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Three female patients with Danon disease presenting with predominant cardiac phenotype: a case series

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Background

Danon disease is a rare X-linked multisystemic disorder that has primarily been described in male patients.

Case summary

We present three female patients with Danon disease with a predominantly cardiac phenotype in whom disease onset and expression was very different from that of male patients. Case 1 was first admitted for acute heart failure and then readmitted a few months later for cardiac shock, necessitating mechanical support, and heart transplantation. Case 2 had complex arrhythmias for which many antiarrhythmic drugs were tried with only limited success. Her disease accelerated after her first pregnancy, and she showed reduced left ventricular function and dilated cardiomyopathy. Case 3 was referred for near syncope and ablated for an accessory pathway; she had extensive left ventricular hypertrophy. In all three cases, a final diagnosis of Danon disease was only made after genetic testing that identified a causal variant in the lysosome-associated membrane protein 2 gene.

Discussion

Danon disease in female patients is a challenging diagnosis that may not be identified until genetic testing has been performed.

Keywords

Danon disease • Women • Cardiomyopathy • Case report

Learning points

- Danon disease is a rare disease. The primarily cardiac phenotype seen in our three female cases is even rarer.
- The presentation of Danon disease in women can be more variable than that typically seen in men.
- Danon disease should be considered in female patients with either heart failure or arrhythmias without a clear diagnosis and/or with a pre-excitation-like electrocardiogram. Genetic testing plays a crucial role in this diagnosis.

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Introduction

Danon disease is a rare X-linked multisystemic disorder that has primarily been described in males.¹ It was first described as a lysosomal glycogen storage disease characterized by proximal myopathy, mental retardation, and hypertrophic cardiomyopathy.² The gene defect underlying Danon disease causes a deficiency of lysosome-associated membrane protein 2 (LAMP2).³ In Danon disease, typical cardiac presentation occurs during adolescence and includes left ventricular hypertrophy (LVH) and a Wolff–Parkinson–White pre-excitation pattern on the electrocardiogram (ECG).¹ Here, we report three individual cases with Danon disease, all female, who presented with an atypical phenotype.

Timeline

| | | |
|--------|---------------|---|
| Case 1 | June 2011 | Admission for acute heart failure. Short PR interval without pre-excitation and broadened and fractioned QRS complexes. Hypertrophic dilated left ventricle with poor function. |
| | December 2011 | Admission for cardiac shock. Mechanical support with biventricular Centrimag. Heart transplantation. |
| | June 2016 | Lysosome-associated membrane protein 2 (LAMP-2) mutation found. |
| Case 2 | December 2003 | Electrophysiological (EP) study for atrial tachycardias and pre-excitation. Fasciculoventricular connection identified (not ablated). Many antiarrhythmic drugs tried in the following years. |
| | June 2013 | Pregnancy, left ventricular ejection fraction dropped to 38%. Cardiovascular magnetic resonance imaging showed dilated cardiomyopathy. |
| | August 2014 | LAMP-2 mutation found. |
| Case 3 | August 2017 | Referral for recurrent near syncope. Electrocardiogram showed short PR interval. Accessory pathway identified by EP study was ablated. |
| | October 2017 | LAMP-2 mutation found. |
| | August 2018 | Implantable cardioverter defibrillator implantation. |

Case presentation

Case 1

Case 1 was admitted to the hospital with acute heart failure at the age of 20 years. She had no medical history aside from an episode of a common cold 2 months earlier. Her ECG (Figure 1A) showed sinus tachycardia, a short PR interval without pre-excitation and

broadened and fractioned QRS complexes with inferolateral repolarization abnormalities. Echocardiographic evaluation showed a hypertrophic dilated left ventricle with poor function and signs suggestive of non-compaction cardiomyopathy. Cardiovascular magnetic resonance imaging did not confirm the presence of non-compaction cardiomyopathy (Figure 2). Coronary angiography was normal, and subsequent myocardial biopsy revealed no signs suggestive of a storage disease or myocarditis. The patient received standard heart failure treatment and an implantable cardioverter-defibrillator. A few months later, she presented at the emergency department with intractable cardiac shock. Mechanical extracorporeal biventricular support was initiated, and the patient underwent heart transplantation 3 weeks later. In the years, thereafter, she remained clinically stable. Genetic testing was performed 5 years later, and a mutation was found in LAMP-2 (c.557-1G>C (NM_002294.2)). The explanted heart was re-examined in 2016 and again showed signs of biventricular hypertrophy and non-compaction cardiomyopathy (mainly posteriorly in the left ventricle), also vacuolization of the cytoplasm was seen (a finding consistent with Danon's disease). The patient was subsequently seen by the neurologist, but no myopathy was found. The ophthalmologist documented Danon disease-associated eye disease in her left eye. At the last follow-up (September 2018), Case 1 was clinically stable in New York Heart Association Class I.

Case 2

Case 2 was 25 years of age when a LAMP-2 mutation was found. Her medical history revealed incessant complex ventricular tachycardias since early childhood. Around the age of 14, she underwent a cardiac electrophysiologic study, because she had developed atrial tachycardias. The electrogram showed signs of pre-excitation (Figure 1B) with a positive deltawave in the inferior leads and negative T waves in the anterior leads. The diagnostic electrophysiologic study identified a fasciculoventricular connection, but no ablation was performed because no sustained tachycardias could be induced during the study. In the years, thereafter, the patient was administered several antiarrhythmic drugs (propafenone, sotalol) for the treatment of ventricular tachyarrhythmias, which had variable effects. She became pregnant at the age of 24 and her left ventricular ejection fraction, which had been normal before pregnancy, reduced to 38%. Cardiovascular magnetic resonance imaging revealed multiple areas of late enhancement. After the pregnancy, angiotensin-converting enzyme inhibitor and diuretics were started and amiodarone was introduced to suppress the ventricular tachycardias. An internal cardioverter defibrillator (ICD) was also implanted (Class IIa indication) as primary prevention. Her left ventricular ejection fraction then increased, going up to 48%. In the 4 years of follow-up after ICD implantation, she underwent electrical cardioversion twice because of atrial fibrillation. Genetic evaluation was proposed, and a frameshift mutation found in LAMP2 (c.966dup p.(Ala323Cysfs*27) (NM_002294.2)). Neurological evaluation was within normal limits, but signs of retinopathy were found by the ophthalmologist. At the last follow-up (September 2018), she was clinically stable in New York Heart Association Class I.

Case 3

Case 3 was referred in August 2017 at the age of 20 years with recurrent near syncope. This was a complaint, she had been having since

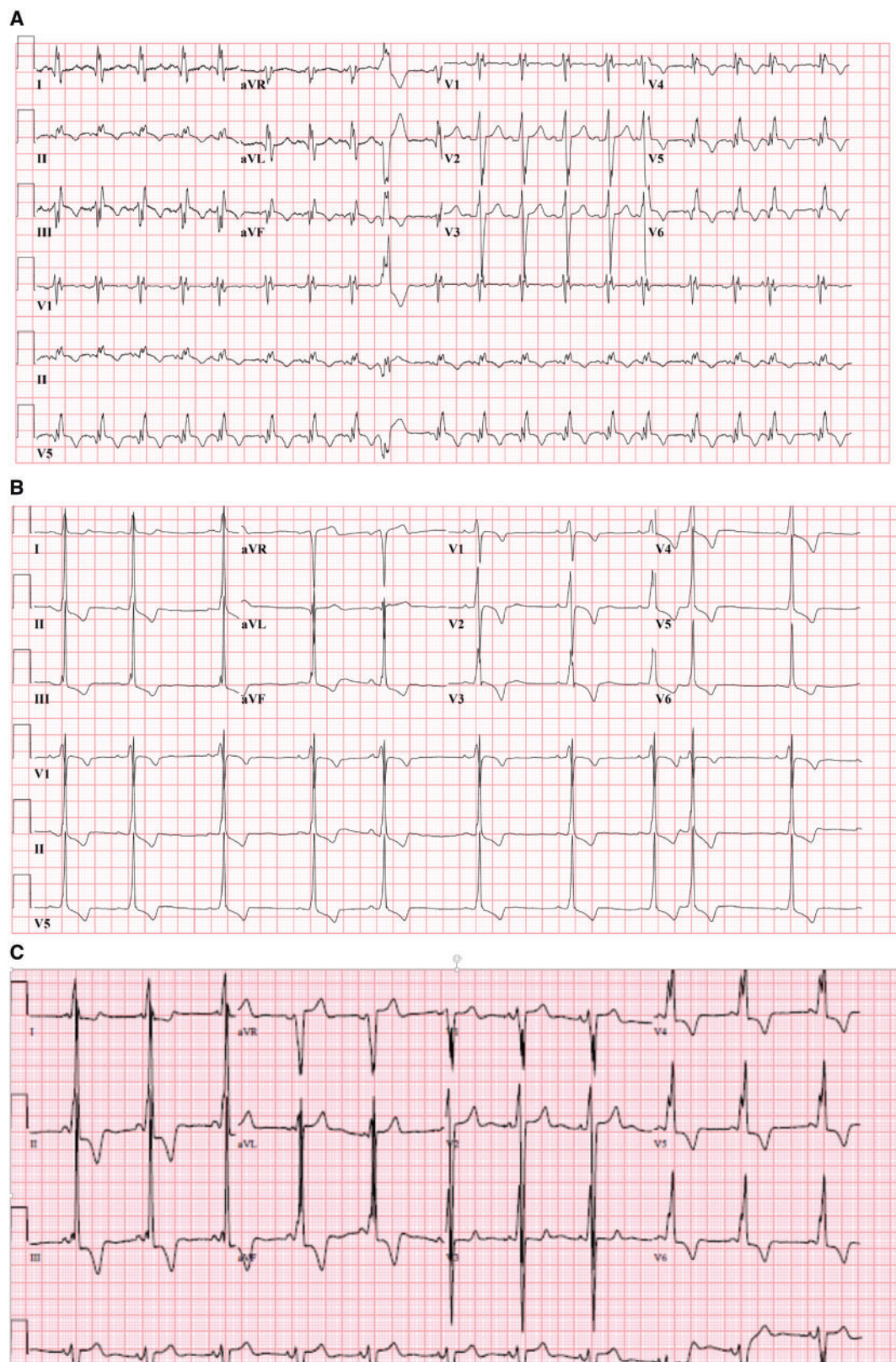


Figure 1 (A) An electrocardiogram of Case 1 showing sinus tachycardia, a short PR interval without pre-excitation and broadened and fractionated QRS complexes with inferolateral repolarization abnormalities. (B) An electrocardiogram of Case 2 showing with signs of pre-excitation with a positive deltawave in the inferior leads and negative T waves in the anterior leads. (C) Electrocardiogram of Case 3 with a short PR interval and pronounced left ventricular hypertrophy with deep negative T waves is shown.

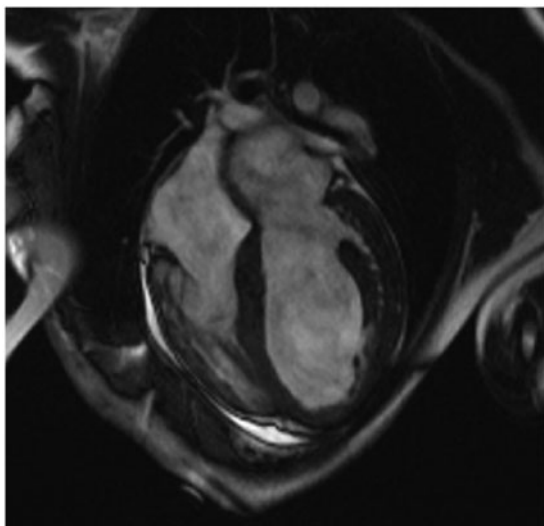


Figure 2 A cardiovascular magnetic resonance imaging of Case 2 without signs of non-compaction cardiomyopathy.

puberty, but it had been occurring much more frequently in the months leading up to her referral. The patient had never lost consciousness or felt palpitations. She had been feeling fatigued for years but had not noticed a decline in exercise tolerance. Echocardiography showed massive LVH with speckles in the myocardium and good contractility (calculated indexed mass 237.3 g/m^2 , maximum septal thickness 18 mm). Cardiovascular magnetic resonance imaging revealed concentric LVH with extensive diffuse mid-myocardial-delayed enhancement (calculated myocardial mass 154 g/m^2) (Figure 3). In systole, there was apical and mid-cavitary obliteration of the left ventricle with a maximum velocity of 2.3 m/s and without left ventricular outflow tract obstruction. Ambulatory monitoring registered frequent supraventricular tachycardia. She was therefore referred for ablation. Her ECG (Figure 1C) showed a short PR interval and pronounced LVH with deep negative T waves. A cardiac electrophysiologic study showed a single accessory pathway with only retrograde conduction properties. Orthodromic circus movement tachycardia was induced (non-sustained). The pathway, which was located infero-anteriorly, was successfully ablated. Since there was no antegrade-conducting accessory pathway, the short PR interval could not be explained by pre-excitation, so it was most likely due to enhanced AV nodal conduction. In October 2017, DNA testing identified a *de novo* frameshift mutation in the *LAMP2* gene (c.929-1G>A). Interestingly, retinal pigment changes had been observed in the patient in early 2000. In 2012, she was diagnosed with a form of ocular albinism but had no complaints about her eyesight. Ophthalmologic re-examination in 2017 showed bilateral retinal pigment changes associated with Danon disease. Since Danon disease has been suggested to have a more progressive clinical course with respect to ventricular arrhythmias and development of heart failure, implantation of an ICD was discussed and an ICD implanted in August 2018. Neurological examination showed no signs of myopathy. At the time of writing (August 2018), she is clinically stable.

Genetic testing/mutations

Targeted sequencing, data analysis and interpretation

Genomic DNA was extracted from peripheral blood. Sample preparation and targeted enrichment were performed according to the manufacturer's instructions (SureSelect XT Custom library and prep kit, Agilent Technologies Inc., Santa Clara, CA, USA) as described previously.⁴ Capture probes for cardiomyopathy-related genes were used. Enriched DNA fragments were sequenced on a MiSeq sequencer (Illumina, San Diego, CA, USA) using 151 bp paired-end reads according to manufacturer's instructions. Data analysis was performed using the MiSeq reporter programme to generate *fastq.gz* output files. These were uploaded to the NextGene software (v2.2.1, Softgenetics, State College, PA, USA) and, upon quality filtering, aligned to the reference genome (Human_v37.2). Single-nucleotide polymorphisms (SNPs) and indels were called, and the respective variant list was converted into the *.vcf file format. These files were uploaded into the Cartagenia software (Cartagenia, Leuven, Belgium). This software was used in combination with the Alamut software (Interactive Biosoftware, Rouen, France) for variant filtering and classification.

CNV analysis (SNP array)

To identify putative copy number variations (CNVs) in Case 1, genome-wide genotyping was performed using HumanCytoSNP-850K SNP array according to the manufacturer's protocols (Illumina). Raw data were normalized and converted into genotypes using the GenomeStudio data analysis software and NEXUS (BioDiscovery). CNVs were predefined as the loss of regions of DNA >150 kbp or of at least one exon of a gene associated with disease in OMIM (<http://ncbi.nlm.nih.gov/omim>) or the gain of regions of DNA >200 kbp in size.

Genetic testing in Cases 1, 2, and 3

Case 1 was referred for genetic testing at 20 years of age. The family history was negative for cardiac disorders. Sanger sequencing of the genes *MYH7*, *MYBPC3*, *TNNT2*, *TNNI3*, *LMNA*, and *PLN* showed no abnormalities. Five years later, the patient was referred for further genetic testing after she was informed about new genetic diagnostic possibilities. Targeted sequencing of 60 cardiomyopathy related genes identified a *de novo* splice mutation, c.557-1G>C, in the *LAMP2* gene. The other 59 genes showed no additional relevant mutations/variants. Because the patient had a slight learning disability, a SNP array was also performed and showed a normal female pattern.

Case 2 was referred for genetic testing at 25 years of age. The family history was negative for cardiac disorders. Targeted sequencing of 53 cardiomyopathy-related genes identified a frameshift mutation, c.966dup p.(Ala323Cysfs*27), in the *LAMP2* gene. No additional relevant mutations/variants were identified in the other 52 genes.

Case 3 was referred for genetic testing at 20 years of age. The family history was unremarkable for cardiac disorders. Targeted sequencing of 64 cardiomyopathy-related genes identified a *de novo* frameshift mutation, c.929-1G>A, in the *LAMP2* gene. The other 63 genes showed no additional relevant mutations/variants.

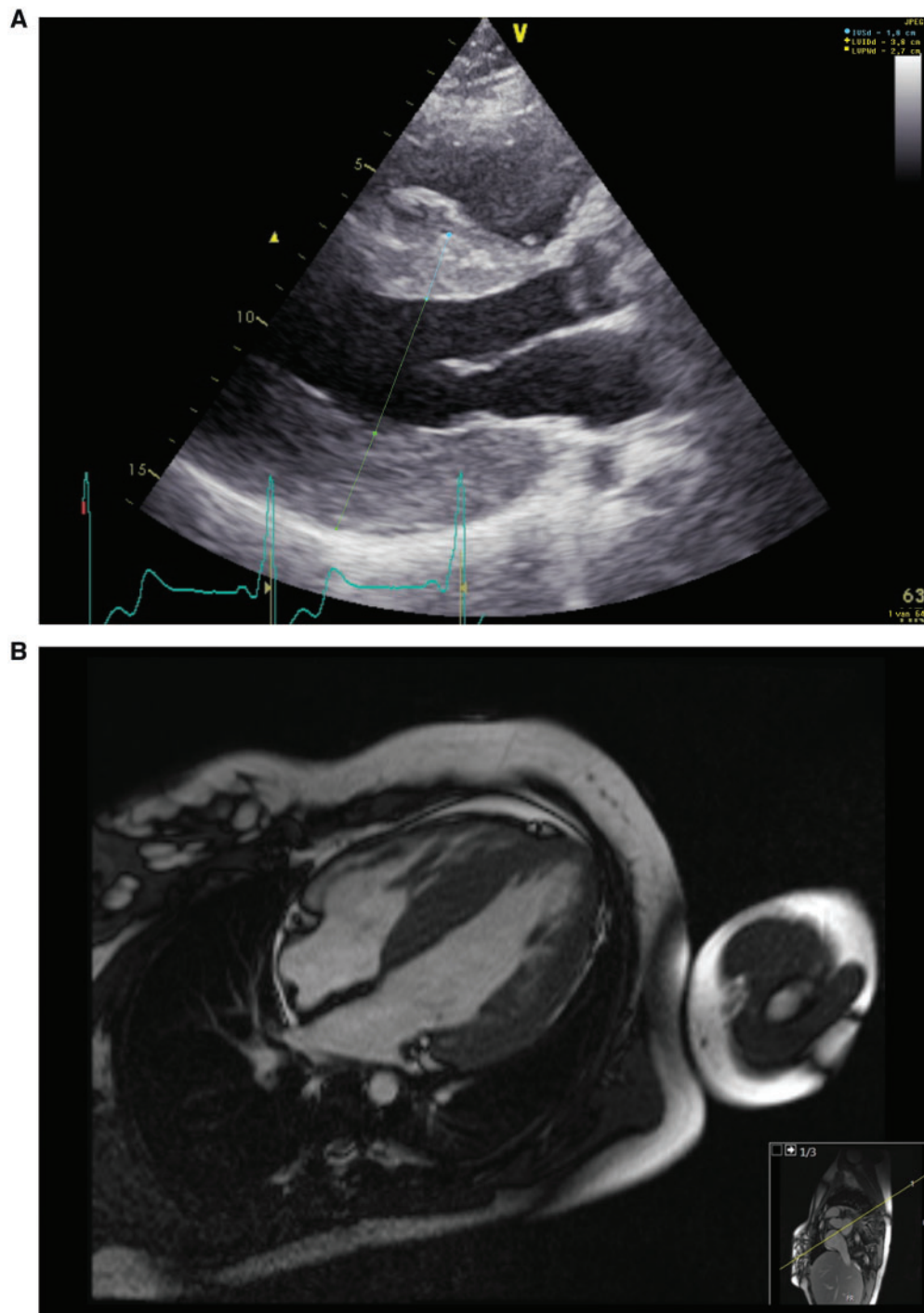


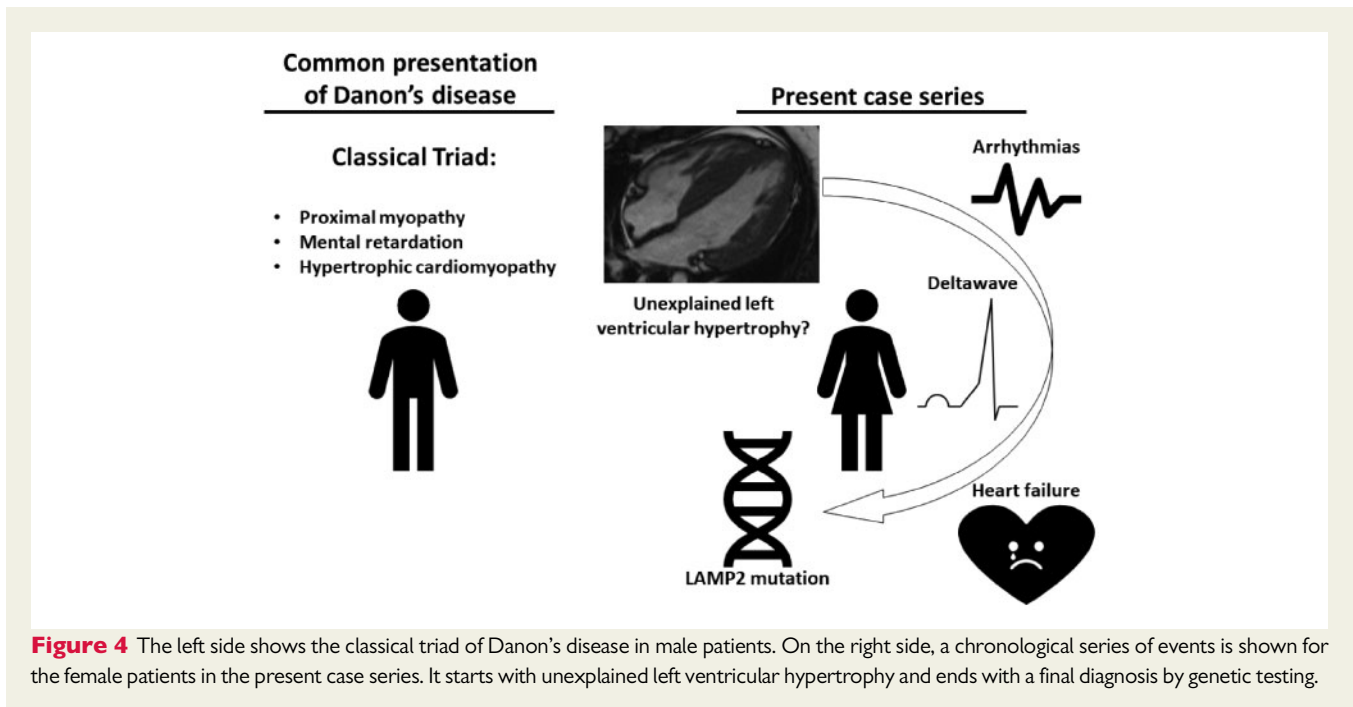
Figure 3 An echocardiogram (A) and cardiovascular magnetic resonance imaging (B) of Case 3 with concentric left ventricular hypertrophy.

Discussion

We report three female patients presenting with unexplained cardiac disease who were eventually diagnosed with Danon disease. All three had a history of cardiac symptoms due to heart failure (Case 1), complex arrhythmias (Case 2), and near syncope (Case 3). All three were

not diagnosed until a LAMP2 mutation was found. None had neurological symptoms. On ophthalmologic examination, all three had retinal pigment changes consistent with Danon disease, and Case 3 had also been diagnosed previously with a type of ocular albinism.

Danon disease is rare in males but is even rarer in females. Moreover, the classic Danon disease triad of clinical characteristics



(proximal myopathy, mental retardation, and hypertrophic cardiomyopathy) is often not present in female patients (Figure 4).² An important diagnostic clue in these female cases is the presence of a kind of 'pre-excitation' (as we saw in Cases 1 and 3).^{5,6} Historically, Danon disease has been associated with hypertrophic cardiomyopathy.¹ However, some female patients present with a dilated cardiomyopathy phenotype during or after delivery of a child, as we saw in Case 2, which could suggest that some cases of peri-partum cardiomyopathy are due to *LAMP2* mutations.^{7,8} Indeed, an equal percentage of dilated and hypertrophic cardiomyopathy cases can be expected in female patients.⁹ In addition, our Case 2 had no clear signs of pre-excitation even though this is a finding commonly described in patients with Danon.⁸

Several other differences can be found between males and females with Danon disease. Males more often report cognitive and skeletal muscle complaints, although recent data suggests that females have these complaints more often than previously recognized.⁹ The mean age of first symptoms is also later in females (27.9 years vs. 12.1 years in males), as is the time to first heart transplantation, and survival is longer in female patients.^{9,10} However, a study in a family with many female carriers showed that the symptoms of heart failure can be rapidly progressive, and early heart transplantation should therefore be considered in these patients.⁶ As Case 2 illustrated, mechanical support is sometimes needed, as bridge to decision, and there are also reports with permanent left ventricular assist devices.^{11,12} Additionally, the incidence of sudden death was reported to be high in this family, with four of six females dying suddenly between 37 and 54 years of age.⁶ Therefore, given the variability of presentation, clinical diagnosis of Danon disease in women can be very challenging, which emphasizes the importance of genetic testing to look for *LAMP2* mutations.

In conclusion, Danon disease is a rare disease in which the primarily cardiac phenotype seen in our three female cases is even rarer.

These cases show that presentation in women can be more variable than that typically seen in men. One should, therefore, consider Danon disease in female patients with either heart failure or arrhythmias without a clear diagnosis and/or with a pre-excitation-like ECG, and genetic testing plays a crucial role in this diagnosis.

Lead author biography



Bart Mulder is a cardiologist in training (final year) with specialty training in electrophysiology and device therapy. He graduated from medical school in 2012 and defended his PhD thesis "Optimizing therapy in patients with atrial fibrillation and heart failure" successfully in 2015.

Supplementary material

Supplementary material is available at *European Heart Journal - Case Reports* online.

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Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as [Supplementary data](#).

Consent: The author/s confirm that written consent for submission and publication of this case report including image(s) and associated text has been obtained from the patient in line with COPE guidance.

Conflict of interest: none declared.

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