

Danon Disease Clinical Features, Evaluation, and Management

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Danon disease is an X-linked dominant skeletal and cardiac muscle disorder with multisystem clinical manifestations. It was first described in boys presenting with cardiomyopathy, skeletal myopathy, and varying degrees of intellectual disability.¹ As histological findings of glycogen buildup in muscle tissue similar to those seen in Pompe disease were noted, the condition was originally considered to be a lysosomal storage disease and was termed glycogen storage disease type IIb. In 2000, Nishino et al² identified the genetic defects in the lysosome-associated membrane protein 2 (*LAMP2*) gene, encoding the LAMP2 protein. Most Danon disease mutations lead to an absence of LAMP2 protein expression,² a situation more problematic in men who are hemizygous for *LAMP2*. For reasons not yet fully understood, reduction in LAMP2 disrupts intracytoplasmic trafficking and leads to accumulation of autophagic material and often glycogen in skeletal muscle and cardiac muscle cells (Figure 1).² Major clinical features include skeletal and cardiac myopathy, cardiac conduction abnormalities, mild intellectual difficulties, and retinal disease. Men are typically affected earlier and more severely than women. The disease is unfamiliar to many practitioners, and the majority of published data stem from case reports with a brief clinical review published in 2002.⁴ Our aim was to perform a systematic review of Danon disease, provide a comprehensive clinical and molecular update, and propose diagnostic and management guidelines for clinicians and researchers working with patients with Danon disease.

Materials and Methods

A literature review was performed using PubMed to identify articles and case reports in the English literature between 1981 and August 2013 on the clinical description, molecular mechanism, genetics, and treatment of Danon disease. Combinations of medical subject heading terms including Danon disease, LAMP2, Antopol disease, Lysosomal Glycogen Storage Disease Without Acid Maltase Deficiency, and Glycogen Storage Disease IIb were used. Identified articles and case reports were reviewed and the related reference lists were also searched to include additional studies.

Information on molecular mechanisms, genetic mutations, and treatment approaches for Danon disease were extracted from the

literature; end point data including age of symptom onset (cardiomyopathy or skeletal muscle weakness), age of heart transplantation, and age of death were retrieved. Mutation data were obtained from our database and the publically available Human Gene Mutation Database (<http://www.hgmd.org/>). Deidentified clinical data from our own Danon disease registry were reviewed under a protocol approved by the Colorado Multiple Institutional Review Board.

Epidemiology

The prevalence of Danon disease is unknown, and as cases have been described around the world, it can likely affect any ethnic group.⁵ The observed prevalence may be rising because of increased detection from wider availability of *LAMP2* testing included in clinical genetic cardiomyopathy gene testing panels. One study identified Danon disease in 2 of 50 pediatric patients with hypertrophic cardiomyopathy (4%).⁶ Arad et al⁷ found Danon disease in 4 of 24 patients (17%) among a subgroup with both thickened left ventricular walls and pre-excitation on ECG. In another selected population, 3 patients with Danon disease (33%) were present in a subgroup of 9 male patients with both vacuolar myopathy on muscle biopsy and hypertrophic cardiomyopathy.⁸

Molecular Mechanism

The *LAMP2* gene codes for 3 major LAMP2 protein isoforms generated by alternative splicing. The LAMP2 protein is a type 1 membrane protein predominantly located in the lysosomal compartment, and its structure consists of a large luminal domain that is heavily glycosylated, a transmembrane region, and a short carboxy-terminal cytoplasmic tail.⁹ The short LAMP-2A cytoplasmic tail is thought to serve as a receptor for uptake of certain proteins into the lysosome for degradation, a process termed chaperone-mediated autophagy.^{9,10} Interestingly, ≈2% to 3% of LAMP2 is present in the plasma membrane, and this percentage increases during malignancy and scleroderma.⁹

The LAMP2 protein isoforms, LAMP-2A, LAMP-2B, and LAMP-2C, differ only at the carboxy-terminal lysosomal transmembrane domain and at the short cytosolic tail.¹¹ Although LAMP-2A is more ubiquitously expressed, there are indications that LAMP-2B is expressed at a higher level in the heart, skeletal muscle, and brain.¹² Because of differences in the cytosolic tail and expression patterns, it is possible that each LAMP2 isoform has a unique biological role.

Different roles for the LAMP2 isoforms have been proposed in the autophagy process. Several studies have established the role of LAMP-2A in chaperone-mediated autophagy.^{10,13} More recently, the LAMP-2C protein has been implicated in novel types of autophagy,

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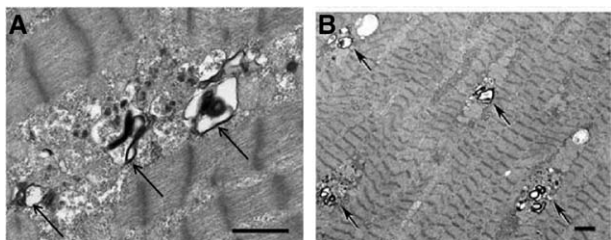


Figure 1. Histological images from skeletal muscle biopsy and endomyocardial biopsy.³ Electron microscopy shows intracytoplasmic vacuoles (arrows) containing autophagic material and glycogen in both (A) skeletal muscle (bar 1 µm) and (B) endomyocardial tissue biopsy (bar 1 µm). Reprinted from Taylor et al³ with permission of the publisher. Copyright © 2007, Nature Publishing Group. Authorization for this adaptation has been obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.

termed RNautophagy and DNautophagy, which are involved in the uptake and degradation of RNA and DNA, respectively, mainly in the brain.^{14,15}

The vast majority of *LAMP2* mutations affect all 3 isoforms, and to date, isoform-specific mutations have only been reported for the LAMP-2B isoform (c.1097–1098 delAA, c.-1137–1140 del TATA/ins GCTGGTCCCAAT, c.1150G>C, c.1201 A>G, c.1204 A>T).^{2,12,16–18} Given that all known mutations affect at least the LAMP-2B isoform, LAMP-2B deficiency seems to be a necessary and central feature to the pathogenesis of Danon disease. Further supporting this notion is the observation that the tissues most affected in Danon disease (myocardium, skeletal muscle, and brain) manifest higher LAMP-2B isoform expression.

LAMP2 Mutations

At the time of this review, 68 *LAMP2* mutations are reported in the English literature (62) and unpublished data (M.R.G. Taylor, 2013) from our registry (6; Table I in the Data Supplement; Figure 2). Although the inheritance pattern is X-linked dominant, de novo mutations have also been reported.^{6,7} The exon-skipping mutation c.928G>A (skips exon 7) is the most frequent mutation reported in the *LAMP2* gene,¹⁹ although mutations may be present in every exon. Most mutations are nonsense or frameshift mutations predicted to truncate the LAMP2 protein, resulting in absence of the transmembrane and cytoplasmic domains and likely disabling its function as a lysosomal membrane protein.² Splicing, large deletion, large duplication, insertion/deletion, and missense mutations that cause LAMP2 deficiency of all isoforms have also been described. Splicing mutations are most prevalent in exon 6 with none being reported in introns 3 or 4. Five mutations restricted to the LAMP-2B isoform have been reported to cause Danon disease.^{2,16,18}

Based on mutation and clinical data (published and unpublished from our registry), we assessed genotype–phenotype correlations (Figure 3). Mutation types (nonsense, frameshift, etc) were used as categories of genotype, whereas age of symptom onset (onset of cardiomyopathy or skeletal myopathy) was used as a measure of phenotypic severity. Of the 68 *LAMP2* mutations, 35 mutations had reported

data on age of symptom onset providing data on 73 cases. Nonsense, frameshift, and large deletion/duplication mutations showed the earliest age of onset with mean and SD of ages of symptom onset for male patients of 13.5±4.9, 12.1±8.4, and 12.3±7.5 years, respectively, and for female patients of 29.9±10.0 and 21.6±11.9 years (no case report for female patients with large deletion/duplication), respectively. Splicing mutations showed a trend of presenting later with ages of symptom onset for male and female patients of 15.4±8.1 years ($P=0.31$) and 37.3±12.3 years ($P=0.059$), respectively. Missense mutations showed the latest age of onset compared with all other mutations at 47.6±19.1 years for men ($P=0.015$; n=5 men). Interestingly, 4 of these 5 male patients were from a single family with a missense mutation restricted to the LAMP-2B isoform (c.1150 G>C),¹⁸ with an average age of onset of 54.2±13.8 years; a single female carrier in this family, formerly healthy, died suddenly at age 28 because of cardiomyopathy^{18,20} and had irregular LAMP2 protein distribution on her muscle biopsy but no clear reduction in total LAMP2 protein by Western blotting. The fifth male patient carried a Trp321Arg missense mutation common to all isoforms²¹ and leading to classic findings at age 21. These cases suggest that missense mutations, particularly those restricted to a single isoform (eg, LAMP-2B), produce a muted phenotype compared with pan-isoform protein-truncating mutations.

Clinical and Diagnostic Manifestations

Danon disease presents classically with the clinical triad of cardiomyopathy, skeletal myopathy, and intellectual disability¹ in boys. Other less prevalent symptoms may also be present, including retinal disease,^{22,23} hepatic disease^{1,8,24,25}, and pulmonary disease.²⁴ Birth and perinatal histories of patients with Danon disease are usually unremarkable. The earliest reported onset of symptoms was at age 4 months in a male patient who presented with hypotonia and cardiac failure.¹⁹ Further diagnostic examination revealed severe obstructive hypertrophic cardiomyopathy on echocardiography and marked vacuolar myopathy on muscle biopsy.¹⁹ Female patients generally present later in childhood or early adulthood and have a more protracted course. The sex differences lend themselves to later presentations in female patients, where the average ages of first symptom, cardiac transplantation, and death occur 10 to 15 years later in female patients (27.9, 33.7, and 34.6 years in female patients and 12.1, 17.9, and 19.0 years in male patients, respectively).¹⁶ Clinical features of male and female patients are described below separately due to the different ages of presentation and clinical courses by sex (Table II in the Data Supplement).

Clinical and Diagnostic Manifestations in Men

Because of haploinsufficiency of the X-linked *LAMP2* gene, male patients with *LAMP2* mutations are more severely affected than female patients and symptom onset is noted at an earlier age (13.3±8.0 years for male patients and 28.9±14.2 years for female patients; $P=0.0008$; *LAMP2* missense mutations excluded from analysis). Data extrapolated from the 2 largest case series on Danon disease show 100% of affected men having cardiomyopathy, 80% to 90% having skeletal muscle weakness, and 70% to 100% of affected men reporting some form of cognitive impairment.^{16,25} Furthermore, symptomatic respiratory disease and gastrointestinal disease were reported in 13 of 26 (50%) and 20 of 26 (77%) affected men, respectively.¹⁶

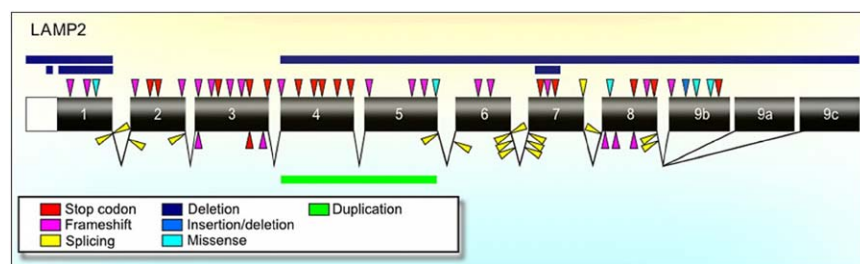


Figure 2. Lysosome-associated membrane protein 2 (*LAMP2*) mutations in Danon disease. This visual display (not to scale) includes locations of previously reported and novel *LAMP2* mutations causing Danon disease. Relative positions of mutations are reflected via arrows and bars (deletion and duplications indicated by bars only). Refer to Table I in the Data Supplement for specific mutation information.

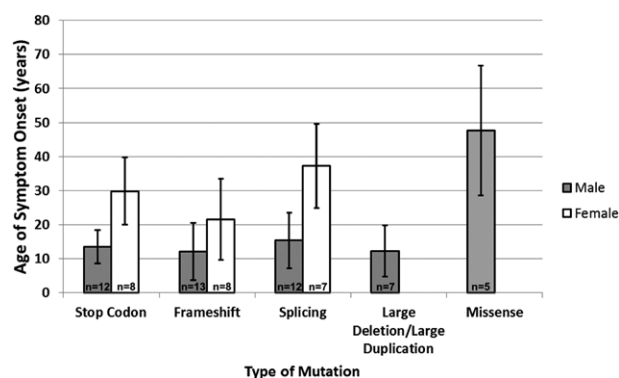


Figure 3. Genotype–phenotype correlation. Age of first symptom onset by sex and mutation type is depicted. Mutation types were used as categories of genotype, whereas age of symptom onset (usually cardiomyopathy but also included skeletal myopathy) was used as a measure of phenotype severity. The utilization of age of death as a measure of phenotype severity (not shown) displayed similar trends, although not enough cases were present in several mutation categories to assess statistical significance. n=number of patients with Danon disease.

Cardiomyopathy

Danon cardiomyopathy is progressive and typically manifests a hypertrophic phenotype, with preserved ejection fraction and normal cavity dimensions early in the course of disease,²⁶ and later progression to dilated features in 11% to 12% of men.^{16,25} Hypertrophy can be extreme, and 1 report noted the largest heart by weight ever reported in medical literature from a 14-year-old boy with a ventricular septal thickness of 65 mm and a weight of 1425 g at autopsy.²⁶ Concentric left ventricular hypertrophy may evolve into dilated cardiomyopathy during follow-up evaluations. The extent and severity of cardiomyopathy is the major prognostic factor, and cardiac transplantation may be inevitable for most men in the second and third decades.¹⁶ Postmortem examination of affected myocardium displays significant fibrosis and necrosis.²⁷ Both atrial and ventricular arrhythmias are seen. Sudden cardiac death, presumably from ventricular arrhythmia, is the ultimate cause of death in many, noted in 2 of 7 (29%) patients in 1 high-profile case series.²⁶

Cardiac Electric Abnormalities

Electric conduction abnormalities are also common, presenting in 86% to 100% of affected men.^{16,25} Pre-excitation with a Wolff–Parkinson–White (WPW) syndrome pattern is the most common ECG finding present in 69% of cases.¹⁶ Because the prevalence of WPW patterns in Danon disease is \approx 45 and 5 times greater in Danon disease than in idiopathic and familial hypertrophic cardiomyopathy, respectively, the presence of WPW pattern in a young male patient with hypertrophic cardiomyopathy strongly suggests Danon disease.²⁸ Arrhythmias and cardiac ablation procedures are common in 53% and 41%, respectively.¹⁶ The mechanism of pre-excitation anomalies is not known but could be because of myocardial hypertrophy²⁹ or directly resulting from abnormal autophagy.²⁵ Supporting the latter hypothesis are mutations in protein kinase, AMP-activated, gamma 2 non-catalytic subunit (*PRKAG2*) gene which result in impaired cellular autophagy and pre-excitation findings.³⁰ In a *PRKAG2* mouse model, Arad et al³¹ found that the annulus fibrosus, which electrically insulates the ventricles from the atria, was disrupted by glycogen-filled myocytes, suggesting that microscopic atrioventricular connections provide the anatomic substrate for ventricular pre-excitation.

Myopathy

Skeletal myopathy manifests as progressive proximal muscle weakness of the shoulders, neck, and legs¹ in 80% to 90% of men.^{16,25} Weakness is seldom debilitating, and patients usually retain the ability to walk as adults. A study utilizing a hand-held dynamometer to

measure muscle strength showed that compared with healthy men, men with Danon disease showed a significantly lower overall generalized strength with an average $60\pm 5\%$ decrease.³² Elevated serum creatine kinase levels with an average level of 944 ± 327 U/L²⁵ may be present. The relative lack of severe and progressive skeletal myopathy may contribute to the favorable rehabilitation outcomes following cardiac transplantation noted by our group (M.R.G. Taylor, unpublished data, 2013). Skeletal muscle biopsy (Figure 1A) shows intracytoplasmic vacuoles containing autophagic material and glycogen^{1,25} with absent expression of LAMP2 protein in men.

Neurological Manifestations

Learning disability and cognitive deficits were reported in 70% to 100% of affected men, although the majority was described as mild^{16,25} and affected men are able to learn to read, hold jobs, enter relationships, and usually live independently. In spite of the high prevalence of cognitive problems, a careful characterization of neurocognitive problems has not been published. One psychiatric case report on an affected 19-year-old male patient described significant psychosis, suicidal ideations, and attention-deficit hyperactivity disorder.³³ Another 38-year-old male patient transplanted 15 years previously developed depression, cognitive decline with dementing features, and severe paranoia necessitating psychiatric hospitalization (unpublished data). It is unclear currently if either psychiatric episode was related to Danon disease. Charcot–Marie–Tooth features, including pes cavus, distal lower limb atrophy with mild axonal neuropathy, and sensory loss, were also described in a 24-year-old male patient with Danon disease, suggestive of a neuropathic disease instead of a primary muscular disorder.³⁴ Other mental symptoms in male patients include speech and language delay,^{27,35} attention deficit,³³ behavioral problems,^{25,33} and dysmetria.³⁶

Retinal involvement is common, and visual problems are present in 69% of men¹⁶ who show a higher degree of ophthalmic manifestations than women,²³ including a near-complete and diffuse loss of pigment in the retinal pigment epithelium.²² Thiadens et al²⁰ reported central scotoma, serious color vision disturbances, and a cone-rod pattern of amplitude reduction on electroretinogram in male patients. Cone-rod dystrophy was also reported with a late onset but severe dystrophy (loss of photoreceptors and retinal pigment epithelium cells).²⁰

Clinical and Diagnostic Manifestations in Women

Girls and women with *LAMP2* mutations are generally less severely affected. In the 2 largest case series, 6% to 47% reported cognitive disabilities, 61% to 100% had evidence of cardiomyopathy, and 33% to 50% demonstrated skeletal muscle weakness.^{16,25}

Cardiomyopathy

In contrast to the predominantly hypertrophic cardiomyopathy phenotype in men, affected women show an approximately equal prevalence of dilated cardiomyopathy (28%) and hypertrophic cardiomyopathy (33%); eventually 18% received cardiac transplantation.¹⁶ Explanted hearts show severe interstitial fibrosis, hypertrophic cardiomyocytes with vacuolization, and myofibrillar disarray.³⁷

Cardiac Electric Abnormalities

Electric conduction abnormalities are present in 80% to 100% of affected women,^{16,25} although only 27% display WPW pattern on ECG.¹⁶ A subset of women is severely affected as demonstrated by 1 Italian family where 4 of 6 affected women died suddenly between ages 37 to 54 years. WPW pattern and atrioventricular block were present in 2 of the women, although the latter arrhythmogenic condition (atrioventricular block) may have been exacerbated by the administration of β -blocker or nondihydropyridine calcium-channel blocker medication. Approximately one third of women received cardiac ablation procedures, 31% underwent defibrillator implantation.¹⁶ It is suggested that cardiac MRI might be beneficial to detect fibrosis implying a high arrhythmogenic and sudden death risk.³⁷

Table 1. Differentiating Danon Disease From Other Vacuolar Myopathies

Condition	OMIM Number	Inheritance Pattern	Cardiomyopathy	Skeletal Myopathy	Intellectual Disability	Deposition of Complement C5b-9 on Muscle Fibers	Molecular Defect
Danon disease	300257	X-linked dominant	X	X	X		Mutation in <i>LAMP2</i> gene
Pompe disease	232300	Autosomal recessive	X	X			Mutation in <i>GAA</i> gene (reduced/absent acid maltase)
X-linked myopathy with excessive autophagy	310440	X-linked recessive		X		X	Reduced/absent VMA21 protein
X-linked congenital autophagic vacuolar myopathy	*38	X-linked recessive		X		X	Genetic locus/causative gene unknown
Infantile autophagic vacuolar myopathy	609500	X-linked recessive	X	X		X	Genetic locus/causative gene unknown
Autophagic vacuolar myopathy with late-onset and multiorgan involvement	*39	X-linked	X	X		X	Genetic locus/causative gene unknown
Glycogen storage disease of the heart, lethal congenital	261740	Autosomal recessive	X				Mutation in <i>PRKAG2</i> gene
Chloroquine-induced myopathy	†	Drug induced	X	X			Chloroquine inhibits lysosomal enzymes

Differential diagnoses and associated clinical signs in patients presenting with vacuolar myopathy are displayed. An X-linked dominant inheritance pattern, cardiomyopathy, skeletal myopathy, intellectual disability, *LAMP2* protein deficiency, confirmed *LAMP2* gene mutation, and normal acid maltase levels are clinical signs used to diagnose Danon disease. Note that not every patient with Danon disease presents with all listed clinical symptoms, and *LAMP2* protein deficiency may not always be present. However, the presence of a *LAMP2* gene mutation confirms Danon disease. *LAMP2* indicates lysosome-associated membrane protein 2.

*Online Mendelian Inheritance in Man (OMIM) number currently not present (but reference included).

†No OMIM numbers for nongenetic disorders.

Myopathy

Muscle weakness is usually mild to asymptomatic in women. A quantitative comparison of overall generalized skeletal muscle strength showed that affected women were only 30±5% weaker than healthy women.³² Furthermore, creatine kinase elevations are present in just over half of women⁵ with a mean reported value of only 106±104 U/L.¹⁶

Neurological Manifestations

Reported learning and cognitive problems are less frequent in women, whereas complaints of unspecified neuropathy and muscle cramping are higher in women.¹⁶ Visual problems were also reported in up to 64% of affected women in 1 series¹⁶ and affected women may have peripheral pigmentary retinopathy.²² In contrast to the diffuse and near-complete loss of retinal pigment in male patients, carrier female patients demonstrate a peppered and granular retinal pigment epithelium appearance, which is proposed to be due to lyonization.²²

Diagnosis and Differential Diagnosis

The differential diagnoses for Danon disease are presented in Table 1. Major clinical features that suggest and ultimately confirm Danon disease include an X-linked dominant inheritance pattern, hypertrophic cardiomyopathy in young male patients, muscle weakness, and some degree of cognitive difficulties. Supporting diagnostic studies include normal acid maltase levels on muscle biopsy¹ (or increasingly by blood-spot analysis), immunohistochemistry showing *LAMP2* protein deficiency,² autophagic vacuole accumulation by electron microscopy, and genetic mutation analysis of *LAMP2* gene.²⁷

The noninvasive nature of DNA-based methods and the inclusion of *LAMP2* gene testing in hypertrophic cardiomyopathy genetic testing panels likely favor genetic testing as the most common route to identifying Danon disease. Men show elevated serum creatine kinase levels ≈2 to 3 times the normal value.^{1,6-8,25,35,36,40,41} Liver function tests display elevated levels of aspartate transaminase, alanine aminotransferase, and lactate dehydrogenase.^{1,6,25,35,40} Hepatic synthetic function is usually normal, although hepatomegaly was reported in 5 of 14 male patients (35%) in a study.²⁵

Treatment Guidelines

Diagnostic and management guidelines for Danon disease have not been published. In Table 2, we propose therapeutic approaches for each specific clinical manifestation. Clinicians may also refer to the 2011 American College of Cardiology Foundation/American Heart Association (ACCF/AHA) Guideline for the Diagnosis and Treatment of Hypertrophic Cardiomyopathy with the caveat that Danon disease may present earlier and progress more rapidly than other forms of hypertrophic cardiomyopathy, especially in men.⁴²

Newly diagnosed patients may be best served by a team approach that includes a primary care physician in conjunction with several specialties, including cardiology, genetics, neurology, ophthalmology, rehabilitation medicine, and physical therapy. Regular cardiology evaluations are critical given the nature of the expected cardiac progression; frequently, input from both Advanced Heart Failure and Transplant and Clinical Cardiac Electrophysiology subspecialties will be beneficial. Newly diagnosed patients should typically be studied by ECG and echocardiography, along with measurements of serum natriuretic peptide levels and consideration for 24-hour Holter

Table 2. Suggested Treatment Guidelines for Danon Disease Manifestations

Manifestations	Diagnostic Testing*	Recommended Treatment
Cardiomyopathy	Echocardiography at least every 1–2 yr (more frequent as cardiac structural changes and symptoms progress or for clinical change)	Standard treatment approaches for heart failure, including
	Cardiac magnetic resonance with delayed contrast enhancement: consider in place of echocardiography to assess extent of fibrosis	Meticulous volume/fluid management, with avoidance of dehydration or overdiuresis
	ECG at least annually	Reliance on hypertrophic cardiomyopathy guidelines for patients with hypertrophy but preserved LVEF
	Holter/event monitor: if arrhythmia symptoms are present or to risk stratify for risk of sudden cardiac death	Prompt consideration for cardiac transplantation in patients with progressive symptoms or significant decrease in LVEF
	Serum BNP: consider baseline measure and for clinical change	Early involvement of electrophysiology and early consideration of ICD implantation for symptomatic arrhythmias
Skeletal myopathy	Formal neuromuscular evaluation	Physical therapy and rehabilitation
	Muscle biopsy may be performed as part of diagnostic workup	
Intellectual disability	Neuropsychological evaluation, at baseline and for clinical changes	Educational interventions as needed based on deficits Enrollment in rehabilitation center for educational, psychological, and social support
Ocular disease	Formal eye examination	Ophthalmologic referral for evidence of ocular disease
Genetic	Genetic testing of <i>LAMP2</i> gene and cascade testing of at-risk relatives	Genetic counseling, including reproductive risk counseling

BNP indicates brain natriuretic peptide; ICD, implantable cardioverter defibrillator; *LAMP2*, lysosome-associated membrane protein 2; and LVEF, left ventricular ejection fraction.

*This table is intended as a basic guide and is by no means complete or definitive. Suggested frequencies of evaluations are provided for reference and should be adjusted on the basis of individual patient symptoms and disease progression.

or event monitoring. Cardiac MRI may be sensitive for fibrotic changes that may predict higher risks of arrhythmogenic events.³⁷ Our experience is that progression of moderate hypertrophic disease can be rapid in some men, and therefore, evaluations every 3 to 6 months, including consideration of transplant evaluation, may be appropriate in patients with evidence of significant cardiac involvement. Girls and women with progressive cardiac disease should be treated similarly.

Implantable cardioverter-defibrillator therapy should be strongly considered in patients with symptomatic arrhythmias, moderate to severe hypertrophy, substantial fibrosis burden on cardiac MRI, and family history of premature sudden death.³⁷ Cardiac ablation has also achieved some success in eliminating arrhythmias in patients with Danon disease^{7,43,44}; however, anecdotally several patients in our registry have required multiple ablation procedures possibly reflecting diffuse and progressive fibrosis that is challenging to eliminate by ablation therapy.

Other symptoms in Danon disease, including skeletal myopathy, intellectual disability, and eye disease, are considered mild and not life-threatening. Physicians should aim to prevent progressive loss of muscle strength and flexibility in affected patients through standard physical therapy and light exercise. Assessment of muscle strength, particularly the proximal muscles of the shoulder, neck, and legs, should be performed during scheduled physical examination visits.

Intellectual difficulties should be anticipated and identified for early intervention. From registry data, most boys have areas of academic weakness in mathematics and reading. We suggest that comprehensive neuropsychological exams may be useful to assess other neurocognitive problems, such as attention-deficit hyperactivity and autism-spectrum disorders. Enrollment in a rehabilitation center for educational, psychological, and social support is suggested. Eye-related problems can be present in the form of choriocapillary ocular atrophy,^{6,36} diminished retinal pigmentation,^{22,23} lens changes, myopia, and abnormal visual fields,²² maculopathy,³⁴ and cone-rod dystrophy.^{20,45} A baseline

examination with a retinal specialist seems prudent with prospective ophthalmologic examinations based on initial findings.

Genetic counseling should also be offered to affected families so that they are knowledgeable about the inheritance pattern and reproductive risks. With improved survival from cardiac transplantation, the expectation is that men may be more capable of fathering children. Thus, both men and women of sufficient health and reproductive potential should be advised of the inheritance risks for *LAMP2* mutations to be transmitted to future offspring. As has been suggested previously, this may be ideally performed in centers with expertise in cardiomyopathy genetic counseling.⁴⁶

Conclusions

In summary, Danon disease is a rare cardiac and skeletal muscle disorder caused by *LAMP2* mutations and presenting with systemic symptoms of cardiomyopathy, skeletal myopathy, and intellectual disability. Symptom severity tends to be much greater in affected men, and Danon disease should be strongly suspected in young men presenting with pre-excitation and moderate to severe cardiac hypertrophy. Family history analysis may reveal affected women, and both symptomatic men and women in affected families should receive diagnostic genetic testing and case-specific therapy, particularly cardiac treatment. The literature supports that truncating mutations tend to cause more detrimental phenotypes and that the *LAMP2B* isoform may play a crucial role in Danon disease pathogenesis. In addition, along with previously published *LAMP2* mutations in Danon disease, we report novel *LAMP2* mutations from patients in our registry. Finally, the overall major goals of our proposed management guidelines include

slowing progression to heart failure, eliminating arrhythmias, slowing muscle loss and flexibility, and preventing loss of cognition. Future research efforts should investigate the role of the *LAMP2* gene in Danon disease by identifying biochemical pathways involving LAMP2 protein and describing the molecular function of each LAMP2 isoform.

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Disclosures

None.

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