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CASE REPORT

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Danon disease for the cardiologist: case report and review of the literature

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ABSTRACT

Danon disease is a rare, X-linked dominant genetic disorder that is caused by defects in the lysosome-associated membrane protein 2 (LAMP2) gene. It manifests predominantly in young males with a classic triad of cardiomyopathy, skeletal myopathy, and intellectual disability. Death from cardiac disease is the ultimate cause of demise in many patients if left untreated. Given the rarity of the condition, the natural history is poorly understood. Here, we present a case report on a 14-year-old Hispanic boy with Danon disease, highlighting major clinical events and diagnostic study findings over a six-year period from age of symptom onset to age of death. He had significant hypertrophic cardiomyopathy (ventricular septal thickness 65 mm) and experienced various arrhythmias during his clinical course including Wolf-Parkinson-White syndrome, non-sustained ventricular tachycardia, and pre-excited atrial fibrillation with a fasciculoventricular anomalous accessory pathway. He had sudden cardiac death from ventricular fibrillation at age 14 and his heart had a weight of 1425 grams at autopsy. We also provide a review of the cardiac Danon disease literature related to diagnostic and management approaches to aid cardiologists in evaluating and treating cardiac manifestations in Danon disease patients.

1. Introduction

Danon disease is an X-linked dominant disorder that manifests with a classic triad of cardiomyopathy, skeletal myopathy, and intellectual disability in teenage boys [1]. It is caused by mutations in the lysosome-associated membrane protein 2 (*LAMP2*) gene [2]. While the major clinical features include skeletal and cardiac myopathy, cardiac conduction defects, and intellectual disability, other less prevalent manifestations include retinal disease [3], hepatic disease [1,4,5], and pulmonary disease [6]. Males usually manifest at an earlier age of onset (average 12.1 years old) with more severe symptoms than females (average 27.9 years old), and males invariably require heart transplantation [7]. Death from heart failure and arrhythmias are common events, arguing for low thresholds for consideration of defibrillator therapy and cardiac transplantation [8].

Danon disease is rare and the exact prevalence is unknown and the majority of published summary data on Danon disease comes from two major case series [4,7]. The disorder is likely unfamiliar to many cardiologists and has no formally established management guidelines outside of expert opinion. Multiple cases studies have been reported where cross-sectional clinical data is provided. Longitudinal data from case-reports or cohort studies are generally lacking. Here we detail a case report of a now deceased 14-year-old boy with Danon disease from age eight years, when symptoms began, until age 14 when he succumbed to his disease. This case was previously included in a case series by Maron et al. [9], although only select clinical data were reported. Here we report extensive longitudinal data from this case and also provide an overview of diagnostic and management options for the practicing cardiologist who may encounter this diagnosis.

2. Case report – initial presentation

An eight-year-old Hispanic boy presented with persistent palpitations. Past medical history included asthma, myopia, hypothyroidism, and speech delay. Family history was unremarkable for muscular dystrophies, cardiomyopathy, arrhythmias, or sudden cardiac death. On physical examination, he was hemodynamically stable. A grade 3/6 pansystolic murmur along the left lower sternal border was appreciated. Interestingly, no skeletal muscle disease was appreciated as the patient had 5/5 strength present bilaterally in upper and lower extremities.

Pertinent labs (Table 1) included elevated brain natriuretic peptide (average 5228 ± 3660 pg/mL; normal <100 pg/mL), elevated creatine kinase (average 649 ± 105 U/L; normal 94–499 U/L), elevated AST (average 363 ± 44 U/L; normal 10–40 U/L), and

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ⓘ Supplemental data for this article can be accessed here.

Table 1. Clinical laboratory values.

Laboratory test	Range	Average	Normal range
Brain Natriuretic peptide (pg/mL)	1208–9074	5228 (±3660)	<100
Total Creatine Kinase (U/L)	568–768	649 (±105)	94–499
Aspartate aminotransferase (U/L)	298–431	363(±44)	10–40
Alanine aminotransferase (U/L)	160–285	225(±47)	7–56
Total cholesterol (mg/dL)	201	-	<170
LDL cholesterol (mg/dL)	138	-	<110
TSH (U/mL)	3–53	33(±26)	0.3–5
T4, total (ug/dL)	2–7	4(±2)	4.6–12

Laboratory values are provided, consisting of a range, an average value, and standard deviation from all documented visits. A significantly elevated BNP level is consistent with heart failure; an elevated total creatine kinase level indicates skeletal myopathy. Liver function tests (AST, ALT) are elevated, which is typical in Danon disease [1,4,10–12]. Patient's thyroid function tests are consistent with hypothyroidism.

elevated ALT (average 225 ± 47 U/L; normal 7–56 U/L) levels. No troponin levels were reported. Electrocardiogram (ECG) showed a Wolf-Parkinson-White (WPW) with a left bundle branch block pattern, and peaked QRS complexes consistent with hypertrophic cardiomyopathy (Figure 1). Echocardiogram revealed hypertrophic cardiomyopathy (HCM) with initial septal thickness of 26 mm.

3. Case report – clinical course

He was started on atenolol and underwent radiofrequency ablation (RFA) of two right posterior septal accessory connections. He proved intolerant to beta-blockers due to asthma exacerbations and was transitioned to verapamil. One month post-RFA, he was admitted for syncopal episodes; telemetry revealed brief runs (<10 beats) of atrial tachycardia, and periods of prolonged PR interval with intrinsic atrioventricular conduction. His history of unexplained syncope and significant left ventricular dysfunction prompted implantation of an automatic implantable cardioverter-defibrillator (AICD).

At age 10 years, seventeen months post-AICD implantation, the AICD was triggered by atrial tachycardia and discharged (Figure 1(b)). He was also transitioned to dual-chambered pacing with the goal of decreasing left ventricular outflow tract (LVOT) obstruction (peak LVOT and mean LVOT gradient of 90 and 28 mm Hg, respectively).

At age 13 years, he was hospitalized for palpitations, dyspnea, lightheadedness, and syncope due to pre-excited atrial fibrillation, and was found to have a fasciculoventricular anomalous accessory pathway. He subsequently underwent synchronized cardioversion, but ultimately required an amiodarone drip to control his atrial fibrillation. He was transitioned to oral amiodarone, and revision of his AICD and cryoablation of the anomalous pathway were performed. However, he had progressive systolic and diastolic dysfunction as his echocardiograms revealed

severe hypertrophic cardiomyopathy with increasing septal and left ventricular (LV) wall thickness, and decreasing left ventricular ejection fraction (LVEF) over time (Figure 2). He also had high LVOT peak and mean pressure gradients that decreased over time after initiation of dual-chambered pacing. The mechanism of outflow obstruction was predominantly due to muscular apposition (direct insertion of the anterolateral papillary muscle into the anterior mitral leaflet), rather than systolic anterior motion of the mitral valve. Genetic evaluation confirmed a diagnosis of Danon disease with a *LAMP2* gene variant predicting a Y109ter truncation mutation.

At age 14 years, he experienced sudden cardiac death. Interrogation of his AICD revealed ventricular fibrillation (280/min) which persisted despite five defibrillation shocks until ICD capacity was exhausted. On autopsy, the patient's heart had a ventricular septal thickness of 65 mm and a weight of 1425 grams, exceeding all human hearts documented in the literature at that time [9]. Genotyping of family members was negative for *LAMP2* mutations, indicating that the patient had a *de novo LAMP2* mutation.

Clinical data, pathological data, and cardiac catheterization studies are displayed in Supplemental Tables 1 and 2. Additional diagnostic studies and pathological specimen visuals from this patient are noted in Maron et al. [9]

4. Systematic review of the literature

The management of cardiac manifestations in Danon disease has no consensus guidelines. We performed a systematic review to address this knowledge gap in management. Although Danon disease is unfamiliar to many practicing community cardiologists, there is increasing utilization of HCM genetic testing by the broader cardiology community. This raises the likelihood that community cardiologists will be increasingly involved in the initial molecular diagnosis of HCM, and will need to become more familiar with the role of genetic diagnosis in HCM.

5. Materials and methods

A PubMed search was completed from 1981 to January 2017 to identify articles and case reports on the cardiac manifestations, diagnostic modalities, and treatment of cardiac symptoms in Danon disease. Medical subject heading terms including 'Danon disease', 'Lysosomal Glycogen Storage Disease Without Acid Maltase Deficiency', 'Glycogen Storage Disease IIb', 'Hypertrophic cardiomyopathy guidelines', and 'Dilated cardiomyopathy guidelines' were searched. Identified articles were reviewed and related reference lists were searched to include more studies on cardiac disease management.
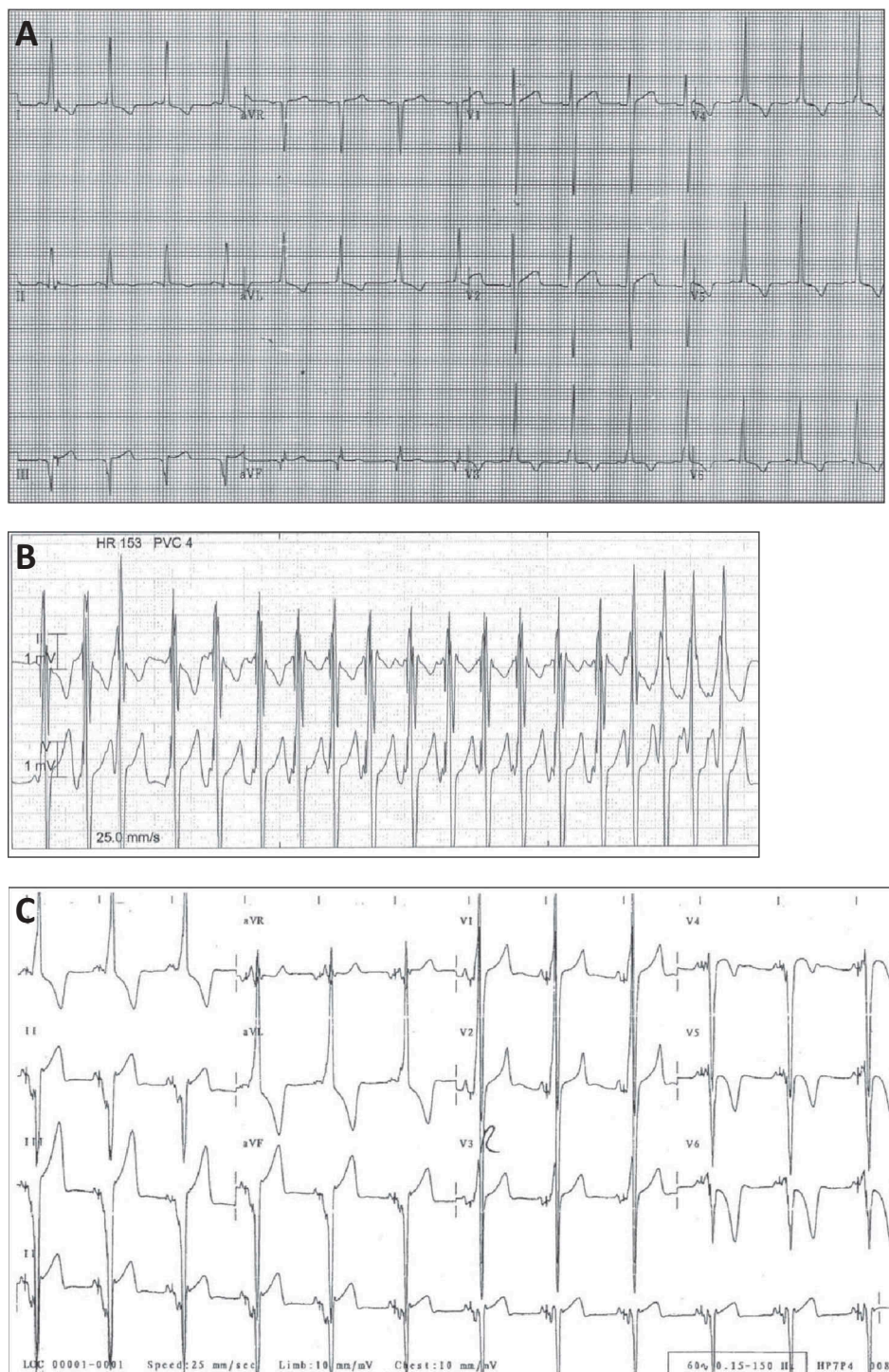
Figure 1. (a) Patient's ECG is displayed at age eight, showing normal sinus rhythm, LV hypertrophy, and T wave inversion in leads I, II, AVL, V3-V6. (b) Patient's ECG is displayed at age 10, seventeen months post-AICD implantation, showing atrial tachycardia at 125 beats per minute. (c) Patient's ECG is displayed at age 14, showing dual-paced, dual-sensed, dual-inhibited (DDD) pattern, left axis deviation, right ventricular hypertrophy, and prominent T wave inversion in leads V4-V6.

6. Epidemiology

The prevalence of Danon disease is unknown [8], but has been frequently reported in selected populations [13]. One study reported Danon disease in two of 50 (4%) pediatric patients with HCM [10], while another study found Danon disease in four of 24 patients (17%) among a subgroup with both thickened LV walls and pre-excitation on electrocardiogram [8,14]. All three criteria, including HCM, thickened LV walls, and pre-excitation were present in our case report patient. Boys are more severely affected, manifesting at an earlier age (13.3 ± 8.0 years old) compared to women (28.9 ± 14.2 years old; p = 0.0008) [7,8].

7. Cardiac manifestations

7.1. Cardiomyopathy

Males manifest with HCM early in disease [9], but may progress onto a dilated cardiomyopathy (DCM) phenotype (11–12%) [4,7]. The severity of cardiomyopathy
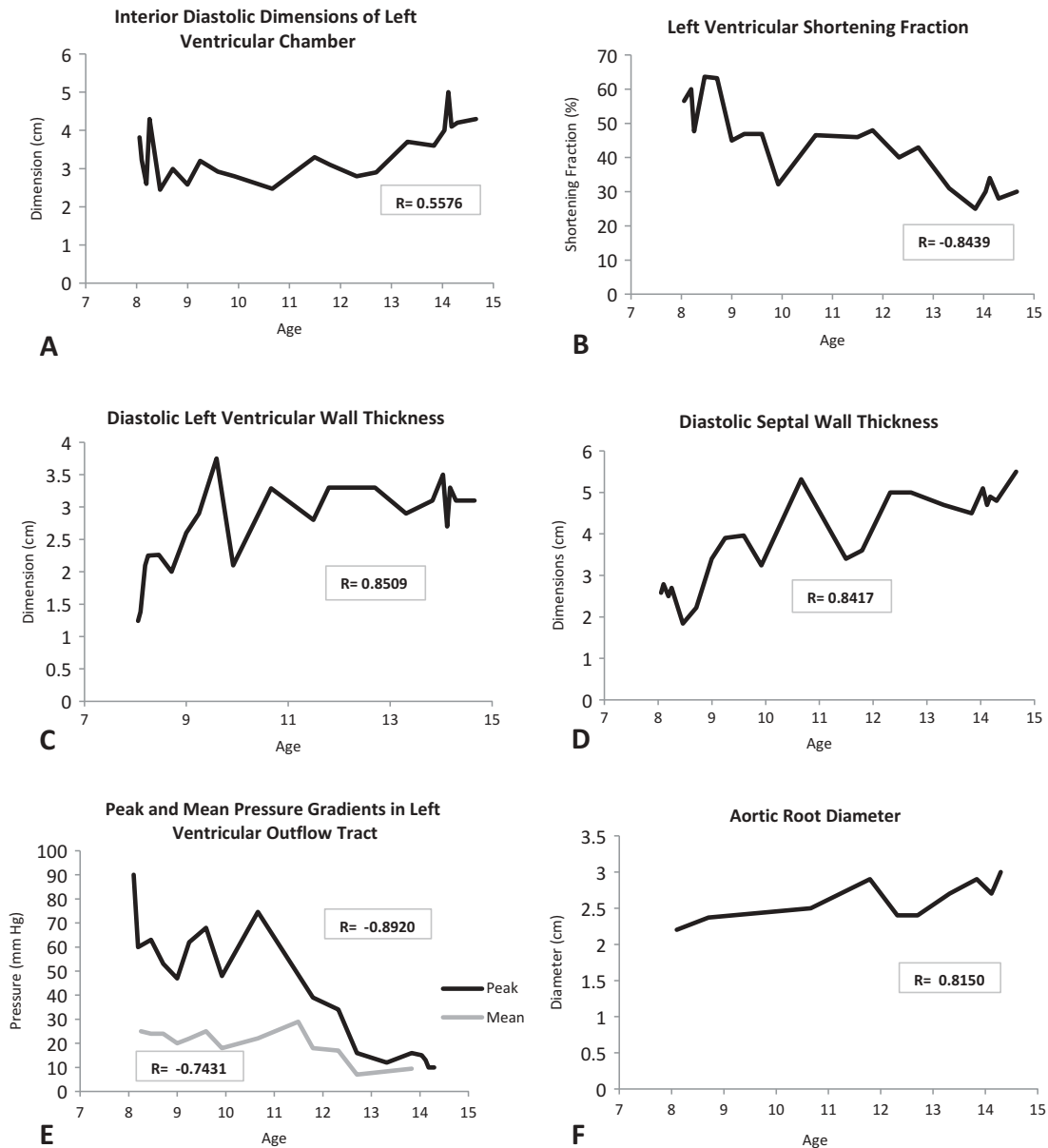
Figure 2. Echocardiographic variables are tracked over age. (a) Patient's diastolic LV interior dimensions increased over time (moderate to strong correlation; R = 0.5576). (b) LV shortening fraction decreased considerably over time, reaching a minimum of 25% (strong correlation; R = −0.8439). (c) and (d) Diastolic LV wall thickness and diastolic septal wall thickness increased over time (both strong correlation; R = 0.8509 and R = 0.8417, respectively), consistent with worsening HCM. (e) Peak and Mean LVOT gradient decreased over time (both strong correction; R = −0.8920 and −0.7431, respectively), indicating successful treatment with dual-chamber pacing. (f) Aortic root diameter increased over time (strong correlation; R = 0.8150).

is the major prognostic factor [7,8]. Most males require a heart transplant during the second to third decade of life [8]. In contrast, females may develop either DCM (28%) or HCM (33%) and cardiac transplantation in females typically occurs much later in life [7,8].

7.2. Cardiac electrical abnormalities

Electrical conduction abnormalities are very common in both males and females [4,7]. Pre-excitation with a WPW pattern is the most common ECG abnormality [7]. Both atrial and ventricular arrhythmias are typically present, as was noted in our case report patient. SCD, likely due to a ventricular arrhythmia, is the major cause of death [8,9].

8. Diagnostic guidelines

An X-linked dominant inheritance, HCM in young teenage males, HCM or DCM in adult females, and concurrent skeletal muscle weakness should prompt the clinician to investigate for Danon disease. Muscle biopsy will show normal acid maltase levels [1], immunohistochemistry will show LAMP2 protein deficiency [2], and genetic mutation analysis will reveal a *LAMP2* truncation mutation [15]. Patients typically have elevated serum creatine kinase levels [1,4,5,10,11,14], and elevated liver function tests (aspartate transaminase, alanine aminotransferase, lactate dehydrogenase) [1,4,10,12], consistent with the laboratory values in our case report patient.

9. Management guidelines

Danon disease patients may have multiple medical needs and treatment teams may include a combination of primary-care physicians, cardiologists, geneticists, neurologists, ophthalmologists, rehabilitation medicine specialists, and physical therapists [8]. Evaluation for neurocognitive problems in young boys should also be considered. Consensus management guidelines are unavailable and to date there have been no clinical trials in Danon disease. Based on the available literature, we present cardiac disease guidelines under three distinct categories: *Asymptomatic carrier with known LAMP2 mutation, symptomatic Danon disease with congestive heart failure (CHF) predominant symptoms secondary to HCM or DCM, and symptomatic Danon disease with cardiac conduction abnormalities.* A treatment algorithm is presented in Figure 3.

9.1. Management of asymptomatic patient with LAMP2 mutation

An asymptomatic patient carrying a known *LAMP2* mutation might be identified after a family history of Danon disease prompts the clinician to test other family members. This scenario typically applies to adult female patients as they manifest with symptoms at a later age (average 27.9 years old), and are mostly asymptomatic during childhood [7]. Documentation of chest pain, palpitations, and shortness of breath, and a thorough cardiac physical exam noting for murmurs and signs of heart failure are important. An initial workup to investigate degree of heart disease in asymptomatic patients is recommended, consisting of an ECG and an echocardiogram. Consideration should be given to ordering brain natriuretic peptide (BNP) levels, and Holter monitoring for arrhythmia. No specific medical or surgical intervention is necessary, but annual ECG and echocardiography are recommended.

9.2. Management of patient with congestive heart failure secondary to HCM or DCM

CHF is a major prognostic factor, and typically presents earlier in males during puberty. CHF can complicate progressive HCM in young males [9], but may also be the result of a dilated phenotype (11–12%) in later stages of disease [4,7]. Females have a nearly equal prevalence of DCM (28%) and HCM (33%) [8], and typically have adult-onset CHF. Frequent cardiac workup every six months to one year is recommended, and includes ECG, Holter Monitor, echocardiogram, and serial BNP measurements. A cardiac
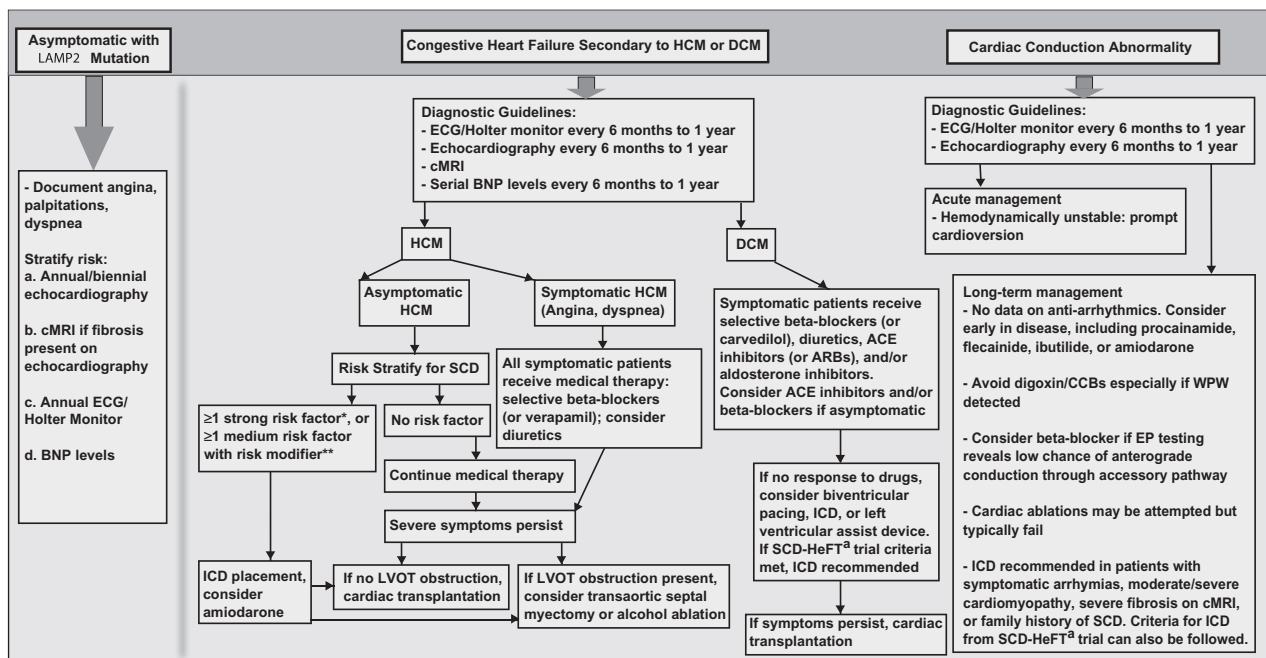

Figure 3. An algorithm is presented for managing cardiac symptoms in Danon disease.
*Risk factors from 2011 ACCF/AHA Guidelines for Diagnosis and Treatment of HCM:
history of ventricular fibrillation, sustained ventricular tachycardia, or sudden cardiac arrest (very strong risk factor)
family history of SCD (strong risk factor)episodes of unexplained syncope (strong risk factor)
Maximal ventricular wall thickness ≥30 mm (strong risk factor)
Episodes of NSVT on Holter monitoring (medium risk factor)
Failure of a systolic blood pressure response (medium risk factor)
**Risk modifiers include LVOT gradient ≥30 mm Hg, LGE on cMRI, LV apical aneurysm, and known genetic mutation.
[a]SCD-HeFT trial: Single-lead, shock-only ICD therapy is recommended for patients who classify under NYHA class II or III and have a LVEF of 35% or less.

MRI (cMRI) is recommended to assess the degree of cardiac fibrosis; a study by Miani et al. demonstrates the utility of cMRI in risk stratification for arrhythmias and SCD [16]. Consideration is given to measuring troponin levels, which may also be elevated in severe cardiomyopathy. Due to the rapidly progressive nature of Danon disease, patients with moderate to severe symptoms should have more frequent evaluations with early consideration of transplant evaluation [8]. Anecdotally, in our experience once moderate HCM is present, the progression towards cardiac transplant is more rapid than in HCM due to other genetic causes.

In Danon disease patients with HCM, clinicians may refer to the 2011 ACCF/AHA Guidelines for the Diagnosis and Treatment of HCM, with the aforementioned exception that Danon disease may have an earlier onset with more rapid progression than other forms of HCM, especially in males [8,17]. Medical management includes selective beta-blockers, with cautionary measures in the case of sinus bradycardia and severe conduction defects [17]. Verapamil therapy is used sparingly if the patient is intolerant to beta-blockers, as was documented in our case report patient [17].

Patients with HCM are also risk-stratified for SCD per 2011 ACCF/AHA guidelines (risk factors listed in Figure 3) [17–19]. The risk factors present in our case report patient included episodes of unexplained syncope, ventricular wall thickness ≥30 mm, and documented episodes of NSVT, placing him at very high risk for SCD. Clinical decisions are also guided by SCD risk modifiers (listed in Figure 3) [17]. The risk modifiers present in our case report patient included a LVOT gradient ≥30 mm Hg and presence of a known genetic mutation. The presence of a single risk factor may merit ICD placement, but the final plan should be individualized based on age, strength of risk factor, presence of risk modifiers, and adverse effects associated with ICD.

A study by Maron et al. demonstrates that sarcomeric HCM patients with a LVOT gradient ≥30 mm Hg were at increased risk of total mortality, death from heart failure or stroke, and SCD [20]. The LVOT gradient was a major target in the management of our patient; his LVOT gradient was elevated during his initial cardiac evaluation with a peak gradient of 90 mm Hg and a mean gradient of 28 mm Hg, but declined after dual-chambered pacing (See Figure 2(e)) [17,21–23].

For Danon disease patients with DCM, typically adult females, clinicians may refer to the 2016 ACC/AHA/HFSA Focused Update on New Pharmacological Therapy for Heart Failure [24]. Medical treatment includes standard heart failure medications (selective-beta blockers, angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARB) or angiotensin receptor–neprilysin inhibitors (ARNI), diuretics, and aldosterone inhibitors) [24–26]. Clinicians may refer to recommendations from the SCD-HeFT trail on determining when to initiate single-lead, shock-only ICD therapy depending on New York Heart Association (NYHA) class [27]. However, given the frequency of arrhythmias in Danon disease, early consideration of defibrillator therapy is appropriate when arrhythmias are documented, even if LVEF is preserved. Data is not available on managing asymptomatic DCM, although studies suggest that early use of ACE inhibitors and/or selective beta-blockers may slow disease progression; this is particularly applicable to Danon disease as DCM progresses more rapidly than DCM due to other causes [8,25].

Ultimately, regardless of cardiomyopathy type and severity of CHF, prompt evaluation for a heart transplant is recommended in Danon disease, especially in patients with reduced LVEF. Studies indicate that certain interventions, such as ICD implantation, are less effective in Danon disease than in other cardiac disease [9,28]. A study by Maron et al. described five of seven Danon disease patients, including the patient reported here, who failed to terminate lethal ventricular tachyarrhythmias while carrying an ICD [9]. Thus, due to the rapid progression of Danon disease and its refractory nature to medical or device interventions, early heart transplant application and evaluation is recommended. Systemic outcome data after transplantation has not been published for this rare disease, although anecdotally, males at our center have done well clinically post-transplant with minimal progression of their muscle disease (unpublished).

9.3. Management of patient with cardiac conduction abnormalities

Cardiac conduction abnormalities manifest approximately equally in men and women, with studies citing 86–100% in affected men and 80–100% in affected women [7,8]. WPW syndrome is the most common arrhythmia in Danon disease, although other conduction defects are common including atrial fibrillation, complete heart block, supraventricular tachycardia, and sinus node dysfunction. Notably, our case report presented with WPW syndrome, non-sustained ventricular tachycardia, pre-excited atrial fibrillation with a fasciculoventricular accessory pathway, and ultimately ventricular fibrillation leading to SCD. Frequent cardiac workup with ECG and/or Holter monitor, and echocardiogram is recommended.

No data from controlled trials are available on anti-arrhythmic use, but this option could be utilized early in the disease. Due to the increased occurrence of WPW pattern in Danon disease, atrioventricular nodal blocking agents (calcium channel blockers, digoxin) should be avoided because increased

anterograde transmission through the accessory pathway could cause the arrhythmia to deteriorate into ventricular fibrillation [29]. Long-term pharmacologic therapy is experiential due to paucity of clinical trials, but studies suggest beta-blocker therapy may be useful in WPW if electrophysiological (EP) testing reveals a low chance of rapid anterograde conduction through the accessory pathway [29–31]. Use of anti-arrhythmics that slow conduction through the accessory pathway have also been reported, including class Ia drugs (procainamide), class Ic drugs (flecainide), and class III drugs (amiodarone, ibutilide) [29].

Cardiac ablation of the accessory pathway is the next step in management, although this has achieved variable success in Danon disease patients [14,32,33]. This is likely due to diffuse and progressive fibrosis that is resistant to ablation therapy [8]. ICD placement is recommended in patients with symptomatic arrhythmias, moderate to severe hypertrophy, severe fibrosis on cMRI imaging, and/or family history of premature SCD [8,16]. Recommendations for ICD from the SCD-HeFT trial based on reduced LVEF may also be utilized in management [27].

10. Conclusion

Danon disease is a rare X-linked dominant genetic disorder presenting with cardiomyopathy, skeletal myopathy, and intellectual disability. Prognosis is primarily dependent on severity of cardiac disease, and many patients ultimately die from sudden cardiac death. Our case report provides longitudinal clinical data from disease onset to sudden cardiac death in a classic Danon disease patient. Our systematic review on treating cardiac manifestations in Danon disease should also aid cardiologists in managing this unfamiliar yet fatal disorder.

Disclosure statement

No potential conflict of interest was reported by the authors.

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