 2012;119:144–50.
- [20] Liao R. Worming along in amyloid cardiotoxicity. *Blood*. 2014;123(23):3525–6.
- [21] Mishra S, Guan J, Plovie E, Seldin DC, Connors LH, Merlini G, Falk RH, MacRae CA, Liao R. Human amyloidogenic light chain proteins result in cardiac dysfunction, cell death, and early mortality in zebrafish. *Am J Physiol Heart Circ Physiol*. 2013;305:H95–103.
- [22] Lousada I, Comenzo RL, Landau H, et al. Light chain amyloidosis: patient experience survey from the Amyloidosis Research Consortium. *Adv Ther*. 2015;32:920–8.

- [23] Gillmore JD, Maurer MS, Falk RH, Merlini G, Damy T, Dispenzieri A, Wechalekar AD, Berk JL, Quarta CC, Grogan M, Lachmann HJ, Bokhari S, Castano A, Dorbala S, Johnson GB, Glaudemans AW, Rezk T, Fontana M, Palladini G, Milani P, Guidalotti PL, Flatman K, Lane T, Vonberg FW, Whelan CJ, Moon JC, Ruberg FL, Miller EJ, Hutt DF, Hazenberg BP, Rapezzi C, Hawkins PN. Nonbiopsy diagnosis of cardiac transthyretin amyloidosis. *Circulation*. 2016;133(24):2404–12.
- [24] Grogan M, Dispenzieri A, Gertz MA. Light-chain cardiac amyloidosis: strategies to promote early diagnosis and cardiac response. *Heart*. 2017;103(14):1065–1072.
- [25] Carroll JD, Gaasch WH, McAdam KP. Amyloid cardiomyopathy: characterization by a distinctive voltage/mass relation. *Am J Cardiol*. 1982;49:9–13.
- [26] Quarta CC. 2015. A simple voltage/mass index increases the suspicion of amyloidotic cardiomyopathy: an electrocardiographic and echocardiographic study of 767 patients with increased left ventricular wall thickness due to different causes. Doctoral Thesis Università di Bologna.
- [27] González-López E, Gagliardi C, Dominguez F, Quarta CC, de Haro-Del Moral FJ, Milandri A, Salas C, Cinelli M, Cobo-Marcos M, Lorenzini M, Lara-Pezzi E, Foffi S, Alonso-Pulpon L, Rapezzi C, Garcia-Pavia P. Clinical characteristics of wild-type transthyretin cardiac amyloidosis: disproving myths. *Eur Heart J*. 2017;38(24):1895–1904.
- [28] Longhi S, Quarta CC, Milandri A, Lorenzini M, Gagliardi C, Manuzzi L, Bacchi-Reggiani ML, Leone O, Ferlini A, Russo A, Gallelli I, Rapezzi C. Atrial fibrillation in amyloidotic cardiomyopathy: prevalence incidence risk factors and prognostic role. *Amyloid*. 2015;22(3):147–55.
- [29] Sayed RH, Rogers D, Khan F, Wechalekar AD, Lachmann HJ, Fontana M, Mahmood S, Sachchithanatham S, Patel K, Hawkins PN, Whelan CJ, Gillmore JD. A study of implanted cardiac rhythm recorders in advanced cardiac AL amyloidosis. *Eur Heart J*. 2015;36(18):1098–105.
- [30] Drayson M, Tang LX, Drew R, Mead GP, Carr-Smith H, Bradwell AR. Serum free light-chain measurements for identifying and monitoring patients with nonsecretory multiple myeloma. *Blood*. 2001;97:2900–2902.
- [31] Geller HI, Singh A, Mirto TM, Padera R, Mitchell R, Laubach JP, Falk RH. Prevalence of monoclonal gammopathy in wild-type transthyretin amyloidosis. *Mayo Clin Proc*. 2017;92(12):1800–1805.
- [32] Hutchison CA, Harding S, Hewins P, Mead GP, Townsend J, Bradwell AR, Cockwell P. Quantitative assessment of serum and urinary polyclonal free light chains in patients with chronic kidney disease. *Clin J Am Soc Nephrol*. 2008;3:1684–1690.
- [33] Brenner DA, Jain M, Pimentel DR, Wang B, Connors LH, Skinner M, Apstein CS, Liao R. Human amyloidogenic light chains directly impair cardiomyocyte function through an increase in cellular oxidant stress. *Circ Res*. 2004;94:1008–1010.
- [34] Rapezzi C, Arbustini E, Caforio AL, Charron P, Gimeno-Blanes J, Heliö T, Linhart A, Mogensen J, Pinto Y, Ristic A, Seggewiss H, Sinagra G, Tavazzi L, Elliott PM. Diagnostic work-up in cardiomyopathies: bridging the gap between clinical phenotypes and final diagnosis. A position statement from the ESC Working Group on Myocardial and Pericardial Diseases. *Eur Heart J*. 2013;34(19):1448–58.
- [35] Martinez-Naharro A, Kotecha T, Norrington K, Boldrini M, Rezk T, Quarta C, Treibel TA, Whelan CJ, Knight DS, Kellman P, Ruberg FL, Gillmore JD, Moon JC, Hawkins PN, Fontana M. Native T1 and extracellular volume in transthyretin amyloidosis. *JACC Cardiovasc Imaging*. 2018; Mar 12. pii: S1936-878X(18)30198-0.
- [36] Leone O, Veinot J, Angelini A, et al. 2011 consensus statement on endomyocardial biopsy from the Association for European Cardiovascular Pathology and the Society for Cardiovascular Pathology. *Cardiovasc Pathol*. 2012;21:245–74.
- [37] Gillmore JD, Damy T, Fontana M, Hutchinson M, Lachmann HJ, Martinez-Naharro A, Quarta CC, Rezk T, Whelan CJ, Gonzalez-Lopez E, Lane T, Gilbertson JA, Rowczenio D, Petrie A, Hawkins PN. A new staging system for cardiac transthyretin amyloidosis. *Eur Heart J*. 2017; Oct 18.
- [38] Hanson JLS, Arvanitis M, Koch CM, Berk JL, Ruberg FL, Prokaeva T, Connors LH. Use of serum transthyretin as a prognostic indicator and predictor of outcome in cardiac amyloid disease associated with wild-type transthyretin. *Circ Heart Fail*. 2018;11(2):e004000.
- [39] Kumar S, Dispenzieri A, Lacy MQ, Hayman SR, Buadi FK, Colby C, Laumann K, Zeldenrust SR, Leung N, Dingli D, Greipp PR, Lust JA, Russell SJ, Kyle RA, Rajkumar SV, Gertz MA. Revised prognostic staging system for light chain amyloidosis incorporating cardiac biomarkers and serum free light chain measurements. *J Clin Oncol*. 2012;30:989–995.
- [40] Muchtar E, Gertz MA, Kumar SK, Lin G, Boilson B, Clavell A, Lacy MQ, Buadi FK, Hayman SR, Kapoor P, Dingli D, Rajkumar SV, Dispenzieri A, Grogan M. Digoxin use in systemic light-chain (AL) amyloidosis: contra-indicated or cautious use? *Amyloid*. 2018;1–7.
- [41] Kristen AV, Kreusser MM, Blum P, Schönland SO, Frankenstein L, Dösch AO, Knop B, Helmschrott M, Schmack B, Ruhparwar A, Hegenbart U, Katus HA, Raake PWJ. Improved outcomes after heart transplantation for cardiac amyloidosis in the modern era. *J Heart Lung Transplant*. 2017; Nov 15. pii: S1053-2498(17)32116-2.
- [42] Grupper A, Park SJ, Pereira NL, Schettle SD, Gerber Y, Topilsky Y, Edwards BS, Daly RC, Stulak JM, Joyce LD, Kushwaha SS. Role of ventricular assist therapy for patients with heart failure and restrictive physiology: Improving outcomes for a lethal disease. *J Heart Lung Transplant*. 2015;34(8):1042–9.
- [43] Waddington Cruz M, Amass L, Keohane D, Schwartz J, Li H, Gundapaneni B. Early intervention with tafamidis provides long-term (5.5-year) delay of neurologic progression in transthyretin hereditary amyloid polyneuropathy. *Amyloid*. 2016;23(3):178–183.

- [44] Maurer MS, Elliott P, Merlini G, et al. Design and rationale of the phase 3 ATTR-ACT clinical trial (tafamidis in transthyretin cardiomyopathy clinical trial). *Circ Heart Fail*. 2017;10(6).
- [45] Hosoi A, Su Y, Torikai M, et al. Novel antibody for the treatment of transthyretin amyloidosis. *J Biol Chem*. 2016;291:25096–105.
- [46] Mookadam F, Smith T, Jiamsripong P, et al. Cardiac abnormalities in primary hyperoxaluria. *Circ J*. 2010;74(11):2403–9.
- [47] Kingma SD, Bodamer OA, Wijburg FA. Epidemiology and diagnosis of lysosomal storage disorders; challenges of screening. *Best Pract Res Clin Endocrinol Metab*. 2015;29(2):145–57.
- [48] Burton BK, Charrow J, Hoganson GE, Waggoner D, Tinkle B, Braddock SR, Schneider M, Grange DK, Nash C, Shryock H, Barnett R, Shao R, Basheeruddin K, Dizikes G. Newborn screening for lysosomal storage disorders in illinois: The initial 15-month experience. *J Pediatr*. 2017;190:130–135.
- [49] Juchniewicz P, Kloska A, Tyłki-Szymańska A, Jakóbkiewicz-Banecka J, Węgrzyn G, Moskot M, Gabig-Cimińska M, Piotrowska E. Female Fabry disease patients and X-chromosome inactivation. *Gene*. 2018;641:259–264.
- [50] Nakao S, Takenaka T, Maeda M, Kodama C, Tanaka A, Tahara M, et al. An atypical variant of Fabry's disease in men with left ventricular hypertrophy. *N Engl J Med*. 1995;333:288–93.
- [51] Linhart A, Kampmann C, Zamorano JL, Sunder-Plassmann G, Beck M, Mehta A, et al. Cardiac manifestations of Anderson-Fabry disease: results from the international Fabry outcome survey. *Eur Heart J*. 2007;28:1228–35.
- [52] Sheth KJ, Thomas JP. Electrocardiograms in Fabry's disease. *Jr. J Electrocardiol*. 1982;15(2):153–6.
- [53] Senechal M, Germain DP. Fabry disease: a functional and anatomical study of cardiac manifestations in 20 hemizygous male patients. *Clin Genet*. 2003;63:46–52.
- [54] Shah JS, Hughes DA, Sachdev B, et al. Prevalence and clinical significance of cardiac arrhythmia in Anderson-Fabry disease. *Am J Cardiol*. 2005;96:842–846.
- [55] von Scheidt W, Eng CM, Fitzmaurice TF, Erdmann E, Hubner G, Olsen EG, et al. An atypical variant of Fabry's disease with manifestations confined to the myocardium. *N Engl J Med*. 1991;324:395–9.
- [56] Barbey F, Qanadli SD, Juli C, Brack N, Palacek T, Rizzo E, et al. Aortic remodelling in Fabry disease. *Eur Heart J*. 2010;31:347–53.
- [57] Yeung DF, Sirrs S, Tsang MYC, Gin K, Luong C, Jue J, Nair P, Lee PK, Tsang TSM. Echocardiographic assessment of patients with Fabry disease. *J Am Soc Echocardiogr*. 2018; Mar 29. pii: S0894-7317(18)30041-5.
- [58] Calcagnino M, O'Mahony C, Coats C, Cardona M, Garcia A, Janagarajan K, Mehta A, Hughes D, Murphy E, Lachmann R, Elliott PM. Exercise-induced left ventricular outflow tract obstruction in symptomatic patients with Anderson-Fabry disease. *J Am Coll Cardiol*. 2011;58(1):88–9.
- [59] Niemann M, Breunig F, Beer M, Hu K, Liu D, Emmert A, et al. Tei index in Fabry disease. *J Am Soc Echocardiogr*. 2011;24:1026–32.
- [60] Walter TC, Knobloch G, Canaan-Kuehl S, Greiser A, Sandek A, Blaschke D, Denecke T, Hamm B, Makowski MR. Segment-by-segment assessment of left ventricular myocardial affection in Anderson-Fabry disease by non-enhanced T1-mapping. *Acta Radiol*. 2017;58(8):914–921.
- [61] Spinelli L, Imbriaco M, Nappi C, Nicolai E, Giugliano G, Ponsiglione A, Diomaiuti TC, Riccio E, Duro G, Pisani A, Trimarco B, Cuocolo A. Early cardiac involvement affects left ventricular longitudinal function in females carrying α -galactosidase a mutation: Role of hybrid positron emission tomography and magnetic resonance imaging and speckle-tracking echocardiography. *Circ Cardiovasc Imaging*. 2018;11(4):e007019.
- [62] Najafian B, Svarstad E, Bostad L, et al. Progressive podocyte injury and globotriaosylceramide (GL-3) accumulation in young patients with Fabry disease. *Kidney Int*. 2011;79:663–670.
- [63] Del Pino M, Andrés A, Bernabéu AA, de Juan-Rivera J, Fernández E, de Dios García Díaz J, Hernández D, Luño J, Fernández IM, Paniagua J, Posada de la Paz M, Rodríguez-Pérez JC, Santamaría R, Torra R, Ambros JT, Vidau P, Torregrosa JV. Fabry nephropathy: An evidence-based narrative review. *Kidney Blood Press Res*. 2018;43(2):406–421.
- [64] Wise AH, Yang A, Naik H, Stauffer C, Zeid N, Liang C, Balwani M, Desnick RJ, Alcalay RN. Parkinson's disease prevalence in Fabry disease: A survey study. *Mol Genet Metab Rep*. 2017;14:27–30.
- [65] Hilz MJ, Arbustini E, Dagna L, Gasbarrini A, Goizet C, Lacombe D, Liguori R, Manna R, Politei J, Spada M, Burlina A. Non-specific gastrointestinal features: Could it be Fabry disease? *Dig Liver Dis*. 2018; Mar 1. pii: S1590-8658(18)30209-3.
- [66] Orteu CH, Jansen T, Lidove O, et al. Fabry disease and the skin: data from FOS, the Fabry outcome survey. *Br J Dermatol*. 2007;157(2):331–7.
- [67] MacDermot KD, Holmes A, Miners AH. Anderson-Fabry disease: clinical manifestations and impact of disease in a cohort of 60 obligate carrier females. *J Med Genet*. 2001;38(11):769–75.
- [68] San Román I, Rodríguez ME, Caporossi O, Zopetti C, Sodi A, Mecocci A, López D, Rodríguez B, Gimeno JR. Computer assisted retinal vessel tortuosity evaluation in novel mutation Fabry disease: Towards New Prognostic Markers. *Retina*. 2017;37(3):592–603.
- [69] Rombach SM, Dekker N, Bouwman MG, Linthorst GE, Zwinderman AH, Wijburg FA, Kuiper S, Vd Bergh Weerman MA, Groener JE, Poorthuis BJ, Hollak CE, Aerts JM. Plasma globotriaosylsphingosine: diagnostic value and relation to clinical manifestations of Fabry disease. *Biochim Biophys Acta*. 2010;1802:741–748.

- [70] Niemann M, Rolfs A, Stork S, Bijmens B, Breunig F, Beer M, Ertl G, Wanner C, Weidemann F. Gene mutations versus clinically relevant phenotypes: lyso-Gb₃ defines Fabry disease. *Circ Cardiovasc Genet*. 2014;7:8–16.
- [71] Lavalle L, Thomas AS, Beaton B, Ebrahim H, Reed M, Ramaswami U, Elliott P, Mehta AB, Hughes DA. Phenotype and biochemical heterogeneity in late onset Fabry disease defined by N215S mutation. *PLoS One*. 2018;13(4):e0193550.
- [72] Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL, ACMG Laboratory Quality Assurance Committee. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med*. 2015;17(5):405–24.
- [73] Ortiz A, Germain DP, Desnick RJ, Politei J, Mauer M, Burlina A, Eng C, Hopkin RJ, Laney D, Linhart A, Waldek S, Wallace E, Weidemann F, Wilcox WR. Fabry disease revisited: Management and treatment recommendations for adult patients. *Mol Genet Metab*. 2018;123(4):416–427.
- [74] Hopkin RJ, Jefferies JL, Laney DA, Lawson VH, Mauer M, Taylor MR, Wilcox WR, Fabry Pediatric Expert Panel. The management and treatment of children with Fabry disease: A United States-based perspective. *Mol Genet Metab*. 2016;117(2):104–13.
- [75] Sirrs S, Bichet D, Iwanochko M, Khan A, Moore D, Oudit G, et al. 2016. Canadian Fabry disease treatment guidelines.
- [76] Ausems MG, Verbiest J, Hermans MP, Kroos MA, Beemer FA, Wokke JH, et al. Frequency of glycogen storage disease type II in the Netherlands: implications for diagnosis and genetic counselling. *Eur J Hum Genet*. 1999;7:713–716.
- [77] Chien YH, Lee NC, Thurberg BL, Chiang SC, Zhang XK, Keutzer J, et al. Pompe disease in infants: improving the prognosis by newborn screening and early treatment. *Pediatrics*. 2009;124:e1116–e1125.
- [78] Mechtler TP, Stary S, Metz TF, De Jesus VR, Greber-Platzer S, Pollak A, et al. Neonatal screening for lysosomal storage disorders: feasibility and incidence from a nationwide study in Austria. *Lancet*. 2012;379:335–341.
- [79] Pathogenic variants database from Pompe Center. <http://cluster15.erasmusmc.nl/klgn/pompe/mutations.html?lang=en>.
- [80] Lim JA, Li L, Raben N. Pompe disease: from pathophysiology to therapy and back again. *Front Aging Neurosci*. 2014;6:177.
- [81] Chen M, Zhang L, Quan S. Enzyme replacement therapy for infantile-onset Pompe disease. *Cochrane Database Syst Rev*. 2017;11:CD011539.
- [82] Tarnopolsky M, Katzberg H, Petrof BJ, Sirrs S, Sarnat HB, Myers K, Dupré N, Dodig D, Genge A, Venance SL, Korngut L, Raiman J, Khan A. Pompe Disease: Diagnosis and management. Evidence-based guidelines from a canadian expert panel. *Can J Neurol Sci*. 2016;43(4):472–85.
- [83] Charron P, Villard E, Sébillon P, Laforêt P, Maisonobe T, Duboscq-Bidot L, Romero N, Drouin-Garraud V, Frébourg T, Richard P, Eymard B, Komajda M. Danon's disease as a cause of hypertrophic cardiomyopathy: a systematic survey. *Heart*. 2004;90(8):842–6.
- [84] Nishino I, Fu J, Tanji K, Yamada T, Shimiojo S, Koori T, et al. Primary LAMP-2 deficiency causes X-linked vacuolar cardiomyopathy and myopathy (Danon disease). *Nature*. 2000;406:906–10.
- [85] D'Souza RS, Levandowski C, Slavov D, et al. Danon disease: clinical features, evaluation, and management. *Circ Heart Fail*. 2014;7:843–849.
- [86] Boucek D, Jirikowic J, Taylor M. Natural history of danon disease. *Genet Med*. 2011;13:563–568.
- [87] Sugie K, Yamamoto A, Murayama K, Oh SJ, Takahashi M, Mora M, Riggs JE, Colomer J, Iturriaga C, Meloni A, Lamperti C, Saitoh S, Byrne E, DiMauro S, Nonaka I, Hirano M, Nishino I. Clinicopathological features of genetically confirmed danon disease. *Neurology*. 2002;58:1773–1778.
- [88] Nishino I. Autophagic vacuolar myopathy. *Semin Pediatr Neurol*. 2006;13:90–95.
- [89] Yardeni M, Weisman O, Mandel H, et al. Psychiatric and cognitive characteristics of individuals with Danon disease (LAMP2 gene mutation). *Am J Med Genet Part A*. 2017;9999:1–6.
- [90] Maron BJ, Roberts WC, Arad M, Haas TS, Spirito P, Wright GB, et al. Clinical outcome and phenotypic expression in LAMP2 cardiomyopathy. *JAMA*. 2009;301:1253–9.
- [91] Konrad T, Sonnenschein S, Schmidt FP, Mollnau H, Bock K, Ocete BQ, Münzel T, Theis C, Rostock T. Cardiac arrhythmias in patients with Danon disease. *Europace*. 2017;19(7):1204–1210.
- [92] Nucifora G, Miani D, Piccoli G, Proclemer A. Cardiac Magnetic Resonance Imaging in Danon Disease. *Cardiology*. 2012;121:27–30.
- [93] Kishnani PS, Austin SL, Arn P, Bali DS, Boney A, Case LE, Chung WK, Desai DM, El-Gharbawy A, Haller R, Smit GP, Smith AD, Hobson-Webb LD, Wechsler SB, Weinstein DA, Watson MS, ACMG. Glycogen storage disease type III diagnosis and management guidelines. *Genet Med*. 2010;12(7):446–63.
- [94] Lee YC, Chang CJ, Bali D, Chen YT, Yan YT. Glycogen-branching enzyme deficiency leads to abnormal cardiac development: novel insights into glycogen storage disease IV. *Hum Mol Genet*. 2011;20(3):455–65.
- [95] Laforêt P, Richard P, Said MA, Romero NB, Lacene E, Leroy JP, Baussan C, Hogrel JY, Lavergne T, Wahbi K, Hainque B, Duboc D. A new mutation in PRKAG2 gene causing hypertrophic cardiomyopathy with conduction system disease and muscular glycogenosis. *Neuromuscul Disord*. 2006;16:178–182.
- [96] Kim M, Hunter RW, Garcia-Menendez L, Gong G, Yang YY, Kolwicz Jr SC, Xu J, Sakamoto K, Wang W, Tian. Mutation in the γ 2-subunit of AMP-activated protein kinase stimulates cardiomyocyte proliferation and hypertrophy independent of glycogen storage. *R Circ Res*. 2014;114(6):966–75.

- [97] Oliveira SM, Zhang YH, Solis RS, Isackson H, Bellahcene M, Yavari A, Pinter K, Davies JK, Ge Y, Ashrafian H, Walker JW, Carling D, Watkins H, Casadei B, Redwood C. AMP-activated protein kinase phosphorylates cardiac troponin I and alters contractility of murine ventricular myocytes. *Circ Res*. 2012;110:1192–1201.
- [98] Thevenon J, Laurent G, Ader F, Laforêt P, Klug D, Duva Pentiah A, Gouya L, Maurage CA, Kacet S, Eicher JC, Albuisson J, Desnos M, Bieth E, Duboc D, Martin L, Réant P, Picard F, Bonithon-Kopp C, Gautier E, Binquet C, Thauvin-Robinet C, Faivre L, Bouvagnet P, Charron P, Richard P. High prevalence of arrhythmic and myocardial complications in patients with cardiac glycogenosis due to PRKAG2 mutations. *Europace*. 2017;19:651–659.
- [99] Frustaci A, Russo MA, Chimenti C. Diagnostic contribution of left ventricular endomyocardial biopsy in patients with clinical phenotype of hypertrophic cardiomyopathy. *Hum Pathol*. 2013;44:133–41.
- [100] Licht M. Molecular pathogenesis of familial Wolff-Parkinson-white syndrome. *J Med Invest*. 2018;65(1.2):1–8.
- [101] Porto AG, Brun F, Severini GM, Losurdo P, Fabris E, Taylor MRG, Mestroni L, Sinagra G. Clinical spectrum of PRKAG2 syndrome. *Circ Arrhythm Electrophysiol*. 2016;9(1):e003121.
- [102] Pöyhönen P, Hiippala A, Ollila L, Kaasalainen T, Hänninen H, Heliö T, Tallila J, Vasilescu C, Kivistö S, Ojala T, Holmström M. Cardiovascular magnetic resonance findings in patients with PRKAG2 gene mutations. *J Cardiovasc Magn Reson*. 2015;17:89.
- [103] Ben Jehuda R, Eisen B, Shemer Y, Mekies LN, Szantai A, Reiter I, Cui H, Guan K, Haron-Khun S, Freimark D, Sperling SR, Gherghiceanu M, Arad M, Binah O. CRISPR correction of the PRKAG2 gene mutation in the patient's induced pluripotent stem cell-derived cardiomyocytes eliminates electrophysiological and structural abnormalities. *Heart Rhythm*. 2018;15(2):267–276.
- [104] Ramratnam M, Sharma RK, D'Auria S, Lee SJ, Wang D, Huang XY, Ahmad F. Transgenic knockdown of cardiac sodium/glucose cotransporter 1 (SGLT1) attenuates PRKAG2 cardiomyopathy, whereas transgenic overexpression of cardiac SGLT1 causes pathologic hypertrophy and dysfunction in mice. *J Am Heart Assoc*. 2014;3(4): pii: e000899.
- [105] Naqvi TZ, Luthringer D, Marchevisky A, Saouf R, Gul K, Buchbinder NA. Chloroquine-induced cardiomyopathy-echocardiographic features. *J Am Soc Echocardiogr*. 2005;18(4):383–7.
- [106] Barriales-Villa R, Gimeno-Blanes JR, Zorio-Grima E, Ripoll-Vera T, Evangelista-Masip A, Moya-Mitjans A, Serratos-Fernández L, Albert-Brotons DC, García-Pinilla JM, García-Pavía P. Plan of action for inherited cardiovascular diseases: Synthesis of recommendations and action algorithms. *Rev Esp Cardiol (Engl Ed)*. 2016;69(3):300–9.