Case Report

Journal of INTERNATIONAL MEDICAL RESEARCH

Journal of International Medical Research
49(2) 1–10

DOI: 10.1177/0300060520986676
journals.sagepub.com/home/imr
SAGE

Progression of Danon disease with medical imaging: two case reports

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Abstract

Danon disease is a rare X-linked dominant genetic disorder caused by loss-of-function mutations in the lysosome-associated membrane protein 2 gene. Progression of Danon disease is unknown because of its rare incidence in a diverse ethnic population. We report longitudinal data from two patients who were diagnosed with Danon disease by a genetic test. The evaluation protocol included electrocardiographic monitoring, echocardiography, and magnetic resonance imaging. Progression of hypertrophic cardiomyopathy to dilated cardiomyopathy was observed in the first patient. He died from sudden cardiac arrest. The second patient is currently suffering from hypertrophic cardiomyopathy. Development of the hypertrophic phase progressing into the dilated phase in Danon disease may provide useful information for early identification and clinical decisions in patients with this disease.

Keywords

Danon disease, hypertrophic cardiomyopathy, dilated cardiomyopathy, medical imaging, lysosome-associated membrane protein 2 gene, Wolff–Parkinson–White syndrome

Date received: 30 September 2020; accepted: 15 December 2020

Introduction

Danon disease is a type of lysosomal glycogen storage disease with normal acid maltase.[1] Danon disease is a rare X-linked

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dominant genetic disorder caused by loss-of-function mutations in the lysosome-associated membrane protein 2 (*LAMP-2*) gene. This disease can be distinguished from other vacuolar myopathies by the presence of glycogen particles in cell debris, and acetylcholine and nonspecific esterase activity in small basophilic vacuolar membranes.[2] The triad of hypertrophic cardiomyopathy, myopathy, and intellectual disability are some of the classical clinical features of Danon disease in boys.[1–4] Cardiomyopathy in Danon disease classically presents as hypertrophic cardiomyopathy (HCM) in most male patients and progresses as dilated cardiomyopathy (DCM) in some of the patients.[5–8] In contrast, in female patients, DCM and HCM have equal prevalence.[6] Other conduction defects are common in Danon disease, including atrial fibrillation, complete heart block, supraventricular tachycardia, and sinus node dysfunction.[9] Late gadolinium enhancement (LGE) in cardiomyocytes shows a marked progression of fibrosis, which is useful for distinguishing ischemic cardiomyopathies from nonischemic cardiomyopathies.[10,11]

We report here longitudinal data from two cases of Danon disease. Clinical and biochemical data, electrocardiograms (ECGs), echocardiography, and magnetic resonance imaging (MRI) were performed to show the features of Danon disease. One of our patients who had Danon disease with a 10-year follow-up showed progress of HCM to DCM.

Case report

Case 1

A 23-year-old man had Danon disease from the age of 12 years, when symptoms began, until 23 years old when he succumbed to his disease. He was first admitted to the Affiliated Hospital of Jining Medical University at 12 years old because of transient loss of consciousness with palpitation. He had suffered from a poor ability of physical activity, mild mental retardation, and learning difficulty. Pansystolic murmur along the left lower sternal border was not observed. Echocardiography showed HCM with a maximum left ventricular end-diastolic diameter (LVEDd) of 45 mm, left ventricular posterior wall (LVPW) thickness of 12 mm, maximum interventricular septal (IVS) thickness of 11 mm, and left ventricular ejection fraction (LVEF) of 60%. Electromyography showed normal muscle strength and deep tendon reflexes. He was diagnosed with Danon disease at 13 years of age in Beijing Union Hospital by genetic testing, which showed that he carried a deletion mutation (c.257_258delCC) in exon 3 of the *LAMP-2* gene. An endomyocardial biopsy and electron microscopic examination showed autophagic vacuoles. ECG showed type B Wolff–Parkinson–White (WPW) syndrome, a high voltage in the left ventricle, and an inverted T wave (Figure 1a). He then underwent successful ablation in Beijing Union Hospital.[12] He was asymptomatic for the next 3 years.

At the age of 17 years, he had persistent palpitations and visited the hospital. ECG (Figure 1b) showed an ectopic rhythm, paroxysmal supraventricular tachycardia, complete left bundle branch block, and high voltage in the left ventricle. He switched to sinus rhythm following treatment with propafenone. However, an ECG (Figure 1c) showed ventricular premature contraction. At a physical examination, a heaving apical impulse and a grade 4/6 pansystolic murmur along the left lower sternal border were observed. Follow-up echocardiography indicated that left ventricular hypertrophy of the patient progressively worsened (Figure 2a, b). MRI was performed and showed LGE in the muscular interventricular septum and the front wall of the left ventricle. However, the liver and bilateral gastrocnemius skeletal muscles were negative for LGE (Figure 3a). This

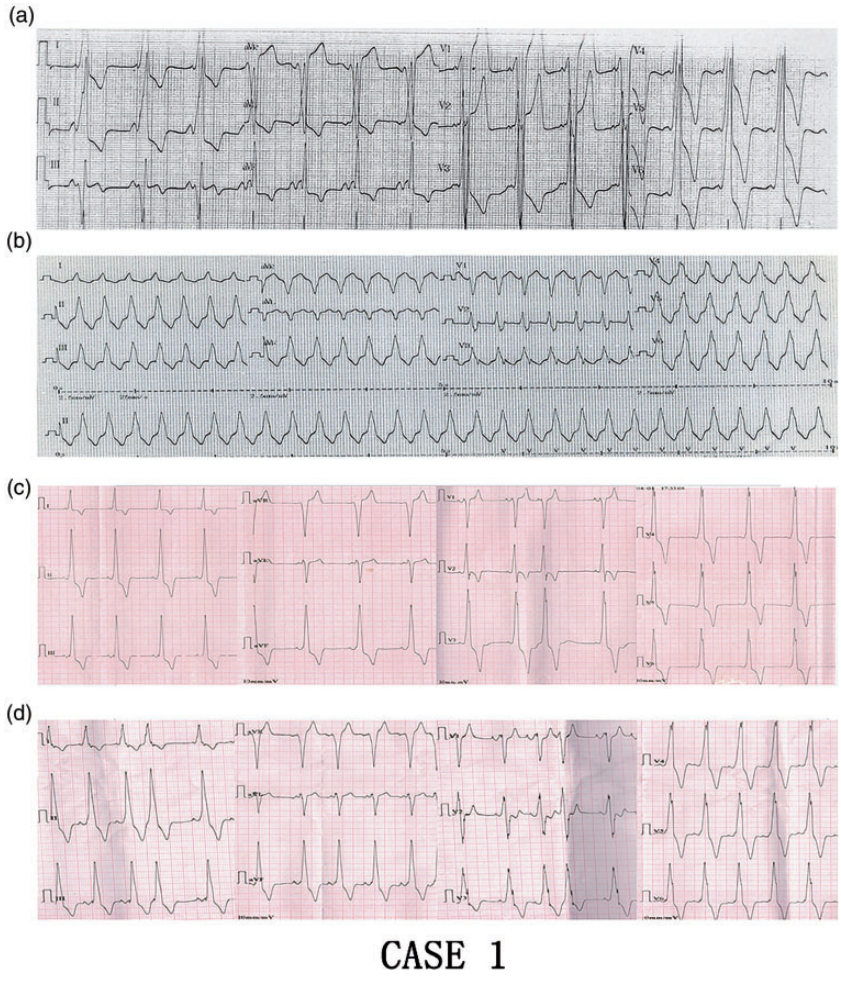

Figure 1. Electrocardiogram of case 1. (a) An electrocardiogram shows Wolff–Parkinson–White syndrome with a high voltage in the left ventricle and an inverted T wave. An electrocardiogram shows supraventricular tachycardia and complete left bundle branch block (b), ventricular premature contraction (c), and atrial fibrillation (d).

process of cardiac hypertrophy was rapidly advancing at this stage.

In the next 4 years, HCM progressed to the dilated phase. The LVEDd increased from 44 to 58 mm, while the IVS decreased from 24 to 19 mm and LVPW decreased from 31 to 17 mm. The LVEF was reduced from 60% to 22% (Figure 2c, d). At the age of 23 years, an ECG (Figure 1d) showed atrial fibrillation. An MRI (Figure 3b) showed that gadolinium contrast enhancement was visible in the liver, psoas muscle, and bilateral gastrocnemius muscles. These abnormal findings manifested with the classic triad of cardiomyopathy, skeletal myopathy, and intellectual disability in this patient. He received an automatic implantable cardioverter-defibrillator, even after considering a heart transplant, which he refused, and he finally succumbed to his disease with sudden cardiac arrest. Unfortunately, the patient did

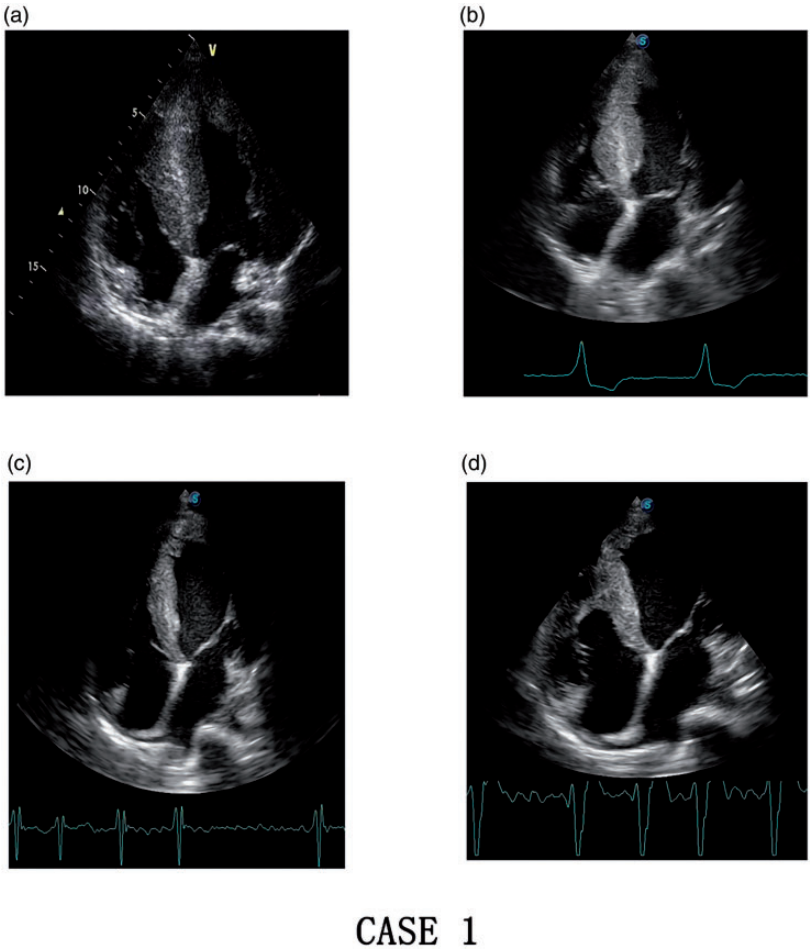

Figure 2. Echocardiography of case 1. (a) Hypertrophic cardiomyopathy with a maximum LVEDd of 43 mm, LVPW of 31 mm, IVS of 27 mm, and LVEF of 60%. (b) Hypertrophic cardiomyopathy with a maximum LVEDd of 45 mm, LVPW of 31 mm, IVS of 24 mm, and a preserved LVEF of 60%. (c) Dilated cardiomyopathy with a maximum LVEDd of 54 mm, LVPW of 27 mm, IVS of 22 mm, and LVEF of 34%. (d) Dilated cardiomyopathy with a maximum LVEDd of 58 mm, LVPW of 17 mm, IVS of 19 mm, and LVEF of 22%.
LVEDd, left ventricular end-diastolic diameter; LVPW, left ventricular posterior wall; IVS, interventricular septum; LVEF, left ventricular ejection fraction.

not undergo an investigation of his device to identify the trigger for cardiac death.

During the 10-year follow-up, pertinent laboratory examination values, including creatine kinase (CK), creatine kinase isoenzyme (CK-MB), hydroxybutyrate dehydrogenase, alanine aminotransferase (ALT), aspartate aminotransferase, and lactic dehydrogenase levels, were considerably elevated (Table 1). Echocardiographic data indicated that HCM had progressed into DCM (Table 2).

Case 2

A Chinese boy has been followed up from 10 years old. Genetic analysis at 10 years old showed that he had Danon disease and was

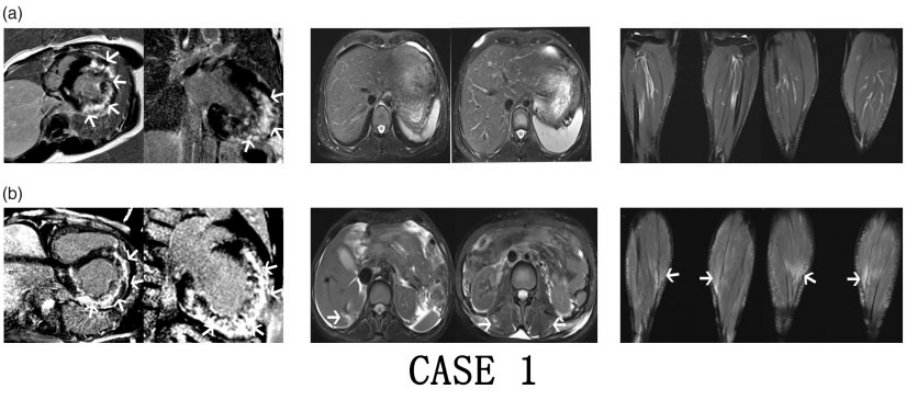

Figure 3. Magnetic resonance imaging of case 1. (a) There is a late gadolinium enhancement pattern in the myocardium, but the liver, psoas muscle, and bilateral gastrocnemius muscles are negative for this enhancement. (b) Late gadolinium enhancement pattern in the liver, psoas muscle, and bilateral gastrocnemius muscles.

Table 1. Laboratory examination values in case 1.

Biomarker	Range	Median	Normal range
CK (U/L)	1628–2423	1978.05	5–200
CK-MB (U/L)	20–54	45.5	<25
HBDH (U/L)	1099–1397	1245.5	80–220
LDH (U/L)	866–1499	1329.5	90–240
ALT (U/L)	286–478	318.95	<50
AST (U/L)	296–685	419	15–40

CK, creatine kinase; CK-MB, creatine kinase isoenzyme; HBDH, hydroxybutyrate dehydrogenase; LDH, lactic dehydrogenase; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Table 2. Echocardiographic data of the two cases with *LAMP-2* gene mutation.

	Year	LVEDd (mm)	IVS (mm)	LVPW (mm)	LVEF (%)
Case 1	2010	45	11	12	60
	2014	43	27	31	60
	2016	45	24	31	55
	2017	54	22	27	34
	2018	57	21	23	23
	2019	58	19	17	22
Case 2					
	2014	48	8	8	55
	2017	55	15	15	63
	2019	51	21	24	61

LAMP-2, lysosome-associated membrane protein 2; LVEDd, left ventricular end-diastolic diameter; IVS, interventricular septum; LVPW, left ventricular posterior wall; LVEF, left ventricular ejection fraction.

hemizygous for an *LAMP-2* mutation, c.257_258delCC, in exon 3 of *LAMP-2*. Biomarker levels were also considerably elevated (CK: 1986 U/L, CK-MB: 42 U/L, ALT: 339 U/L, aspartate aminotransferase: 398 U/L, hydroxybutyrate dehydrogenase: 1080 U/L, and lactic dehydrogenase: 1151 U/L). An ECG showed high voltage in the left ventricle and an inverted T wave (Figure 4a), and echocardiography was normal (LVEDd, IVS, LVPW thickness, and LVEF were 48 mm, 8 mm, 8 mm, and 53%, respectively). An ECG showed WPW syndrome, a high voltage in the left ventricle, and an inverted T wave at 13 years old (Figure 4b). Findings at this time were similar to those in case 1 at 13 years old. Changes in the LVEDd (55 to 51 mm), IVS (15 to 21 mm), LVPW (15 to 24 mm), and LVEF (63% to 61%) were recorded in the next 2 years (Figure 5a, b), as well as changes in MRI (Figure 6). However, he was too overweight to ensure good image quality. MRI showed an expanded scope of gadolinium contrast enhancement, which was visible in the myocardium. However, the

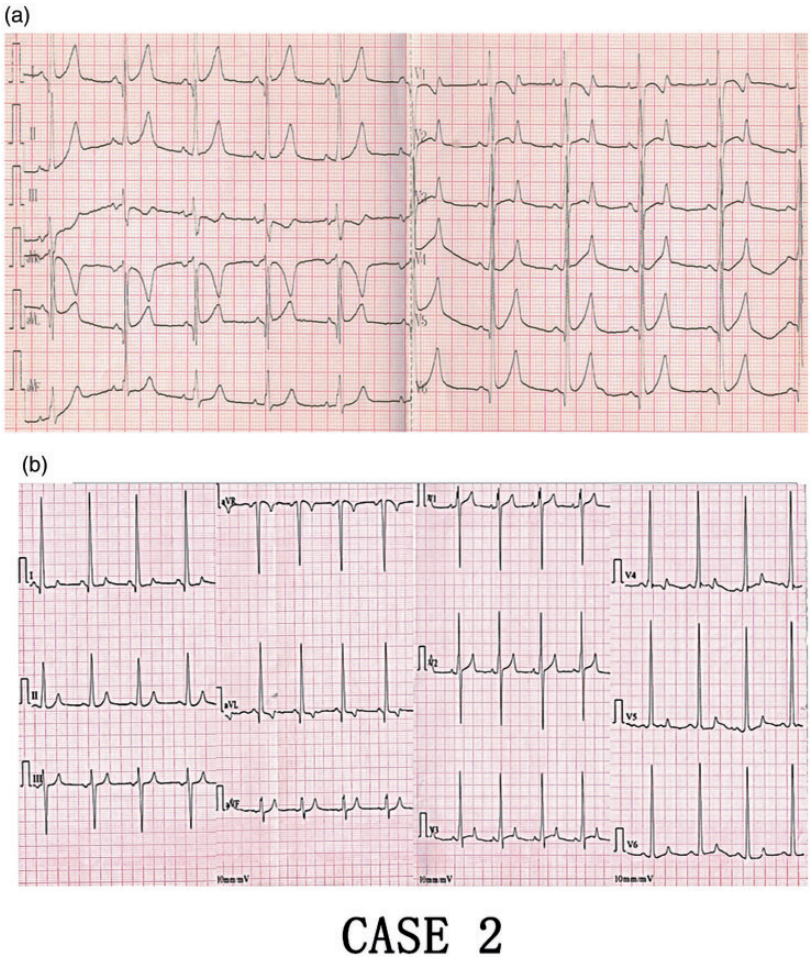

Figure 4. Electrocardiographic changes in case 2. (a) High voltage in the left ventricle and an inverted T wave. (b) Wolff–Parkinson–White syndrome with high voltage in the left ventricle and an inverted T wave.

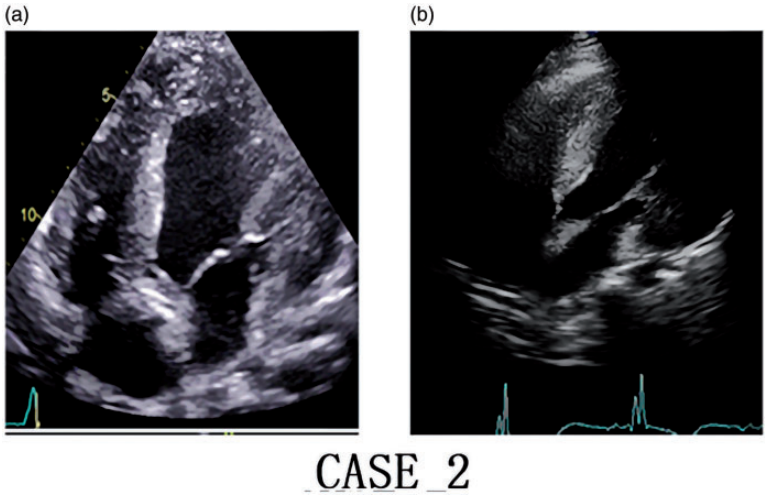

Figure 5. Echocardiography of case 2. (a) Hypertrophic cardiomyopathy with a maximum LVEDd of 55 mm, LVPW of 15 mm, IVS of 15 mm, and LVEF of 63%. (b) Hypertrophic cardiomyopathy with a maximum LVEDd of 54 mm, LVPW of 24 mm, IVS of 21 mm, and LVEF of 61%.
LVEDd, left ventricular end-diastolic diameter; LVPW, left ventricular posterior wall; IVS, interventricular septum; LVEF, left ventricular ejection fraction.

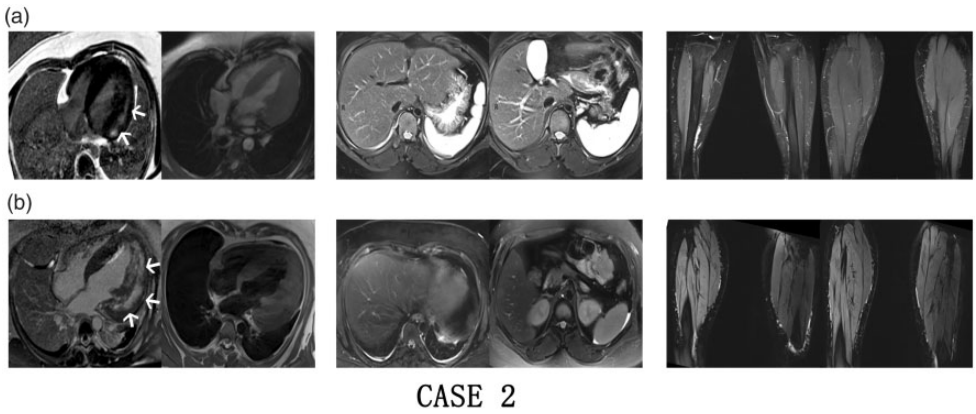

Figure 6. Changes in magnetic resonance imaging in case 2. (a) A late gadolinium enhancement pattern is visible in the myocardium, but negative in the liver, psoas muscle, and bilateral gastrocnemius muscles. (b) Expanded scope of a late gadolinium enhancement pattern in the myocardium, but the liver, psoas muscle, and bilateral gastrocnemius muscles are negative for this enhancement.

liver, psoas muscle, and bilateral gastrocnemius muscles were normal. The boy was deprived of education owing to his intellectual disability. Based on these data, the boy will be followed up in the hypertrophic stage to monitor progression of HCM to DCM.

Discussion

Follow-up of case 1 showed two phases of rapidly progressing hypertrophy and rapidly progressing dilation of hypertrophy. In these two phases, typical and atypical arrhythmias occurred, and clinical

evaluation, echocardiograms, and MRI were performed. In Danon disease, *LAMP-2* mutations cause a significant variety of clinical manifestations. This disease is a multisystem disorder that predominantly affects cardiac and skeletal muscles, and its morbidity is unknown. Malignant arrhythmias and heart failure are the leading causes of death in patients with this disease.[13]

The average age of the first symptoms, diagnosis, and death in male patients with Danon disease is younger than that in female patients.[14] Electrical conduction abnormalities are equally common and present in almost all affected men.[14,15] WPW syndrome is a common ECG abnormality in this disease.[14] Atrial and ventricular arrhythmias are also present in Danon disease. The majority of male patients with Danon disease are mainly accompanied by HCM, but 10% show the DCM phenotype.[15] Congestive heart failure partly complicates progression of HCM to the dilated phenotype in later stages of this disease in young men.[15,16] Two phenotypes were noted in one of our patients. Follow-up of case 1 suggests that HCM is a characteristic feature of the early stage of Danon disease, but DCM may occur in the late stage. Because there is phenotypic variation of Danon disease and progression to DCM is not common in these patients, we are unsure if case 2 will develop DCM.

MRI has recently been used for cardiomyopathies. MRI enables accurate assessment of left ventricular wall thickness, size, and function because of its high spatial resolution. Furthermore, LGE detects the presence of myocardial fibrosis.[17] In our patients, extensive LGE was consistently found in the anterior wall of the left ventricle and was normal in the liver and skeletal muscles in the HCM phase, but it showed myocardial fibrosis, liver damage, and skeletal muscles in the DCM phase. This finding indicates a possible limitation of LGE in the early stage of Danon disease and diffusion in the late stage.

Unfortunately, patients with Danon disease succumb to lethal ventricular tachyarrhythmia.[16] A heart transplant is the most effective form of treatment for this condition.[18] Danon disease should be taken into consideration for adolescents with cardiomyopathy. A cardiac physical examination, ECG, echocardiography, and biochemical examination are the most common examinations for Danon disease. Especially for patients with HCM, risk stratification for sudden cardiac death needs to be identified, with performance of programed ventricular stimulation and techniques, such as MRI, for an individualized prevention strategy.[19,20] Genetic counseling should be provided to families with a family history of Danon disease. Because of the rapidly progressive nature of Danon disease, genetic testing should be performed as soon as possible in HCM.[9] With the latest developments in gene therapy and cell transplantation techniques, genetic manipulations and pharmaceutical approaches may provide a novel therapy for patients with genetic diseases, including Danon disease.

In conclusion, we obtained longitudinal clinical data from disease onset to sudden cardiac death in a patient with classical Danon disease. In our other case, 10-year follow-up showed progression of the hypertrophic phase to the dilated phase. This development may provide useful information for early identification and clinical decisions in patients with Danon disease.

Ethics statement

The study was approved by the Ethics Committee of the Affiliated Hospital of Jining Medical University (approval no.: 2017-Article-001). The patients or parents provided informed consent for publication of the cases.

Author contributions

S.W. and L.G. wrote the manuscript. Q.W. and N.Z. provided the references. Z.L. and X.W. analyzed the data. Y.C. reviewed and edited the manuscript. All authors read and approved the final manuscript.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

Funding

This study was supported by the Natural Science Foundation of China (No. 81670341).

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