International Journal of Cardiology 286 (2019) 92–98

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Danon disease: Gender differences in presentation and outcomes

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ARTICLE INFO

Article history:
Received 7 December 2018
Accepted 2 January 2019
Available online 16 February 2019

Keywords:
Danon disease
LAMP2 mutation
Hypertrophic cardiomyopathy
Dilated cardiomyopathy
Genetic testing
Gender

ABSTRACT

Background: Danon disease (DD) is a rare X-linked autophagic vacuolar myopathy, characterized by high penetrance and severe cardiomyopathy. Because of its rarity, the natural history (NH) is uncertain.
Objectives: We aimed to describe disease variability and outcomes through a systematic review of all published DD cases.
Methods: Among 83 manuscripts in MEDLINE and EMBASE on DD cases published until October 2017, we identified 146 patients with positive genetic testing for DD or positive muscle biopsy in a relative of a genetically diagnosed proband.
Results: 56 females and 90 males were identified. 92.5% of patients had cardiac abnormalities. Females presented with either hypertrophic cardiomyopathy (HCM, 70.3%) or dilated cardiomyopathy (DCM, 29.3%) whereas males presented with HCM 96.2% of the time. The composite outcome of death, heart transplant or ventricular assist devices occurred equally in both sexes (32% of females and 37% of males, $p = 0.60$) but later in females (median age 38 years) than in males (median age 21 years, $p < 0.001$). Whereas women present with isolated cardiac disease 73% of the time, in males DD was frequently multisystemic and presented as a triad of cognitive impairment, skeletal myopathy, and HCM in 42% of patients.
Conclusions: In this first systematic review of DD, we confirmed the severe morbidity and mortality associated with disease in both sexes. Women presented with both HCM and DCM and generally with isolated cardiac disease, whereas in men DD usually presented as HCM and was frequently multi-systemic. Further prospective NH studies will be required to confirm these findings.

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1. Introduction

Danon Disease (DD) is a rare, X-linked vacuolar myopathy caused by mutations in the Lysosomal-Associated Membrane Protein 2 (*LAMP2*) gene. The LAMP-2 protein is integral to cellular autophagy, and its absence or reduced expression results in intracytoplasmic vacuoles containing autophagic material [1,2]. Sequelae of DD include cardiac and skeletal myopathies, neurodegeneration, and pigmentary retinopathy. The exact prevalence of DD is unknown but is generally believed to as high as 5% of all cases of pediatric hypertrophic cardiomyopathy (HCM) [3]. Although no specific diagnostic criteria have been established, the diagnosis is usually made by identifying a mutation in *LAMP2* in the context of either a typical clinical triad (cardiomyopathy, skeletal myopathy, and cognitive impairment) or pathognomonic findings of vacuolar myopathy after a skeletal or cardiac muscle biopsy. As in other rare diseases, delayed diagnosis and misdiagnosis are common [4].

Because of the rarity of this condition, a high degree of uncertainty remains in regards with its clinical presentation and the natural history. Since DD is X-linked, the disease generally arises earlier in males, who typically die or require heart transplantation (HTx) in the second or third decade of life due to progressive heart failure (HF) [5,6]. This phenomenon is presumably related to the hemizygous male status of the *LAMP2* gene, with many mutations leading to a complete absence of the LAMP-2 protein. Notably, specific cases of severely affected females have also been described [7,8], possibly caused by non-random or defective X-inactivation [9].

As DD can be misdiagnosed as sarcomeric HCM, it is critical to understand the variable ways DD can present itself so that providers can distinguish the separate clinical entities that require different management strategies [10]. Furthermore, recent insights into the molecular mechanisms [2,11–13] and potential therapeutic targets of DD may lead to the initiation of clinical trials. However, before clinical trials are started a

Abbreviations: DD, Danon disease; HCM, hypertrophic cardiomyopathy; DCM, dilated cardiomyopathy; HTx, heart transplantation; LVAD, left ventricular assist device; Q1, first quartile; Q3, third quartile; LGE, late gadolinium enhancement; LVEF, left ventricular ejection fraction; LV, left ventricle.

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https://doi.org/10.1016/j.ijcard.2019.01.020
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better understanding of the natural history is required to identify appropriate endpoints. To address these knowledge gaps, we performed a systematic review of all published case reports and series of DD to assess the disease variability, phenotypic patterns, and outcomes.

2. Methods

2.1. Search strategy

We conducted a systematic review of the DD literature according to the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analysis) guidelines for its design, implementation, analysis, and reporting. A database of the DD literature was created using a specific search strategy with the terms ((Glycogen Storage Disease Type 2B) OR (Disease, Antopol) OR (Antopol Disease) OR (X Linked Vacuolar Cardiomyopathy and Myopathy) OR (X-Linked Vacuolar Cardiomyopathy and Myopathy) OR (Vacuolar Cardiomyopathy and Myopathy, X-linked) OR (Vacuolar Cardiomyopathy and Myopathy, X-linked) OR (Pseudoglycogenosis IIs) OR (Pseudoglycogenosis II) OR (Pseudoglycogenosis 2s) OR (Pseudoglycogenosis 2) OR (Lysosomal Glycogen Storage Disease without Acid Maltase Deficiency) OR (Lysosomal Glycogen Storage Disease with Normal Acid Maltase) OR (Glycogen Storage Disease Limited to the Heart) OR (Glycogen Storage Disease IIb) OR (Glycogen Storage Cardiomyopathies) OR (Cardiomyopathy, Glycogen Storage) OR (Cardiomyopathies, Glycogen Storage) OR (Glycogen Storage Cardiomyopathy) OR (Danon Disease) OR (Glycogen Storage Disease Type IIb) OR (Danon disease)) AND ((Human) OR (*Homo sapiens*) OR (Man (Taxonomy)) OR (Modern Man) OR (Man, Modern) OR (Humans) OR (humans)) in PubMed (MEDLINE) and EMBASE and included all case reports and case-series published until October 27, 2017 in English, Italian, French, and Spanish. Reference lists of all studies previously identified as having met the inclusion criteria were manually reviewed for additional relevant publications. Case series were considered only if clinical data were available for each case (Fig. 1).

2.2. Data extraction and management

After the completion of all search queries, references were uploaded into Rayyan (http://rayyan.qcri.org), and duplicates were removed. Two independent authors (M.B., and E.K.) performed an analysis of the full texts and abstracts. All data were extracted from article texts, tables, and figures. Discrepancies were resolved by consensus or by a third author (A.M.), if necessary. A positive diagnosis of DD for study inclusion was defined as either positive genetic testing for DD or positive muscle biopsy (skeletal or cardiac) in a relative of a genetically diagnosed proband. Muscle biopsies were considered diagnostic (positive) if the exam showed intracytoplasmic vacuolar structures, including autophagic material. Data were collected and managed using Research Electronic Data Capture (REDCap) [14]. The primary outcome of the analysis was defined as a composite outcome of death, HTx, or long-term left ventricular assist device (LVAD) implantation.

2.3. Statistical analysis

Continuous variables are presented as medians and quartiles (Q1–Q3). Categorical variables were described as numbers and percentages. Group differences in continuous variables were tested using the Mann-Whitney *U* test. Associations between categorical variables were tested using Fisher's exact or chi-square tests. Kaplan–Meier (KM) curves were generated and compared with the use of the log-rank statistic. Patient events included death, HTx, or LVAD implantation. A p-value <0.05 was considered significant. All Statistical analyses were performed using SPSS 25 (SPSS Inc., Chicago, IL, USA) and GraphPad Prism 5 (GraphPad Software Inc., La Jolla, CA, USA).

3. Results

3.1. Identification, screening, and inclusion of Danon disease cases

The identification, screening, and exclusion/inclusion process are summarized in Fig. 1. The comprehensive query process identified 572 unique publications that mapped to DD. Of these, 439 were eliminated based on reports indicating that DD was not a possible diagnosis, was excluded, or could not be confirmed. An additional 50 papers were excluded because of inappropriateness/incompleteness of data or unavailability of study text. Eighty-three manuscripts (including 21 case series, the largest series accounting for ten patients) met the eligibility criteria

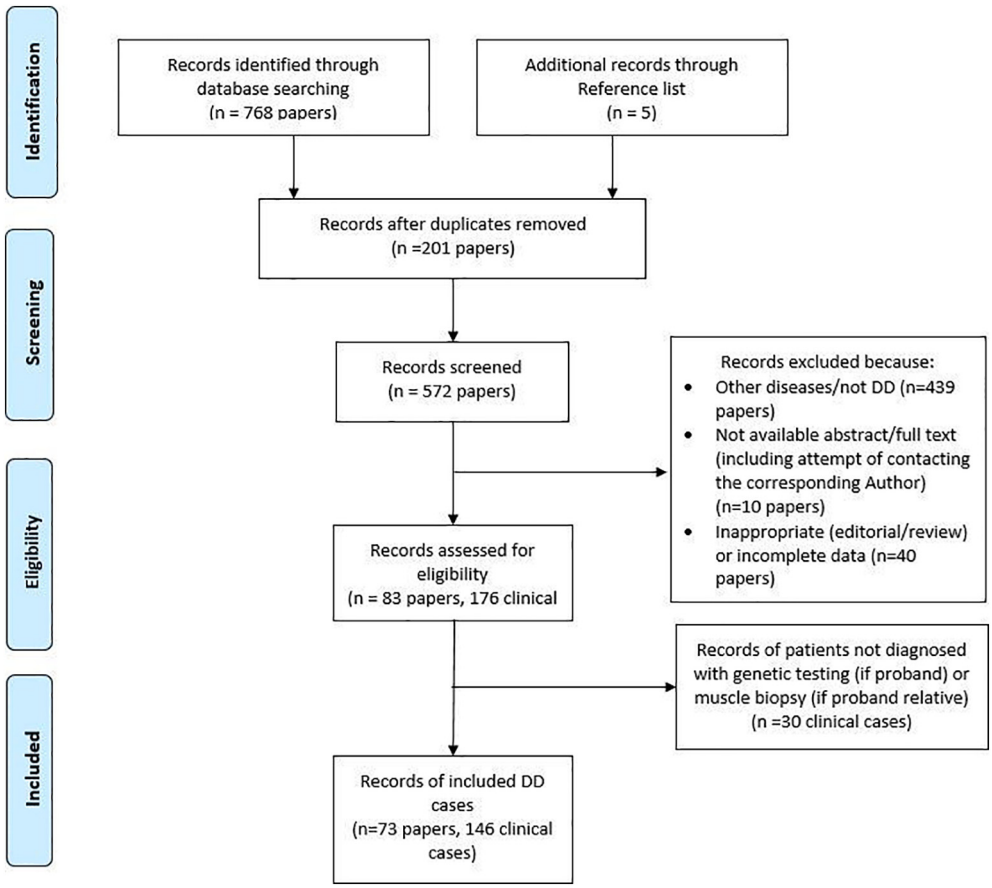

Fig. 1. Study selection flow diagram. Identification, screening, and inclusion process through Medline and EMBASE databases that led to the inclusion of 146 clinical cases of Danon Disease in the study. DD = Danon disease.

for the study. A total of 176 clinical cases were identified in these manuscripts. Of these, 30 cases were excluded from the analysis due to a lack of reported genetic tests (if proband) and/or lack of cardiac and muscle biopsy (if proband relative). In summary, 146 patients (73 manuscripts; for the complete list of articles, see the **Online Appendix**) with a confirmed diagnosis of DD were included in the primary analysis.

3.2. Demographics

Of the 146 DD identified there were 90 males (61.6%) and 56 females (38.4%). The ethnicity of patients was reported in the minority of cases (n = 66, 45.2%). In most cases, patients were Caucasian (72.7%). DD cases were mostly reported by hospitals in Europe (54.1%), followed by North America (21.9%), and Asia (20.6%). The remaining cases were reported from hospitals in Australia (3.4%, **Supp. Fig. 1**). Additional demographic characteristics are shown in **Suppl. Table**.

3.3. Clinical outcomes

The composite outcome of death, HTx, or LVAD implantation occurred in 34.9% of the patients. Males (33 events (36.7%); one LVAD implantation, 19 HTx, 13 deaths) had a similar risk for the reported composite outcome when compared to females [18 events (32.1%); two LVAD implantations, nine HTx, seven deaths; $p = 0.60$] However, Kaplan-Meier analysis identified that the combined outcome occurred at an earlier age for males (median 26 years) compared to that of females (median 52 years, log-rank $p < 0.001$, **Supp. Fig. 2**). The cause of death was reported as HF in nine cases (45%), sudden cardiac death in eight cases (40%), strokes in two cases (10%) and unknown in one patient (5%).

Overall, 29 patients received HTx, including one patient bridged with an LVAD. Complications after HTx were only described in males. Two patients required re-transplant because of the allograft rejection, and four patients developed profound muscle weakness, with two of them requiring reinstitution of mechanical ventilatory support because of respiratory failure.

3.4. Genetics

Out of the 146 patients with a confirmed diagnosis of DD, specific mutational information was reported for 113 patients. Mutations were distributed across the *LAMP2* exons one through nine (**Supp. Fig. 3**). Exon 8 (34% of mutations), followed by exon 6 (18%) were the most frequent locations for disease-causing mutations. 19 intronic mutations (16.8%) were identified as well, the majority of which were between introns six and seven.

Concerning the type of mutations (reported in 130 patients), most of them were stop codon or frameshift variants (n = 83, 63.8%). Splicing (n = 32, 24.6%), deletion (n = four, 3%), duplication (n = two, 1.53%), and missense mutations (n = nine, 6.9%) were described in the remaining population.

In 36 cases, the significance of the mutation was obtained using a public archive of genetic report named "ClinVar" (www.ncbi.nlm.nih.gov/clinvar). Among the 36 mutations, 31 were described as pathogenic (21 were stop codon, 5 frameshift, 2 splicing, 3 missense), 3 as likely pathogenic (1 frameshift, 2 stop codon), and 2 as variant of uncertain significance (1 missense, 1 splicing)".

Among male patients with identified mutations (n = 66), no differences in outcomes were found for all mutations, except for those found in exon 9b, which occurred in 6.4% of patients. Male exon 9b mutants showed severe muscle disease with absent to mild cardiac involvement and no cardiac events at a median age of 61 (Q1–Q3, 17.5–69). Of note, one female belonging to the same family as four of the males with exon 9b disorder and carrying the same mutation died suddenly at the age of 28. The autopsy examination revealed HCM.

3.5. Clinical manifestation

3.5.1. Cardiac

One-hundred thirty-five (92.5%) patients exhibited cardiac (structural or electric) abnormalities, as described in Table 1. Among the patients exhibiting cardiac manifestations, imaging data were reported for 120 (82.2%). One-hundred five (87.5%) of these patients showed HCM. HCM was more prevalent in males than in females. Among patients with recorded left ventricular outflow gradients, outflow obstruction was present in 11 patients (26.2%). Among HCM patients, the development of end-stage cardiomyopathy (refractory to maximum medical management) occurred in 43.8%; (Table 1). DCM at presentation was significantly higher in females than males (29.3% vs. 3.8%, $p < 0.001$).

The median left ventricular ejection fraction (LVEF), as the first disclosed value in the case report, either by echocardiography or by cardiac magnetic resonance (CMR), was 50% with no differences between genders. Twenty-six patients underwent CMR, and late gadolinium enhancement (LGE) presence was described in 92.3% and 69.2% of males and females, respectively. When reported, LGE distribution was reported as "patchy" in 10 cases and "diffuse" in 9 cases.

Cardiac conduction abnormalities were reported in 57.5% of DD patients with no significant difference between genders (Table 1). Wolff-Parkinson-White (WPW), an accessory pathway mediated arrhythmia, was reported in 41.8% of the patients with no clear gender differences. The rate of reported ventricular tachycardia was relatively low for both genders (10% of males and 3.6% of females). In the majority of patients, the status of cardiac implantable electronic device (CIED) implantation was reported (n = 108, 74%), with 45% of the patients described having an intracardiac defibrillator (ICD). 76.5% of these patients had ICD placed for primary prevention. An exemplificative case demonstrating the cardiac manifestations of DD is presented in Online Videos 1, 2, 3 and **Supp. Fig. 4**.

3.5.2. Skeletal myopathy, cognitive and vision impairment

Skeletal myopathy was reported in 71 (50.7%) of the patients but occurred mostly in males ($p < 0.001$), affecting mainly the proximal muscles (Table 2).

Cognitive impairment was noted in 47 (55.6%) of patients, the vast majority being males (80% males vs. 10.3% females, Table 2). Out of 47 patients, the severity of the impairment was reported by authors as mild in the majority of cases (n = 34, 72.3%), moderate in three cases (6.4%), and not specified in ten cases (21.3%). In ten patients (eight males, two females) an intelligence quotient (IQ) was recorded and ranged from 48 to 85 (average value for the general population is 90–110).

Five patients (four males and one female) experienced a stroke at a median age of 23 (Q1–Q3, 20–33), while one male had a transient ischemic attack at the age of 28. Three stroke episodes were secondary to embolus, one was due to post-cardiac arrest hypoperfusion, and one was not described. Strokes were fatal in two out of five patients.

Vision impairment was described in 26 (20.2%) patients and occurred equally in both genders. Patients were diagnosed mostly with retinopathy (n = 14, 10.9%) and myopia (n = 12, 9.3%) at a median age of 15 (Q1–Q3 13.0–22.5). No cases of complete vision loss were reported.

3.6. Laboratory abnormalities

Among 105 patients with available data, 65 (61.9%; 83.3% males and 16.3% females) had abnormal laboratory tests, including elevated liver enzyme levels (aspartate transaminase, AST and alanine aminotransferase, ALT), serum creatine kinase (CK), and lactate dehydrogenase (LDH) at a median age of 14 (IQR 8.25–19.75). Among patients with available data and abnormal values, AST, ALT, CK, LDH and were reported as median values of 284 U/L [Q1–Q3,

Table 1
Cardiac manifestations of study population.

	All		Males		Females		
	Patients with available data	Value	Patients with available data	Value	Patients with available data	Value	P value
Any cardiac abnormality	146	135 (92.5)	90	86 (95.6)	56	49 (87.5)	0.106
Cardiomyopathy classified	146	120 (82.2)	90	79 (87.8)	56	41 (73.2)	**0.044**
Hypertrophic cardiomyopathy at presentation	120	105 (87.5)	79	76 (96.2)	41	29 (70.7)	**<0.001**
LVOT obstruction	42	11 (26.2)	32	10 (31.2)	10	1 (10)	0.245
Concentric HCM	58	52 (89.7)	44	40 (90.9)	14	12 (85.7)	0.624
Age at time of HCM diagnosis, years old	76	14 (10.0–18.0)	52	13 (8.0–16.5)	24	16 (12.5–25.5)	**0.007**
HCM progression to end-stage cardiomyopathy	105	46 (43.8)	76	37 (48.7)	29	9 (31.0)	0.126
Age at end-stage cardiomyopathy, years old	38	21 (17.0–25.0)	29	20 (17.0–24.0)	9	28 (18.0–50.0)	0.153
Dilated cardiomyopathy at presentation	120	15 (12.5)	79	3 (3.8)	41	12 (29.3)	**<0.001**
Age at time of DCM diagnosis, years old	16	39 (26.0–48.5)	3	21.5 (18.0–22.0)	12	42.6 (35.5–50.0)	**0.004**
Diagnostic							
LVEF (%)-first reported value	77	50 (32.0–63.0)	47	50 (33.0–60.0)	30	58 (30.0–65.0)	0.430
LGE presence at CMR	26	21 (80.8)	13	12 (92.3)	13	9 (69.2)	0.322
Cardiac conduction abnormalities	146	84 (57.5)	90	52 (57.8)	56	32 (57.14)	1.000
WPW reported	146	61 (41.8)	90	43(47.8)	56	18 (32.1)	0.084
Atrial fibrillation, atrial flutter or other SVT reported	146	32 (21.9)	90	16 (17.8)	56	16 (28.6)	0.151
Sustained/non sustained VT reported	146	15 (10.3)	90	9 (10.0)	56	2 (3.6)	0.205
CIED reported	146	108 (74.0)	90	70 (77.8)	56	38 (67.9)	0.840
ICD	108	40 (37.0)	70	26 (37.1)	38	14(36.8)	1.000
CRT	108	5 (4.7)	70	3 (4.3)	38	2 (5.3)	1.000
Pacemaker	108	10 (9.1)	70	7 (10.0.)	38	3 (7.7)	1.000
Age at CIED, years old	50	25 (17.0–28.0)	35	21.3 (16.0–25.0)	15	33.5 (21.0–43.0)	**<0.001**
Age at first outcome, years old (combined outcome: HTx, VAD, death)	51	23 (19.0–32.0)	33	21 (17.0–25.0)	18	38 (28.0–52.0)	**<0.001**

Values are median (Q1–Q3), or n (%). HCM, Hypertrophic Cardiomyopathy; DCM, Dilated Cardiomyopathy; LVOT, left ventricle outflow tract; WPW, Wolff-Parkinson-White; SVT, supraventricular Tachycardia; CIED, cardiac implantable electronic devices, ICD, implantable cardioverter defibrillator, CRT, cardiac resynchronization therapy; LVEF, left ventricular ejection fraction; LGE, late gadolinium enhancement; CMR: cardiac magnetic resonance; HTx, heart transplant, LVAD, left ventricular assist device.
Bold values indicates significance at p-value <0.05

Table 2
Other clinical manifestation of study population.

	All		Males		Females		P value
	No. of patients with available data	Value	No. of patients with available data	Value	No. of patients with available data	Value	
Neurological manifestations							
Cognitive impairment	84	47 (55.6)	55	44 (80.0)	29	3 (10.3)	**<0.001**
Skeletal muscle manifestations							
Myopathy	140	71 (50.7)	84	64 (76.2)	56	7 (12.5)	**<0.001**
Muscle weakness	140	45 (32.14)	84	38 (45.2)	56	7 (12.5)	**<0.001**
Difficulty in walking/delay in motor milestone	140	26 (18.6)	84	25 (29.8)	56	1 (1.8)	**<0.001**
Not specified	140	12 (8.5)	84	12 (14.3)	56	0	**0.002**
Muscles involved:							
• **Proximal**	28	13 (46)	24	11 (45.8)	4	2 (50.0)	-
• **Distal**	28	6 (21.4)	24	5 (20.8)	4	1 (25.0)	-
• **Both**	28	9 (32.1)	24	8 (33.3)	4	1 (25.0)	-
Age at time of myopathy manifestation, years old	61	13 (6.0–20.0)	54	13 (5.0–19.0)	7	23 (11.0–28.5)	0.154
Ophthalmological manifestations							
Vision abnormalities	129	26 (20.2)	84	17 (20.0)	45	9 (20.0)	1
• **Retinopathy**	129	14 (10.9)	84	8 (9.5)	45	6 (13.3)	0.559
• **Myopia**	129	12 (9.3)	84	8 (9.5)	45	4 (8.9)	1
• **Not specified**	129	2 (2.4)	84	2 (2.4)	45	0	0.542
Age at time of vision impairment diagnosis, years old	23	15 (13.0–22.5)	15	18 (14.0–23.0)	8	13 (12.3–20.8)	0.325

Values are median (Q1–Q3), or n (%).
Bold values indicates significance at p-value <0.05

193.5–353.5; normal value (n.v.) 10–40 U/L] in 33 patients; 241 U/L (Q1–Q3, 175–380; n.v. 7–56 U/L) in 31 patients; 867.5 U/L (Q1–Q3, 667.7–1322.5 U/L, n.v. 22–198 U/L) in 32 patients; 1106 U/L (Q1–Q3, 875–1602 U/L, n.v. 100–190 U/L in older than 12) respectively. Seven patients were further investigated, and the results of liver biopsies in four cases (three males and one female) were abnormal. In two of those four cases, the liver pathology was described as related to DD, another case was described as hepatitis, and one case revealed mild portal fibrosis.

3.7. Natural history

In males, the initial presentation of DD was reported as a triad of cognitive impairment at a median age of 13 years, skeletal myopathy at a median age of 13 years, and HCM at a median age of 14 years. The progression to end-stage cardiomyopathy occurred at a median age of 20 with the occurrence of death or the advanced therapies requirement (HTx or LVAD) at the age of 21 (Tables 1 and 2, Fig. 2). Females primarily presented with solely cardiac manifestations (73%, **Supp. Fig. 5**). HCM females were diagnosed at a median age of 16 and showed progression to end-stage cardiomyopathy at a median age of 28. Finally, the composite outcome (HTx, LVAD, or death) occurred at a median age of 38; (Tables 1 and 2, Fig. 2).

4. Discussion

The present study describes a systematic, contemporary, and thorough review of all confirmed literature cases of DD, conducted according to the PRISMA guidelines. Applying a systematic review strategy allowed us to gather critical insights into a rare disease regarding clinical manifestations and natural history of DD.

Our main finding is that even though DD is X-linked, it is devastating for both genders. In fact, the primary outcome of death, HTx, or LVAD occurred in with nearly the same frequency in both sexes, 32% of females and 37% of males. Females experienced, however, a later, more variable disease onset. Also, females commonly displayed an isolated cardiac phenotype (73%), while in males a complex a triad of skeletal myopathy and cardiac and cognitive impairment was more typical (42%) with only 18% of males presenting an isolated cardiac phenotype. We also found that among DD patients, laboratory abnormalities, such as detectable elevations in hepatic and skeletal muscle enzymes, were common with values greater than three times the normal limit. This finding may be useful to clinicians evaluating patients with cardiac

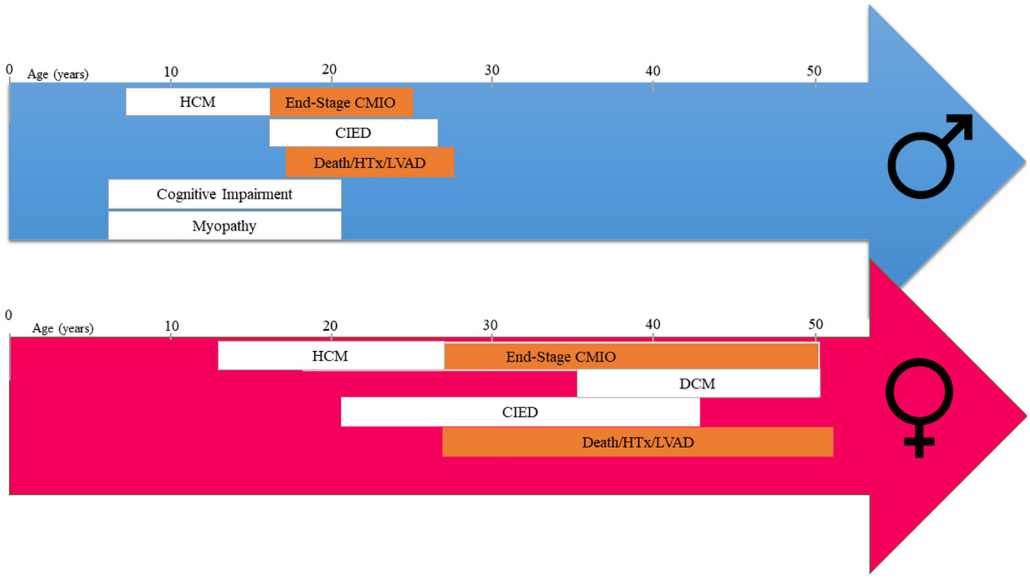

Fig. 2. *Natural history of Danon disease*. Natural History of DD in males (blue) and females (pink). Rectangular boxes inside the arrow represent age (years) at occurrence of each clinical manifestation (the left side of the box is age (years) at the first quartile *Q1* and the right side of the box is age (years) at the third quartile *Q3*, median age (years) at the rectangle centre). HCM-Hypertrophic Cardiomyopathy; CMIO – cardiomyopathy; CIED- cardiac implantable electronic device. HTx, heart transplant; LVAD, left ventricular assist device. Clinical manifestation affecting <10% of the study population, such as cognitive impairment and muscle disease in females and dilated cardiomyopathy in males, are not showed.

and skeletal myopathies of unclear etiology. Finally, we determined that among the DD genetic mutations, those in exon 9b were associated with a milder phenotype in adult males where patients did not reach any of the combined outcomes until the sixth decade of life.

Gender differences in DD phenotypes are expected, given the X-linked pattern of inheritance. As in previous studies, we found that disease onset and the composite outcome (HTx, LVAD implantation, or death) occurred at an earlier age in males compared to females [5,10]. Similar to two recent national registries in Japan [15] and Spain [16], we found that HCM is the most common form of cardiomyopathy at presentation for both genders, but females had a lower prevalence of HCM at presentation and a higher prevalence of DCM compared to males. Although females had a later onset of symptoms and overt disease with a lower reported prevalence of HCM, the reported rate of any type of arrhythmia or CIED use was the same for females and males. Also, among reported cases, females had a predominant presentation pattern consisting of isolated cardiomyopathy (without additional disease hallmarks), while males more commonly presented a triad of neurocognitive manifestations, skeletal myopathy, and cardiomyopathy. These observations suggest that *LAMP2* haploinsufficiency in females is sufficiently pathologic to cause a predominantly isolated cardiac presentation. Furthermore, the wide variation in the female DD phenotype is likely due to variation in X-linked activation in female LAMP2 mutation carriers.

In our study, females had a predominant presentation pattern consisting of isolated cardiomyopathy (without additional disease hallmarks), while males more commonly presented a triad of neurocognitive manifestations, skeletal myopathy, and cardiomyopathy. This is important to consider since normal findings in skeletal muscle biopsy do not exclude LAMP2 associated cardiomyopathy in females [10].

Abnormalities in cardiac conduction were reported for the majority of DD patients as being the most common feature with a similar prevalence across genders. A previous study by Boucek et al. [5] suggests that conduction abnormalities occur in up to 80% of DD patients, which is consistent with our findings. However, whereas Boucek et al. found WPW to be more common in males, our review suggests that it is equally distributed in both genders. It is still unknown if the pre-excitation is a result of autophagy abnormalities [17]. However, lack of WPW does not rule out DD related cardiomyopathy. Also, the reported rate of any arrhythmia or CIED use was the same for females and males. Ventricular arrhythmias were reported in only 10% of our cohort, but this observation is limited as we found that sudden cardiac death as a common cause (40%) of death. Currently, the risk stratification for ICD implantation in DD follows the AHA/ESC HCM guidelines [18,19]. However, further studies are required to elucidate potential disease-specific risk stratifying methodologies as well as novel strategies for risk stratification [e.g., CMR LGE pattern/T1 mapping [20], 3D strain imaging [21], cardiopulmonary exercise testing [22], Troponin and the type of genetic mutation]. Also, the low prevalence of ventricular arrhythmias may suggest that other mechanisms such as atrial-ventricular (AV) block or electromechanical dissociation may contribute to death in a patient with DD.

We noted significant elevations in liver enzymes in DD patients, predominantly in males. It is uncertain if this represents hepatic injury from the absence of LAMP-2 or is secondary to elevated right-sided filling pressures. Furthermore, some of the elevations in AST may represent injury to skeletal muscle [23]. Further studies will be required to determine if liver enzyme levels can be used to follow the progression of the disease.

5. Limitations

The study conducted is a systematic review that has several significant inherent limitations. A fundamental limitation is that the review is based only on the published original reports (case reports and case series) and so did not allow for verification of accuracy and completeness of data Under-reporting from Asia and Africa may have resulted in skewed geographic and ethnic distribution. Furthermore, case reports provide cross-sectional data rather than longitudinal data. Also, occurrence of atrial-ventricular blocks or bundle branch block were not reported, though the incidence and prevalence of this is clearly clinically relevant.

Although publication bias may skew the spectrum of disease manifestations of DD, our results are in line with recent nationwide experiences [15,16]. The natural history of DD as reflected from the data in the current study is based on reports from various disciplines and does not allow a thorough evaluation of the HF drugs prescribed for

DD patients throughout the disease progression. The effect of HF drugs, especially in cases presenting with DCM may alter significantly with guidelines recommended drugs for HF.

6. Conclusions

In this study, we systematically reviewed the disease manifestation and natural history of DD. Male patients have earlier symptom onset, frequent extra-cardiac manifestations, and a relatively rapid progression to severe HCM. DD manifestations in females are diverse; although most patients' pathogenesis occurred over protracted intervals, diagnosis during adolescence or early adulthood with a more rapid clinical deterioration was also observed. The presence of severe forms of DD in females may warrant clinicians to screen for disease manifestations in female relatives of male DD patients. Furthermore, given that 73% of women presented with isolated cardiac disease, consideration of DD is warranted in women with HCM or DCM even if other features of DD are not apparent at presentation.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2019.01.020.

Acknowledgments

This work was selected as finalist at the Northwestern Cardiovascular Young Investigators' Forum 2018.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Disclosure of conflicts of interest

Dr. Eric Adler has an equity interest in Rocket Pharmaceuticals.

Dr. Michela Brambatti is a consultant for Rocket Pharmaceuticals.

Dr. Matthew Taylor is a consultant for Rocket Pharmaceuticals.

Dr. Barry Greenberg, Elliot Koshi, Oren Caspi, and Alessandro Maolo have no conflicts of interest or financial ties to disclose.

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