Review Article

Phenotypic Variability of Cardiac Presentation in Danon Disease: Clinical Case Description

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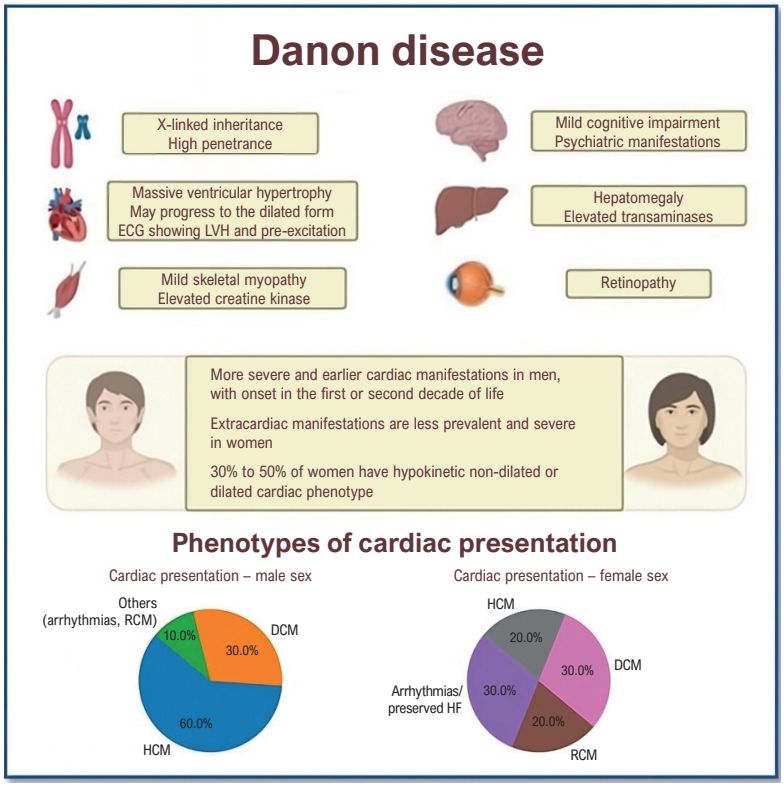
Central Illustration: Phenotypic Variability of Cardiac Presentation in Danon Disease: Clinical Case Description



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DCM: dilated cardiomyopathy; ECG: electrocardiogram; HCM: hypertrophic cardiomyopathy; HF: heart failure; LVH: left ventricular hypertrophy; RCM: restrictive cardiomyopathy.

Keywords

Glycogen Storage Disease; Restrictive Cardiomyopathy; Hypertrophic Cardiomyopathy; Dilated Cardiomyopathy

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Abstract

Danon disease is a rare genetic disorder associated with mutations in the *LAMP2* gene, located on the X chromosome, which encodes the LAMP2 protein that is essential for autophagy. The disease is characterized by a triad of cardiomyopathy, skeletal myopathy, and intellectual disability, with clinical manifestations that vary between the sexes. Men generally present with more severe and earlier forms, with hypertrophic cardiomyopathy and arrhythmias, whereas women present with later progression and less homogeneous symptoms. To illustrate the wide variety of manifestations, we report the clinical case of a young

female patient diagnosed with heart failure, progressing to heart transplantation, where a mutation in the *LAMP2* gene was identified through the anatomopathological findings of the explanted heart. The prevalence of Danon disease is uncertain, but it is believed to affect diverse ethnicities, with a higher prevalence in groups with ventricular thickening. The pathophysiology involves defective autophagy, impaired mitophagy, and oxidative stress, leading to cardiomyocyte hypertrophy and fibrosis. Diagnosis is confirmed by means of biopsy, immunohistochemistry, and genetic testing, and it is essential to assess family risk. Treatment focuses on the management already defined for heart failure and arrhythmias, with heart transplantation and ventricular assist devices as therapeutic options.

Introduction

The lysosome-associated membrane protein 2 (*LAMP2*) gene is responsible for encoding the LAMP2 protein, belonging to the LAMP family of highly homologous type I transmembrane proteins present in the membrane of lysosomes, which are responsible for the degradation of molecules, in the process known as autophagy.[1-3] Human mutations in the *LAMP2* gene encoded on the X chromosome produce a series of severe clinical manifestations that cause an entity called Danon disease, a multisystemic condition with neurological, hepatic, skeletal, and cardiac muscle abnormalities, which is responsible for up to 3% of myocardial thickening in adolescents and young adults.[1,3] LAMP2 cardiomyopathy shows ventricular hypertrophy, conduction system defects, and ventricular arrhythmias, resulting in heart failure (HF) and early death in young men and women of diverse ages (Central Illustration).[2,3] Women develop symptoms during adolescence or later, generally with more heterogeneous phenotypes, such as hypertrophic and restrictive or, less commonly, dilated cardiomyopathy. In males, the most frequently identified phenotype is hypertrophic, in up to 96% of patients, accompanied by arrhythmias, mild and slowly progressive proximal muscle weakness, leading to delays in motor development milestones, progressive visual impairment due to retinopathy, and mild intellectual disability.[1,3] The importance of this review lies in the possibility of promoting a link between the different disciplines involved in the diagnosis and management of this entity, including cardiologists, clinicians, geneticists, neurologists, pediatricians, and others, given that the heterogeneous presentation, systemic involvement, and different ages of onset require this joint work.

Clinical case

We report the case of a 25-year-old female patient with a history of New York Heart Association (NYHA) functional class II dyspnea, which had progressed for 2 years and worsened 1 month before admission. Upon admission, she presented orthopnea, palpitations, and progression to NYHA functional class III. She denied syncope and lower limb edema. Regarding family history, her mother had died suddenly without an established cause at the age of 38. She reported regular use of carvedilol 6.25 mg twice daily, enalapril 5 mg twice daily, spironolactone 25 mg once daily, furosemide 40 mg once daily, and rivaroxaban 20 mg once daily, the latter due to the presence of a thrombus in the left ventricle. She presented subjective cognitive deficit and had been hospitalized twice for HF in the past 6 months, once requiring inotropic medications. On physical examination, she presented the following vital signs: heart rate of 58 bpm, blood pressure of 80/60 mmHg, oxygen saturation of 95%, signs of congestion characterized by jugular vein distension and hepatojugular reflux, bilateral rales at the bases, and palpable hepatomegaly.

Laboratory tests showed preserved renal function, mild anemia, and BNP of 680 pg/ml. Electrocardiogram showed sinus rhythm, slow progression of R in precordial leads, short PR interval, supraventricular extrasystoles, and diffuse repolarization changes. Transthoracic echocardiogram revealed eccentric hypertrophy, dilated phenotype, 60 × 53 mm, interventricular septum of 13 mm, ejection fraction of 20%, moderate dysfunction, and presence of thrombus in the apical region (Figure 1).

Cardiac magnetic resonance imaging was performed, with the following important findings: ejection fraction of 20%, ventricular dilation of 166 × 132 ml/m^2, important right ventricular dysfunction, presence of intracavitary thrombus, and delayed enhancement, which was multifocal, mesoepicardial (non-ischemic), and diffuse in the mid-apical regions and the basal portion and more expressive in the anterior and inferior segments. There was no myocardial edema (Figure 2). The exam was interpreted as dilated cardiomyopathy, suggesting probable genetic or inflammatory etiologies.

Subsequently, due to advanced HF criteria, such as NYHA III/IV, significant biventricular dysfunction, persistently elevated BNP, 2 hospitalizations requiring inotropic drugs, and no contraindications for heart transplantation, the patient was admitted to the waiting list for heart transplantation. Approximately 50 days later, she underwent heart transplant surgery, with no major postoperative complications. Evaluation of the anatomical specimen (explanted heart) revealed cardiomyopathy with predominant biventricular hypertrophy, diffuse vacuolization of cardiomyocytes, moderate midwall fibrosis in the left ventricle, transmural fibrosis in the free wall of the right ventricle, and hypertrabeculation in the apical myocardium of the left ventricle. Periodic acid-Schiff staining showed numerous positive granules within the cardiomyocyte vacuoles. Clinical investigation regarding the possibility of glycogen storage disease was suggested. Genetic testing was performed, revealing the presence of a mutation in the *LAMP2* gene. The patient is currently in follow-up, with no graft failure, and is using immunosuppressants, with persistent cognitive deficits, as previously mentioned.

Danon disease

Danon disease is an X-linked dominant lysosomal storage disease characterized by the triad of cardiomyopathy, skeletal myopathy, and intellectual disability.[2,3] It is caused by defects in the *LAMP2* gene, which plays an important role in autophagosome-lysosome fusion in autophagy.[2,3]

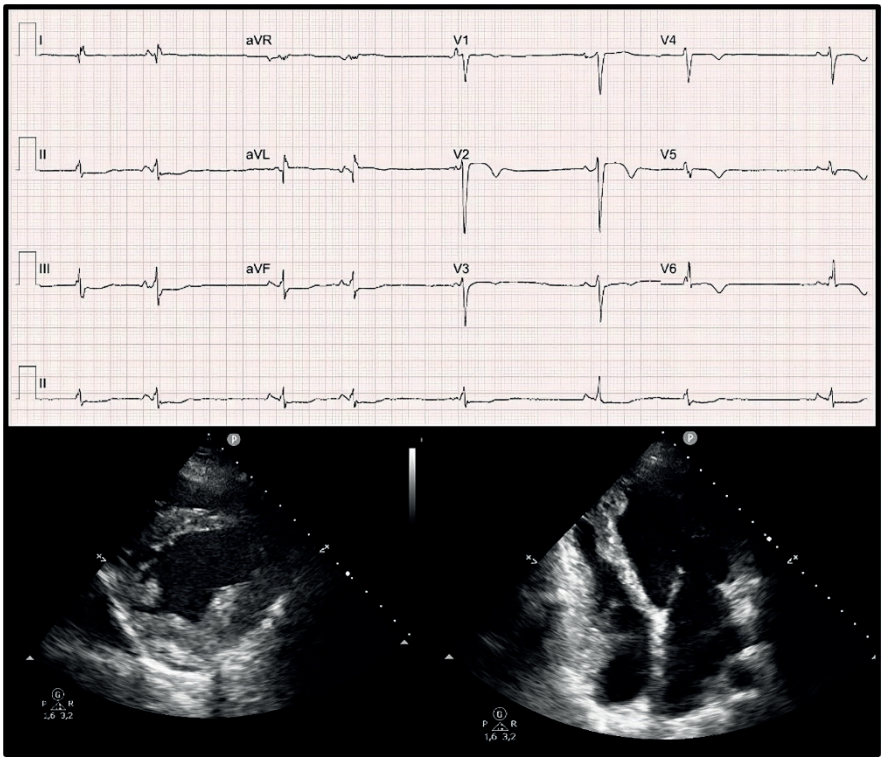

Figure 1 – *Electrocardiogram showing sinus rhythm, slow progression of R in precordial leads, short PR, supraventricular extrasystoles and diffuse repolarization alterations (top). Transthoracic echocardiogram in short-axis (left) and apical 4-chamber (right) view showing eccentric hypertrophy, dilated phenotype, 60 × 53 mm, interventricular septum 13 mm, ejection fraction of 20%, and moderate dysfunction.*

Epidemiology

Although the prevalence of Danon disease is unknown, it is believed to affect all ethnic groups. Reported prevalence rates range from 4% to 17% depending on the cohort studied, and they are higher when the group investigated presents ventricular thickening and the sample is pediatric patients.[4,5] In a cohort study that analyzed the prevalence of Danon disease in a pediatric population of 50 patients diagnosed with hypertrophic cardiomyopathy, 4% (2 of 50) were reclassified as Danon disease after genetic testing identified a mutation in *LAMP2*.[6,7] In another cohort study of pediatric patients diagnosed with hypertrophic cardiomyopathy, Danon disease was identified in 6% of the population (4 of 64).

Pathophysiology

It remains unclear whether cardiomyopathy results from reduced amounts of protein or altered activity of the mutant protein. Therefore, it is a syndrome that presents with wide heterogeneity, which may be explained by the presence of certain amounts of protein compared to those with the null allele, which has been studied in mice. Furthermore, in female patients, it may be attributed to the extension of a pattern of X-chromosome inactivation, which occurs in female cells.[2,3]

Additional mechanisms likely contribute to the development of LAMP2 cardiomyopathy. Recent studies have confirmed the critical role of defective mitophagy, oxidative stress, and energy deficiency in the pathogenesis of LAMP2 cardiomyopathy.[2,8] Intracellular vacuoles containing glycogen and other cytoplasmic components accumulate rather than being degraded and recycled for reuse by the cell, resulting

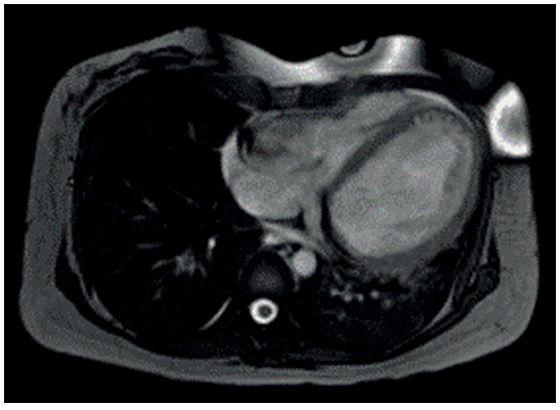

Figure 2 – *Cardiac magnetic resonance imaging showing important ventricular dilation of 166 × 132 ml/m², important right ventricular dysfunction, and important increase in left ventricular trabeculation, not meeting the criteria for noncompaction.*

in cardiomyocyte hypertrophy. Defective autophagy results in a mismatch between the supply and demand of energy and resources within cells and oxidative stress, causing cell death and diffuse fibrosis, which impairs conduction and increases susceptibility to arrhythmias.[2,3,8] Furthermore, calcium dysregulation, abnormal calcium release, and increased sensitivity to catecholamine stimulation contribute to lethal arrhythmia in LAMP2 cardiomyopathy.[2]

Clinical manifestations

Men are normally affected earlier and more severely than women, with severe cardiomyopathy requiring heart transplantation; otherwise, the disease is lethal by the mid-20s.[1,8] It is important to mention that the phenotype may migrate over time, and some patients may have initial hypertrophy, which may progress to a dilated phase depending on disease stage, hence the importance of follow-up.[9] Additional clinical manifestations include retinal disease, liver disease, neurological manifestations, and lung disease.[1,2,8] Table 1 describes the most commonly identified characteristics.

There is growing evidence that hereditary cardiomyopathies are associated with myocardial inflammation, as previously described in arrhythmogenic cardiomyopathy and Fabry disease.[10,11] It is still unclear whether mutations in cardiac proteins make cardiomyocytes more susceptible to inflammation. However, both Danon disease and severe chronic myocarditis can progress to terminal heart failure, requiring heart transplantation. In the literature, there are two documented cases in which the coexistence of Danon disease and myocarditis was demonstrated by endomyocardial biopsy, which underscores the crucial role of this test in differential diagnosis, in addition to the need for complementary imaging methods, such as cardiac magnetic resonance imaging.[12,13]

Complementary exams

Muscular biopsy reveals normal levels of acid maltase, which differentiates Danon disease from Pompe disease, a very similar genetic disorder. Immunohistochemistry reveals LAMP2 protein deficiency and accumulation of autophagic vacuoles when observed under electron microscopy.[3,14] Genetic testing may reveal a mutation in the *LAMP2* gene. Serology studies may show elevated serum creatine kinase levels approximately 2 to 3 times normal, as well as increased liver function tests.[15]

The electrocardiogram may reveal a short PR interval, with or without a delta wave, and an electrocardiographic pattern of left ventricular hypertrophy with repolarization abnormalities. As the disease progresses, supraventricular arrhythmias such as atrial flutter and fibrillation or ventricular arrhythmias may develop. Advanced atrioventricular blocks are also common. Echocardiography and cardiac magnetic resonance imaging can help characterize the degree of cardiac fibrosis, which may be a predictor of future arrhythmogenic events.[3,16] Additionally, a formal neuropsychological examination may identify intellectual disability, and retinal examination may reveal changes in retinal pigment.[3,16] Thus, there is a variety of clinical findings and complementary exams to recognize, due to the heterogeneity of the disease, as illustrated in Table 2. On the other hand, it is essential to apply clinical reasoning and knowledge of likely differential diagnoses, as shown in Figure 3.

Cardiac magnetic resonance imaging

As previously mentioned, presentation differs depending on sex. Myocardial thickening (hypertrophic phenotype) is characteristic in men; on the other hand, in women, the dilated phenotype is predominant, and the hypertrophic

Table 1 – Clinical manifestations of Danon disease

System	Clinical manifestations
Cardiovascular	Hypertrophic or dilated cardiomyopathy, heart failure, arrhythmias (such as atrial fibrillation), sudden death
Musculoskeletal	Skeletal myopathy, proximal muscle weakness, fatigue
Neurological	Learning deficits, mild to moderate intellectual disability
Ocular	Pigmentary retinopathy, visual field defects
Respiratory	Respiratory failure (secondary to muscle weakness), risk of sleep apnea
Gastrointestinal	Delayed gastric emptying, difficulty swallowing

Table 2 – Clinical and complementary findings of Danon disease

Diagnostic criteria	Complementary exams
Cardiomyopathy	Echocardiography (to assess cardiac hypertrophy/dilation) and cardiac magnetic resonance imaging
Skeletal myopathy	Physical examination and electromyography (to assess muscle weakness and skeletal muscle damage)
Pigmentary retinopathy	Ophthalmological examination and electroretinogram (to assess changes in the retina)
Mild to moderate intellectual disability	Neuropsychological assessment (to assess cognitive and learning deficits)
Family history of X-linked disease	Family tree and genetic study (analysis of the LAMP2 gene)
Increased CK and transaminase levels	Serum CPK and AST/ALT levels (to assess enzyme elevation associated with myopathy)
Presence of autophagic vacuoles on biopsy	Muscle biopsy with histopathological study (to confirm the presence of autophagic vacuoles in myocytes)
Genetic confirmation	Genetic sequencing (identification of mutations in the LAMP2 gene)

ALT: alanine aminotransferase; AST: aspartate aminotransferase; CK: creatine kinase; CPK: creatine phosphokinase.

phenotype is less frequent. The most common pattern of thickening is symmetrical and concentric, followed by an asymmetrical phenotype (with interventricular septum thickness 1.3 times greater than that of the lateral wall) in up to 38% of patients.[17,18] The majority of patients have right ventricular hypertrophy (81%). All patients with Danon disease have late enhancement, which is frequently extensive, involving a median of 35% of the ventricular mass. The most commonly described pattern is preservation of the basal to mid-interventricular septum in the majority of patients, and almost all show enhancement at the apex and lateral wall. Subendocardial involvement is the most common (87%). There is a relatively high incidence of abnormal T2 findings in male patients with Danon (62%).[17,18] Presumably, the high T2 signal in these patients reflects myocardial inflammation or edema.[18]

Although there are multiple findings that involve several organs, a flowchart shown in Figure 4 has been adapted in the attempt to simplify the diagnostic algorithm.

The role of genetic testing

The estimated prevalence of individuals with hypertrophic cardiomyopathy who harbor a pathogenic or likely pathogenic variant in the *LAMP2* gene is 1% to 4%.[19-21] In female patients, the phenotypic expression is varied, and it includes presentation as dilated cardiomyopathy. This supports the inclusion of *LAMP2* in multigene panels for common inherited cardiomyopathy in both adult and pediatric populations.[20]

Genetic testing of relatives of a patient with Danon disease is essential in order to assess risk and determine the risk of recurrence. For male patients identified as having a

Differential diagnosis	Similar clinical features	Exams for differential diagnosis
Pompe disease	Hypertrophic cardiomyopathy, proximal muscle weakness, increased CPK	Reduced *GAA* enzyme in leukocytes, specific genetic testing for *GAA* gene mutations
Duchenne muscular dystrophy	Proximal muscle weakness, increased CPK	Genetic testing for *DMD* gene mutations, muscle biopsy with absent or reduced dystrophin
Fabry disease	Cardiomyopathy, retinopathy, renal involvement, neuropathic pain	Reduced alpha-galactosidase A enzyme, genetic testing for *GLA* gene mutations
Familial hypertrophic cardiomyopathy	Cardiac hypertrophy, arrhythmias, heart failure	Genetic testing for mutations in sarcomeric genes (for example, *MYH7*, *MYBPC3*)
Glycogen storage disease type III (Cori disease)	Myopathy, hepatomegaly, elevated liver enzymes	Genetic testing for *AGL* gene mutations, assessment of glycogen storage in liver or muscle biopsy
Restrictive cardiomyopathy	Cardiac involvement with myocardial stiffness, arrhythmias	Echocardiography, cardiac MRI, cardiac biopsy to exclude other causes such as amyloidosis
Barth syndrome	Dilated cardiomyopathy, muscle weakness, delayed growth	Genetic testing for *TAZ* gene mutations
Leigh syndrome	Myopathy, progressive neurological impairment	Genetic testing for mitochondrial mutations, brain MRI for characteristic alterations
Cardiac amyloidosis	Cardiomyopathy, heart failure, arrhythmias	Cardiac biopsy with amyloid staining, pyrophosphate scintigraphy, genetic testing for *TTR* gene mutations

Figure 3 – *Differential diagnosis of Danon disease. CPK: creatine phosphokinase; MRI: magnetic resonance imaging.*

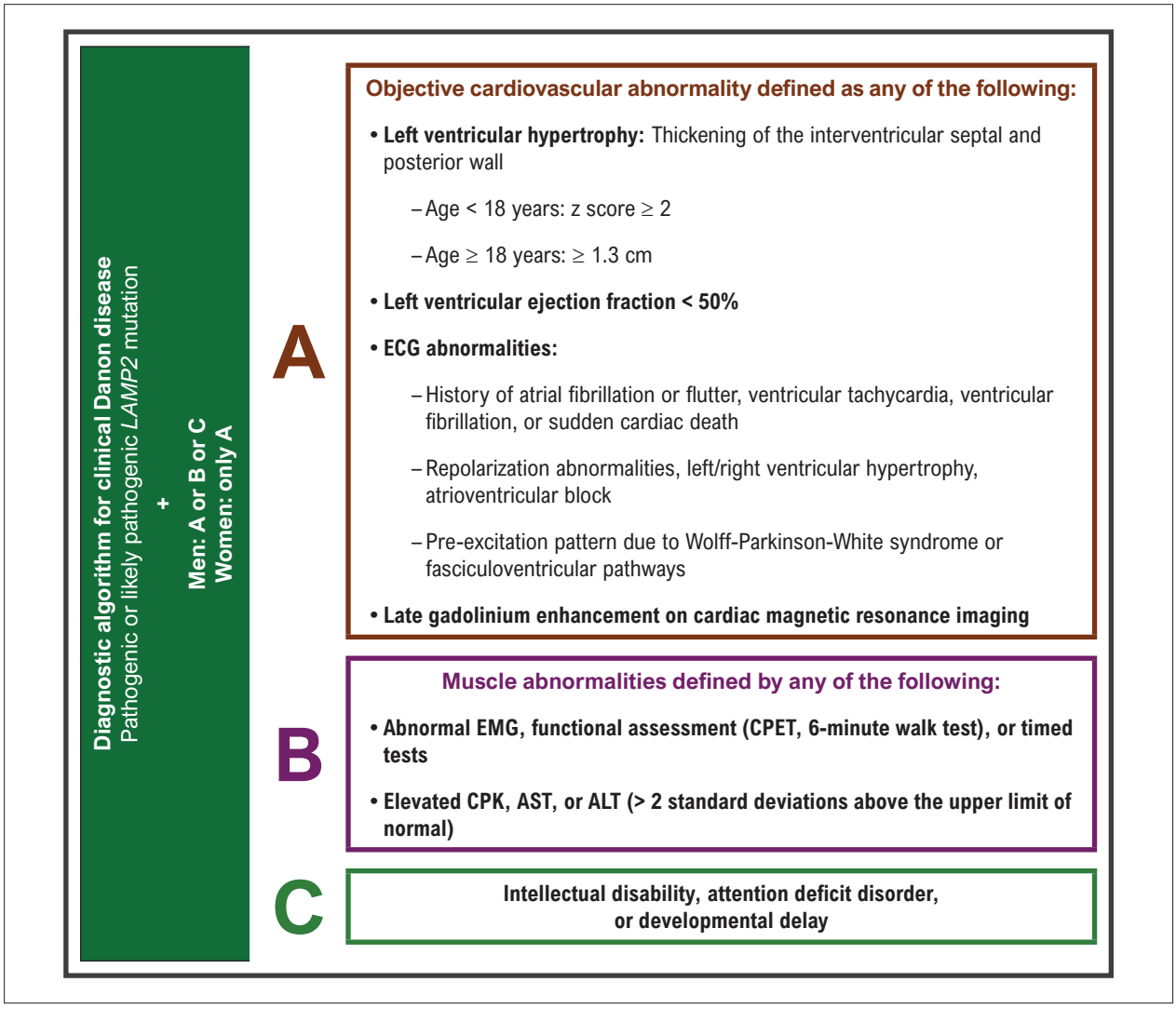

Figure 4 – *Diagnostic algorithm for Danon disease. Adapted and modified from Hong et al.19. ALT: alanine aminotransferase; AST: aspartate aminotransferase; CPET: cardiopulmonary exercise testing; CPK: creatine phosphokinase; EMG: electromyography.*

pathogenic or likely pathogenic variant in the *LAMP2* gene, only genetic testing of the patient's mother is necessary, because the affected X chromosome is maternally inherited. Negative maternal genetic testing results in these cases are compatible with a de novo mutation in the affected son.[20] The estimated de novo mutation rate for this condition is high (up to 40%), reflecting its malignant nature and negative effect on reproduction. Conversely, in female patients, both parents should be tested as soon as a pathogenic variant is identified in the affected proband.[21] It is imperative to test the affected individual's mother, and those who are identified as carrying the same pathogenic variant will have a 50% chance of transmitting that variant to existing or future offspring. Male patients with Danon disease could theoretically transmit a *LAMP2* mutation to all of their daughters. The penetrance of the disease is probably 100% in both sexes.[19-21] However, because female patients are heterozygous for the mutation, whereas males are homozygous, the disease typically presents at an earlier age in males than in females.[22] Furthermore, the genotype-phenotype correlation remains incomplete, and some cases may present with milder or exclusively cardiac involvement, depending on the location and type of mutation in the *LAMP2* gene, which underscores the diagnostic challenge and the importance of genetic testing. Alterations in the *LAMP2* gene, located in *Xq24*, are generally responsible for this condition, following an X-linked inheritance pattern.[22]

Cases of atypical presentations have been reported, which manifest exclusively with severe cardiac involvement, for example, the hemizygous deletion in the coding region of *LAMP2*, characterized by the loss of 7 nucleotides between positions 645 to 651.[22] Additionally, another hemizygous variant was found, namely, *c.35C>A* (*pSer12**), in *LAMP2*. Both have exclusive cardiac involvement, which reinforces the importance of performing genetic testing.[23]

Recommended genetic testing panels

The majority of reported cases of Danon disease are associated with nonsense, frameshift, splicing, and small indel variants detected in the *LAMP2* gene, accounting for approximately 95% of all pathogenic and likely pathogenic variants detected. A multigene next-generation sequencing panel is the rule when an individual's disease presentation is atypical, especially when presenting with isolated hypertrophic cardiomyopathy at < 15 years of age.[19-21] It is a common practice to include other common causes of hypertrophic cardiomyopathy, such as sarcomere genes (for example, *MYH7*, *MYBPC3*, *TNNT2*, *TNNI3*) and syndromic genocopies of hypertrophic cardiomyopathy, especially if diagnostic criteria are not definitively met in an affected patient.

Treatment

The treatment of Danon disease is primarily focused on cardiac manifestations. A left ventricular assist device may be implanted for cardiac output or as a bridge to transplantation, and a cardioverter-defibrillator may be used to prevent sudden cardiac death due to ventricular tachycardia.[21,24] Five-year graft survival for both male and female patients is relatively high, making cardiac transplantation an effective treatment option.[21,25] Ablation of the arrhythmogenic focus may be considered in patients with cardiac pre-excitation and ventricular arrhythmia. Although there is no specific treatment for muscle weakness, physical therapy should be attempted and may be beneficial. Similarly, supportive interventions for developmental delay or intellectual disability, retinopathy, or neuropsychiatric manifestations should be offered.[21,24]

Future perspectives

Danon disease, which has high penetrance, presents malignant development. It rapidly progresses to massive ventricular hypertrophy, heart failure, heart transplant, or sudden death in the early decades of life, especially in carriers of the male variant.[26]

Accordingly, gene therapy, which is beginning to be a possibility of precision treatment for some cardiomyopathies, brings the hope a treatment that can change the natural history of genetic cardiomyopathies that, in the absence of specific therapy, have a dismal prognosis.

A recently published phase I study evaluated the safety and efficacy of a single dose of *RP-A501*, a recombinant adeno-associated virus serotype 9 (AAV9) carrying the full-length transgene *LAMP2B*, in a sample of 7 adult and pediatric patients.[27] Efficacy analysis after a follow-up of 24 to 54 months showed symptomatic improvement in biomarkers and imaging parameters on echocardiography and cardiac magnetic resonance imaging.[27] Most adverse effects were mild or moderate and considered by the investigators to be unrelated to the infused therapy. A multicenter phase 2 study is currently ongoing (ClinicalTrials.gov number, NCT06092034).

Conclusions

Danon disease is a rare genetic condition with predominantly cardiac, muscular, and neurological clinical manifestations caused by mutations in the *LAMP2* gene. Although men present with more severe and earlier forms, women may develop symptoms later and more heterogeneously. Early diagnosis, by means of genetic testing and complementary exams, is essential for appropriate management and family monitoring. Treatment aims mainly to manage cardiac complications, and heart transplantation is an effective option for patients with advanced HF, in addition to motor physical therapy and psychological follow-up. Continuous monitoring is fundamental in order to improve quality of life and optimize clinical outcomes.

Author Contributions

Conception and design of the research, Writing of the manuscript and Critical revision of the manuscript for content: Romero CE, Fernandes F, Mesquita ET, Nunes F; Acquisition of data: Romero CE, Fernandes F, Nunes F; Analysis and interpretation of the data: Romero CE.

Potential conflict of interest

No potential conflict of interest relevant to this article was reported.

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This study is not associated with any thesis or dissertation work.

Ethics approval and consent to participate

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

References

1. Shalata A, Bar-Shai M, Hadid Y, Mahroum M, Mintz H, Shalata ZE, et al. Danon Disease: Entire LAMP2 Gene Deletion with Unusual Clinical Presentation-Case Report and Review of the Literature. Genes. 2023;14(8):1539. doi: 10.3390/genes14081539.
2. Alcalai R, Arad M, Wakimoto H, Yadin D, Gorham J, Wang L, et al. LAMP2 Cardiomyopathy: Consequences of Impaired Autophagy in the Heart. J Am Heart Assoc. 2021;10(17):e018829. doi: 10.1161/JAHA.120.018829.
3. D'Souza RS, Law L. Danon Disease. Treasure Island: StatPearls Publishing; 2025.
4. Charron P, Villard E, Sébillon P, Laforêt P, Maisonobe T, Duboscq-Bidot L, et al. Danon's Disease as a Cause of Hypertrophic Cardiomyopathy: A Systematic Survey. Heart. 2004;90(8):842-6. doi: 10.1136/hrt.2003.029504.
5. Arad M, Maron BJ, Gorham JM, Johnson WH Jr, Saul JP, Perez-Atayde AR, et al. Glycogen Storage Diseases Presenting as Hypertrophic

Cardiomyopathy. N Engl J Med. 2005;352(4):362-72. doi: 10.1056/NEJMoa033349.

6. Yang Z, McMahon CJ, Smith LR, Bersola J, Adesina AM, Breinholt JP, et al. Danon Disease as an Underrecognized Cause of Hypertrophic Cardiomyopathy in Children. Circulation. 2005;112(11):1612-7. doi: 10.1161/CIRCULATIONAHA.105.546481.

7. Fu L, Luo S, Cai S, Hong W, Guo Y, Wu J, et al. Identification of LAMP2 Mutations in Early-Onset Danon Disease with Hypertrophic Cardiomyopathy by Targeted Next-Generation Sequencing. Am J Cardiol. 2016;118(6):888-94. doi: 10.1016/j.amjcard.2016.06.037.

8. Hashem SI, Perry CN, Bauer M, Han S, Clegg SD, Ouyang K, et al. Brief Report: Oxidative Stress Mediates Cardiomyocyte Apoptosis in a Human Model of Danon Disease and Heart Failure. Stem Cells. 2015;33(7):2343-50. doi: 10.1002/stem.2015.

9. Brambatti M, Caspi O, Maolo A, Koshi E, Greenberg B, Taylor MRG, et al. Danon Disease: Gender Differences in Presentation and Outcomes. Int J Cardiol. 2019;286:92-8. doi: 10.1016/j.ijcard.2019.01.020.

10. Leone O, Pieroni M, Rapezzi C, Olivotto I. The Spectrum of Myocarditis: From Pathology to the Clinics. Virchows Arch. 2019;475(3):279-301. doi: 10.1007/s00428-019-02615-8.

11. Campuzano O, Fernández-Falgueras A, Sarquella-Brugada G, Sanchez O, Cesar S, Mademont I, et al. A Genetically Vulnerable Myocardium May Predispose to Myocarditis. J Am Coll Cardiol. 2015;66(25):2913-4. doi: 10.1016/j.jacc.2015.10.049.

12. Popa MA, Klingel K, Hadamitzky M, Deisenhofer I, Hessling G. An Unusual Case of Severe Myocarditis in a Genetic Cardiomyopathy: A Case Report. Eur Heart J Case Rep. 2020;4(4):1-7. doi: 10.1093/ehjcr/ytaa124.

13. Angulo-Lara B, Garrido-González R, Antón CS, Oteo-Domínguez JF, Segovia-Cubero J, Domínguez F. Danon Disease Presenting as Eosinophilic Myocarditis: Key Role of Endomyocardial Biopsy. JACC Case Rep. 2023;11:101765. doi: 10.1016/j.jaccas.2023.101765.

14. Balmer C, Ballhausen D, Bosshard NU, Steinmann B, Boltshauser E, Bauersfeld U, et al. Familial X-Linked Cardiomyopathy (Danon Disease): Diagnostic Confirmation by Mutation Analysis of the LAMP2gene. Eur J Pediatr. 2005;164(8):509-14. doi: 10.1007/s00431-005-1678-z.

15. Sugie K, Yamamoto A, Murayama K, Oh SJ, Takahashi M, Mora M, et al. Clinicopathological Features of Genetically Confirmed Danon Disease. Neurology. 2002;58(12):1773-8. doi: 10.1212/wnl.58.12.1773.

16. Miliou A, Antonopoulos AS, Kouris N, Lazaros G, Tsioufis K, Vlachopoulos C. Danon Cardiomyopathy: Specific Imaging Signs. JACC Case Rep. 2022;4(22):1496-500. doi: 10.1016/j.jaccas.2022.08.007.

17. Nucifora G, Miani D, Piccoli G, Proclemer A. Cardiac Magnetic Resonance Imaging in Danon Disease. Cardiology. 2012;121(1):27-30. doi: 10.1159/000336448.

18. Hanneman K. Cardiac MRI in Danon Disease: Sex-Specific Differences and Characteristic Imaging Findings. Radiology. 2021;299(2):312. doi: 10.1148/radiol.2021210249.

19. Hong KN, Eshraghian EA, Arad M, Argirò A, Brambatti M, Bui Q, et al. International Consensus on Differential Diagnosis and Management of Patients with Danon Disease: JACC State-of-the-Art Review. J Am Coll Cardiol. 2023;82(16):1628-47. doi: 10.1016/j.jacc.2023.08.014.

20. Ommen SR, Mital S, Burke MA, Day SM, Deswal A, Elliott P, et al. 2020 AHA/ACC Guideline for the Diagnosis and Treatment of Patients with Hypertrophic Cardiomyopathy: Executive Summary: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. J Am Coll Cardiol. 2020;76(25):3022-55. doi: 10.1016/j.jacc.2020.08.044.

21. Majer F, Piherova L, Reboun M, Stara V, Pelak O, Norambuena P, et al. LAMP2 Exon-Copy Number Variations in Danon Disease Heterozygote Female Probands: Infrequent or Underdetected? Am J Med Genet A. 2018;176(11):2430-4. doi: 10.1002/ajmg.a.40430.

22. Guerra EC, Beutelspacher-Fernandez K, Silva-Estrada JA, Santa-Ana-Bayona MJ, Martinez-Dominguez P, Agredano-Chavez CP, et al. Danon Disease in a 14-Year-Old: An Exclusively Cardiac Phenotype. JACC Case Rep. 2024;29(19):102603. doi: 10.1016/j.jaccas.2024.102603.

23. Sun YQ, Lv Q, Chen D, Da Y, Zhao XY, Dong JZ. A Case Study and Literature Review of the Diagnosis of Danon Disease in Patients Presenting Only with Severe Cardiac Symptoms. Pharmgenomics Pers Med. 2023;16:767-75. doi: 10.2147/PGPM.S392800.

24. Stack-Pyle TJ, Shah J, Stack L, Arcara V. Dilated Cardiomyopathy and Systolic Heart Failure in a Female Patient with Danon Disease. Cureus. 2022;14(10):e30803. doi: 10.7759/cureus.30803.

25. Hong KN, Battikha C, John S, Lin A, Bui QM, Brambatti M, et al. Cardiac Transplantation in Danon Disease. J Card Fail. 2022;28(4):664-9. doi: 10.1016/j.cardfail.2021.11.007.

26. Pieroni M, Ciabatti M, Saletti E, Tavanti V, Santangeli P, Martinese L, et al. Beyond Sarcomeric Hypertrophic Cardiomyopathy: How to Diagnose and Manage Phenocopies. Curr Cardiol Rep. 2022;24(11):1567-85. doi: 10.1007/s11886-022-01778-2.

27. Greenberg B, Taylor M, Adler E, Colan S, Ricks D, Yarabe P, et al. Phase 1 Study of AAV9.LAMP2B Gene Therapy in Danon Disease. N Engl J Med. 2024. doi: 10.1056/NEJMoa2412392. Epub ahead of print.