

Rare and Ultra-Rare Diseases as Causes of Cardiomyopathy

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Abstract

Several definitions of rare disease have emphasized the low prevalence of genetic diseases that can affect cardiac tissues and cause high psychosocial suffering due to the challenging diagnostic process and the high costs of complementary tests and specific therapies. In addition, there is the need for referral centers with different medical specialists, as well as nurses, social workers, psychologists, physiotherapists, among other professionals. With the rapid advances in genetics and precision medicine, associated with the emergence of specific therapeutic molecules (orphan drugs), many rare diseases are no longer “hidden” in pages’ footnotes, and their diagnoses cannot be neglected. The first step is to understand their physiopathogenesis, clinical signs and symptoms, and complementary diagnosis tools including genotyping. This review aims to present objective and important information to contribute to the investigation of the cardiovascular involvement in some of the rare genetic diseases.

Introduction

Rare disease is a disorder that occurs with a prevalence of below 1 in 2,000 population.¹ To date, less than 8,000 different rare diseases have been described. In contrast, an ultra-rare disorder has a much more limited prevalence, corresponding to one-thousandth of rare disorders, so <1:2,000,000, according to the European definition.^{1,2} In Brazil, it is estimated that nearly 8% of the population have some type of rare disease, i.e., 11-15 million cases.³ The phenotype of some diseases develop early in the fetal period or in the first childhood causing high levels of psychosocial distress for the patient and family members, and death at an early age.³ Most patients do not have access to specific treatment, and the underdiagnosis can be attributed to lack of knowledge by healthcare professionals and unavailability of genotyping analysis in the neonatal period.^{4,5}

Keywords

Rare Diseases; Cardiomyopathies; Mucopolysaccharidoses.

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The formation of study groups, such as the Brazilian Society of Cardiology GEDORAC (*Grupos de Estudos de Doenças Raras Cardiológicas*) and referral centers for rare and ultra-rare disorders is paramount for appropriate identification, diagnosis, management (inter- and multidisciplinary) and treatment of the disease. Advances in precision medicine and the development of a growing number of molecules, the so-called “orphan drugs”, have positively impacted patients’ survival and symptom relief. In this context, while some diseases affect the cardiovascular system alone, others exhibit a multisystemic involvement, as described below.

Rare and ultra-rare diseases that lead to cardiomyopathy

Approximately 80% of rare disorders have a genetic cause, and the others are caused by infections, inflammatory conditions, and autoimmune diseases.⁶ Despite the small number of individuals affected, altogether, these conditions constitute a public health problem in the world due to high morbidity and mortality, the complexity required to reverse the symptoms and the high costs of supplies and medications.⁷

This scenario includes genetic cardiomyopathies (CMPs) such as hypertrophic CMP, amyloidosis, and lysosomal storage diseases (LSDs), such as lysosomal glycosphingolipid storage disorders (e.g. the Anderson-Fabry disease), glycogen (e.g. Pompe disease), and mucopolysaccharidoses (MPs). Clinical manifestations are due to impairment of any heart tissue, including changes in wall thickness (hypertrophy, dilatations) and in the conduction system (arrhythmias), and valvular and vascular disorders. Some physical examination findings may be characteristic and suggestive of specific diseases. However, many signs and symptoms are common to different diseases, making the diagnosis challenging for healthcare professionals (Figure 1). It is worth highlighting the importance of the cascade screening of family members, including the collection of data of the index case, pathological history of family members distributed across three or more generations. This allows the establishment of a transmission standard and the identification of possible carriers of genetic variants who do not develop the genotype.^{8,9}

Amyloidosis (Figure 2) is a systemic disease whose incidence is higher between 60 and 70 years of age, caused by deposition of amyloid proteins. The most frequent and commonly described are light chain (AL) and transthyretin (TTR) – wild-type TTR (wtTTR) or variant / hereditary TTR (vTTR). In both conditions, orthopedic manifestations including bilateral carpal tunnel syndrome are commonly seen five to ten years before amyloid CMP develops. Dysautonomic symptoms and peripheral polyneuropathy are more common in AL and

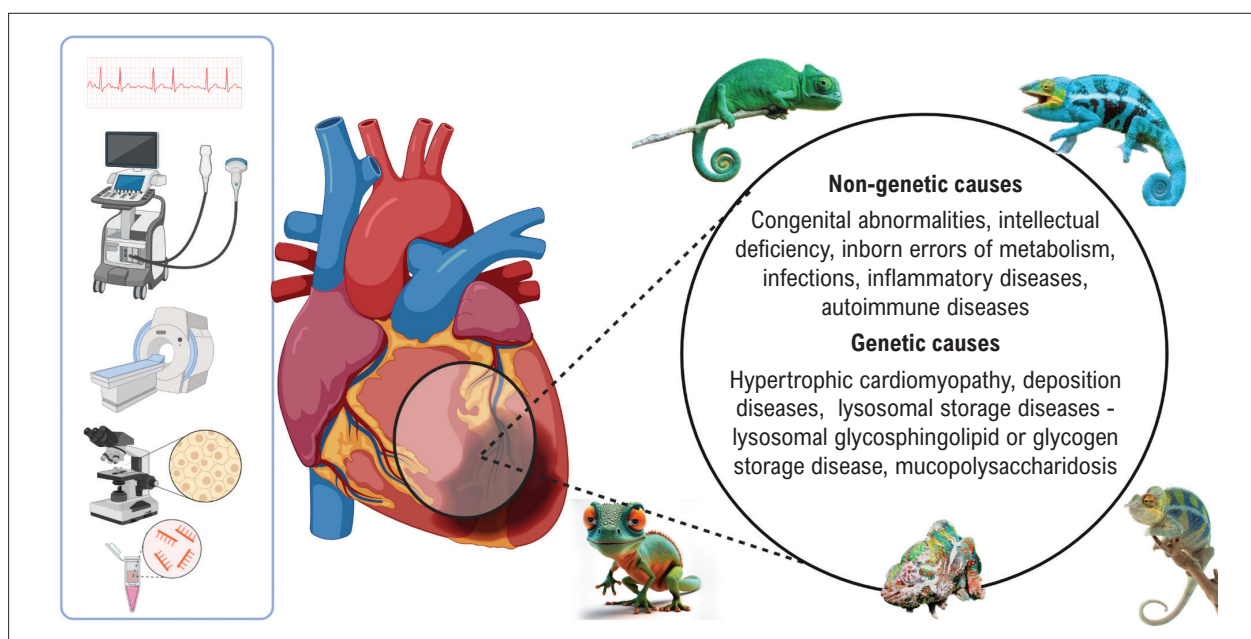


Figure 1 – Rare mycardiopathies: diagnosis, causes and phenotypes.

vTTR; in the former, the intensity of manifestations depends on gene mutation and penetrance. Dyspnea on exertion is the most common clinical manifestation and is classified as heart failure (HF) with preserved ejection fraction. Ventricular systolic dysfunction occurs at later stages and its manifestations include edema, jugular venous distention, hepatomegaly and ascites, and also symptoms of low cardiac output.¹⁰⁻¹² CMP may show variable severity, with left and right ventricular hypertrophy (thickness greater than 12mm), biatrial dilatation, pleural effusion and echocardiographic global longitudinal strain with an apical sparing (cherry on top) pattern (Figure 2). These findings diverge from the electrocardiographic parameters found in up to 80% of the cases, i.e., low-voltage QRS complex in peripheral leads and absence of R wave progression in the precordial leads, suggesting electrically inactive area (pseudoinfarcts) (Figure 2). Late gadolinium enhancement cardiovascular magnetic resonance (CMR) reveals increased diffuse subendocardial enhancement by T1 mapping.⁹⁻¹¹

Anderson Fabry disease (Figure 3) is a multisystem and LSD, linked to the X-chromosome. Deficiency of the α -galactosidase A enzyme (α -Gal A) results in the accumulation of globotriaosylceramide and globotriaosylsphingosine (lyso-GL-3) in the fetus. The symptoms may start either during childhood, known as “classic” Fabry disease, or at adult age (late onset), with predominantly cardiac or renal involvement. The most common manifestations are chronic neuropathic pain, angiokeratoma, cornea verticillate, gastrointestinal disturbances, and renal (proteinuria and renal failure) and central nervous system dysfunction (ischemia).¹² From the cardiovascular point of view, ventricular and supraventricular arrhythmias, angina due to microvascular disease, and HF symptoms (dyspnea) with preserved systolic function may occur. On electrocardiogram, there is short PR interval and signs of left ventricular overload, which differs it from amyloidosis.

On echocardiogram the earliest finding is diastolic relaxation dysfunction not explained by other causes. Hypertrophy with different morphologies, endocardial hyper-refringence (binary signal), valvular dysfunction, and aortic root ectasia. The global longitudinal strain is reduced at the expense of a decreased regional strain in the inferoposterior wall. At this same region, it is also common the presence of fibrosis on late-gadolinium enhancement magnetic resonance imaging, which usually precedes the development of hypertrophy.¹³⁻¹⁵

Pompe disease is another LSD caused by glycogen accumulation due to a deficiency of α -1,4-glucosidase, that has three forms of presentation: infantile (classic), juvenile, and adult. If not diagnosed and treated with enzyme replacement therapy (ERT) with recombinant human α glucosidase alfa, patients with classic infantile-onset Pompe disease die before one year of age due to cardiorespiratory insufficiency, and musculoskeletal and liver dysfunctions. The adult form of the disease has a more slowly progression due to a partial enzyme deficiency and hence less cardiac manifestations. However, it is marked by generalized proximal myopathy, and symptom of dyspnea caused by diaphragm dysfunction and accessory respiratory muscle weakness. The juvenile-onset type is considered an intermediate form between the two forms described.¹⁶

MPs are LSDs due to the absence of enzymes that degrade glycosaminoglycans. It has a multisystemic involvement and different phenotypes, and is characterized, from the cardiovascular standpoint, by the presence of types I, II (Figure 4) and VI heart valve diseases determined by varied phenotypes. In addition, MP patients manifest facial changes, corneal opacity repeated respiratory infections, hepatosplenomegaly, and musculoskeletal change. Specific treatment with ERT is effective in the I, II, IV and VI types, in improving clinical manifestations and long-term morbidity and mortality.¹⁷

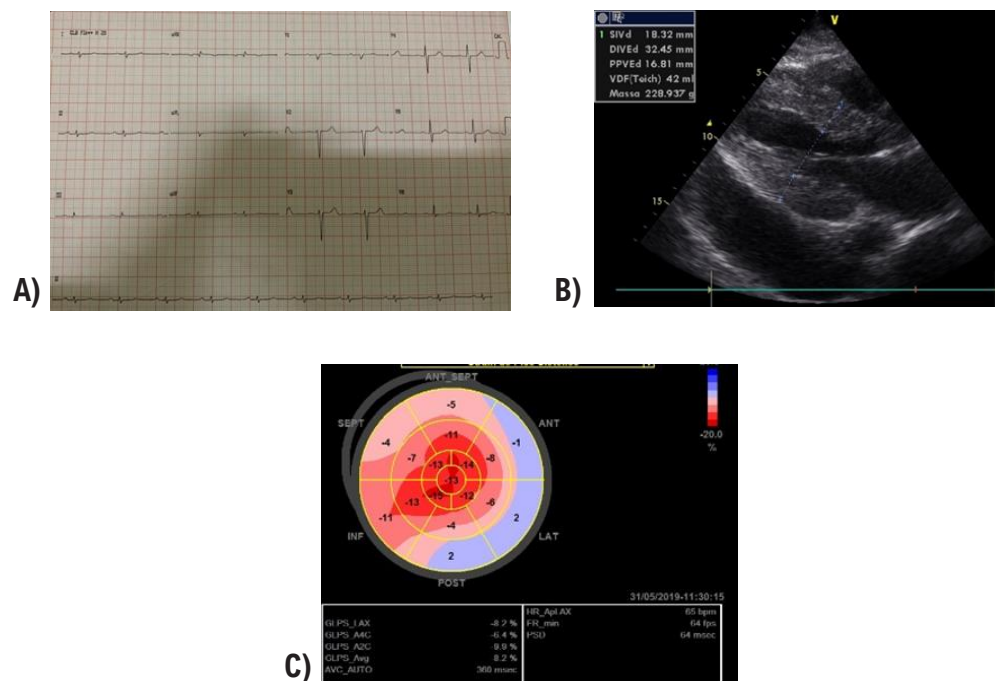


Figure 2 – A) Electrocardiogram of a patient with ATTR amyloidosis showing low voltage in peripheral leads and changes in the R-wave progression and anteroseptal wall (pseudoinfarct); B) Echocardiographic image from a parasternal longitudinal view showing left atrial dilatation, increased left ventricular wall thickness, interatrial septal and mitral valve leaflet thickening and massive pleural effusion; C) Apical sparing of the global longitudinal strain (bull's-eye map) (Source: author's database. The patient consented to the publication of the images; reproduction of images is prohibited).

Danon disease (Figure 5) is not caused by an enzyme deficiency, but by a membrane protein (LAMP2) defect, causing a glycogen storage disease type 2. It is an X-linked inherited disease, with multisystemic involvement, including musculoskeletal and retinal manifestations, and different degrees of cognitive impairment. It usually occurs earlier in men, who present concentric hypertrophic CMP that starts in childhood and rarely progresses to other forms. Cardiac conduction abnormalities (preexcitation) are common findings, with Wolff-Parkinson-White syndrome associated with ventricular and supraventricular arrhythmias. The diagnosis of Danon disease is made based on the phenotype associated with either a pathological homozygotic variant (in men) or heterozygotic (in women) of the LAMP2 gene, detected by a molecular genetic test. The hypertrophic cardiomyopathy patient without a suggestive family history exhibits an extensive myocardial fibrosis, but with no involvement of the basal mid-septum. The lack of specific therapy makes cardiac transplantation the therapeutic option for those with unfavorable prognosis.¹⁸

Primary hyperoxaluria (PH) is an inherited autosomal recessive disorder, potentially systemic, that results from the overproduction of endogenous oxalate, leading to urolithiasis, nephrocalcinosis and eventually kidney failure requiring transplant. In the heart, it manifests as infiltrative CMP, with secondary HF and severe mitral regurgitation and need for surgery. There are promising available therapies based on RNA interference that may change the natural course of the disease.^{19,20}

Autoimmune and inflammatory diseases are also among the rare and ultra-rare conditions that may cause MCPs. For example, giant cell myositis is an ultra-rare, acquired inflammatory disease that affects the skeletal muscle, causes ventricular arrhythmias, rapidly leads to HF or sudden death, and the combination of myositis with myocarditis may be fulminant and fatal. Its diagnosis depends on endomyocardial biopsy, presence of diffuse giant cells without granuloma formation. For suspected cases, immunosuppressive therapy with corticosteroids is always indicated, with a generally good response and recurrence prevention. Thymoma and orbital myositis may be associated myopathies.²¹

Chronic inflammatory myopathy, associated with antimitochondrial antibodies (AMA) with severe cardiac involvement, is a rare heterogeneous immune-mediated disease. It should always be considered in patients with myositis or inflammatory myopathy and history of severe cardiac arrhythmias, mainly in the absence of myositis-specific antibodies (polymyositis, dermatomyositis and immune-mediated necrotizing myopathies). Similarly, if AMA are detected in patients with inflammatory myopathy, screening and monitoring of cardiac disease should be performed. The diagnosis is confirmed by imaging-guided endomyocardial biopsy that may also be performed during ventricular assist device implantation; late gadolinium enhancement CMR and Positron emission tomography 18F-fluorodeoxyglucose also help in the diagnosis. Immunosuppressive therapy is a

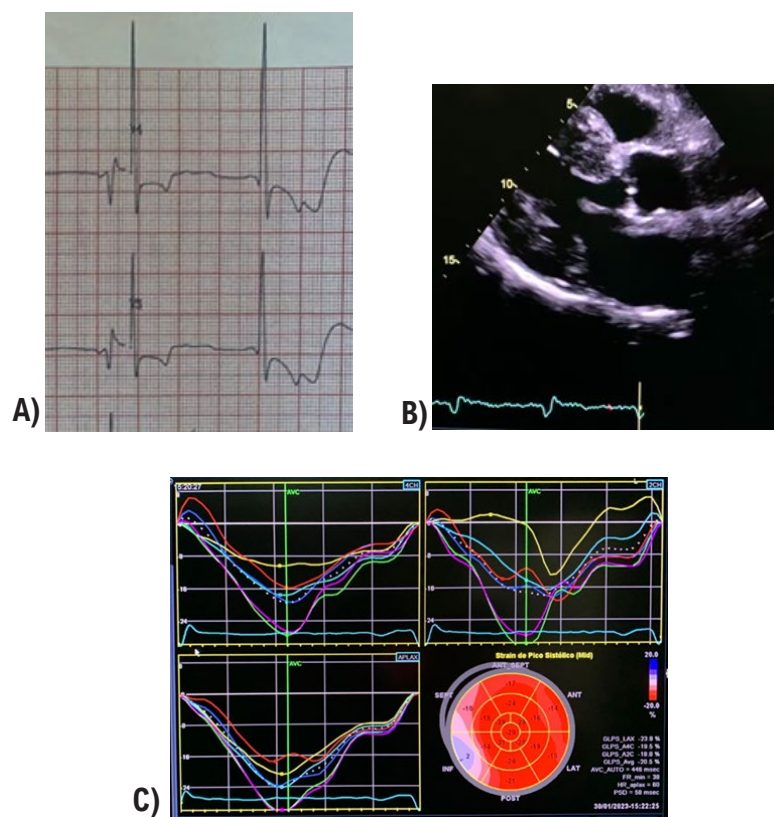


Figure 3 – A) Electrocardiogram of a patient with Anderson Fabry disease, pathogenic variant Arg356Trp of late manifestation and predominance of cardiac involvement, with a short PR interval and signs of left ventricular overload; B) Echocardiographic image from a parasternal longitudinal view showing increased left ventricular wall thickness and hyper-refractive of left ventricular endocardium (binary signal); C) Representation of a reduced global longitudinal strain (bull's-eye map) at the expense of a decreased longitudinal strain in the septal and inferior walls (Source: author's database. The patient consented to the publication of the images; reproduction of images is prohibited).

promising approach, and hence the correct recognition of this pathological entity is important for better prognosis.²²

Eosinophilic granulomatosis with polyangiitis, formerly called Churg–Strauss syndrome, is another rare inflammatory condition that exhibits eosinophilic or vasculitic mechanisms. It usually starts with asthma and sinusitis, and eight–10 years later, gastrointestinal symptoms, pulmonary infiltrate and HF due to eosinophilia are manifested. More lately, other events resulting from vasculitis, such as glomerulonephritis, palpable purpura and neuropathy can be seen, but these events are variable and may overlap. Thrombotic events have been also described. In this context, CMR is highly sensitive to detect inflammation and fibrosis. Conventional immunosuppressive therapy is not always favorable and, more recently, monoclonal antibodies have demonstrated better survival and relapse prevention.²³

Another CMP, characterized by ventricular subendocardial fibrosis, is endomyocardial fibrosis. It is a rare condition, with poor prognosis and difficult management, and commonly associated with hypereosinophilic syndrome. The relationship with hypereosinophilic endocarditis in some cases has led to the search for genetic, infectious, autoimmune, and nutritional causes, however, the etiology of endomyocardial

fibrosis remains uncertain. Although imaging methods such as echocardiography and CMR are crucial for the initial diagnosis, the definite diagnosis is established by endomyocardial biopsy. Immunosuppressive therapy is useful in the beginning of the disease and is usually ineffective if implemented at later stages, when signs of HF are present. The surgical approach is generally used for palliation only.²⁴

Multidisciplinary assessment and care

Considering the huge diversity of diseases, complexity of clinical manifestations, and the psychosocial distress of patients and family members, the multidisciplinary approach is crucial and should include different medical and healthcare specialties.²⁵

Cardiologists should not refrain from working together with geneticists, nephrologists, pediatricians, rheumatologists, ophthalmologists, or other specialists. The dialogue among specialties is paramount for a diagnostic definition, by the performance and interpretation of genetic tests, and enables an optimized therapeutic planning aimed not only at alleviating symptoms but also increasing life expectancy.

Familial screening of at least three consecutive generations and genetic counseling with reproductive/contraceptive instructions

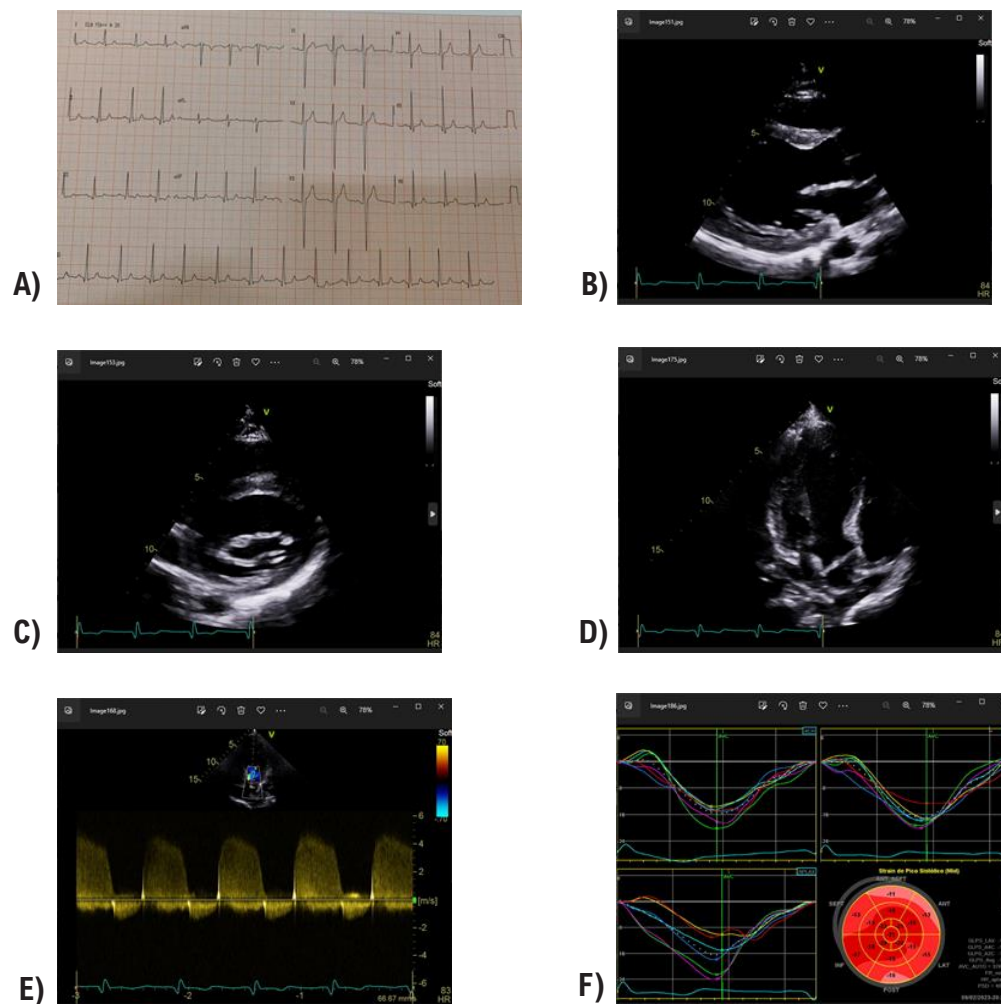


Figure 4 – A) Electrocardiogram of a patient with mucopolysaccharidosis type II showing signs of left ventricular overload associated with secondary changes of ventricular repolarization; B) Transthoracic echocardiographic image from a parasternal longitudinal showing mitral valve thickening; C) Transthoracic echocardiographic image from a cross-sectional view at the mitral valve showing thickening of the leaflets; D) Transthoracic echocardiographic image from the apical five-chamber view showing aortic leaflet thickening; E) Transthoracic echocardiographic image using continuous-wave Doppler showing moderate aortic insufficiency (PHT = 453 ms); F) Representation of a reduced global longitudinal strain (bull's-eye map) at the expense of a decreased longitudinal strain in the septal and inferior walls (Source: author's database. The patient consented to the publication of the images; reproduction of images is prohibited)

requires a trained and specialized personnel in the approach of genetic diseases. Nurses and social workers use auxiliary instruments that may aid in people tracking, personal care and drug storage.²⁶

Psychological support is fundamental not only for the index case but also for the family members affected and not affected, to overcome difficulties, that range from the delay in the diagnosis to the start of specific treatment, if available.²⁷ Finally, physiotherapy support contributes to symptom relief, improvement of physical limitations, socialization and prevention of disorders related to overweight and cardiovascular risk factors.²⁸

Role of study groups, referral centers and patient associations

In 2014, the Brazilian Ministry of Health instituted the national policy on an integral care of rare diseases, aiming at channeling financial resources to reduce mortality or improve the quality of life of people by actions for the promotion, early detection, timely treatment, reduction of disability and palliative care. This document emphasizes the importance of a multidisciplinary approach and patient follow-up by different specialties.²⁹

To diagnose and treat diseases is a challenging process for requiring different specialists with different perspectives, and expensive, complex tests that are usually available in large

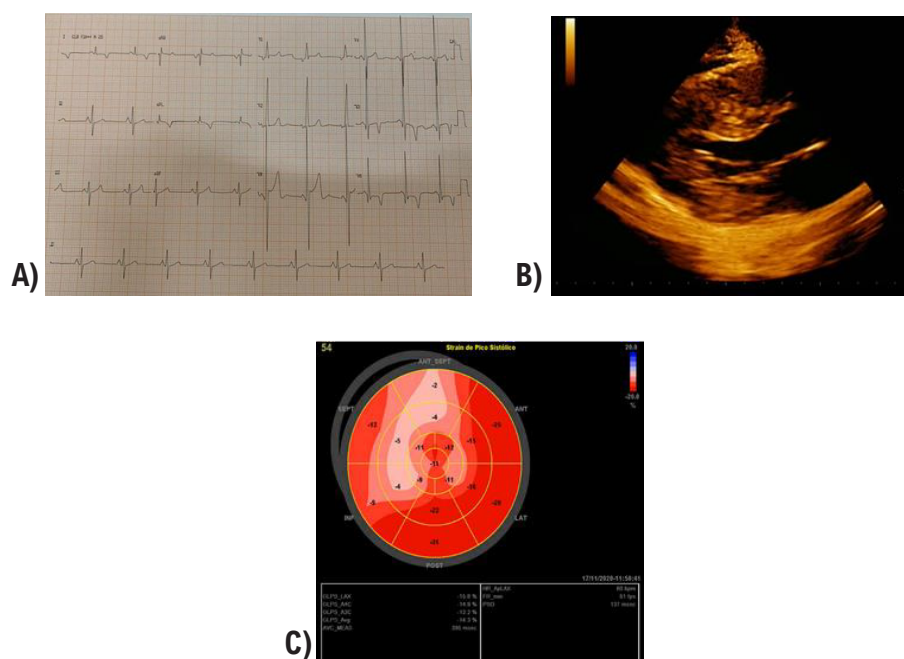


Figure 5 – A) Electrocardiogram of a patient with Danon disease, pathogenic variant Val64Asnfs*11 of late manifestation and predominance of cardiac involvement, with signs of left ventricular overload with strain; B) Echocardiographic image from a parasternal longitudinal view showing increased thickness and hyper-refringence of left ventricular wall and mitral valve leaflets; C) Representation of a reduced global longitudinal strain (bull's-eye map) at the expense of a decreased longitudinal strain in the septal and inferior walls (Source: author's database. The patient consented to the publication of the images; reproduction of images is prohibited)

centers and capital cities. The referral centers for rare disease are mostly located in the southeast and south regions of Brazil, making the access of patients specialized care difficult. Besides that, the unavailability of specific drugs capable of changing the natural course of the disease should not hamper the control of symptoms and the use of adjuvant therapies directed at reducing hospitalizations and increasing life expectancy of patients with genetic diseases. Although clinical protocols of some diseases are already available in high-cost drug pharmacies of the Brazilian Unified Health System, most diseases still lack these instruments. Consequently, there is a need for judicialization of drug prescriptions, which implicates an economic impact on health insurance and Brazilian government for the high costs and lack of budget planning for the acquisition of orphan drugs.³⁰

Medical societies have united in the support of spreading high-quality, science-based medical information through specific study groups such as the Brazilian Society of Cardiology GEDORAC and the Brazilian Society of Nephrology committee on rare diseases COMDORA. The interchange between these groups and other medical specialty societies has the potential to bring about official positionings aiming at systematizing multidisciplinary care.

Conclusion

With a better understanding about the molecular basis of monogenic myocardial diseases, further knowledge about rare genetic diseases and their incorporation into the therapeutic

horizon of cardiologists has become imperative. Advances in precision medicine with expensive, innovative therapeutic targets have changed the natural course of these entities and increased both time and quality of patient survival.

Author Contributions

Conception and design of the research; Acquisition of data; Writing of the manuscript; Critical revision of the manuscript for important intellectual content: Avila DX, Silva SM.

Potential conflict of interest

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Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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