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

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Introduction
Danon disease is a type of lysosomal glycogen storage disease with normal acid maltase.¹ Danon disease is a rare X-linked
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. The triad of hypertrophic cardiomyopathy, myopathy, and intellectual disability are some of the classical clinical features of Danon disease in boys. In contrast, in female patients, DCM and HCM have equal prevalence. Other conduction defects are common in Danon disease, including atrial fibrillation, complete heart block, supraventricular tachycardia, and sinus node dysfunction. Late gadolinium enhancement (LGE) in cardiomyocytes shows a marked progression of fibrosis, which is useful for distinguishing ischemic cardiomyopathies from nonischemic cardiomyopathies.

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. 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).
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

**CASE 1**

*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).
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 \textit{LAMP-2} mutation, c.257_258delCC, in exon 3 of \textit{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

\begin{figure}
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\caption{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.}
\end{figure}
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.\textsuperscript{13}

The average age of the first symptoms, diagnosis, and death in male patients with Danon disease is younger than that in female patients.\textsuperscript{14} Electrical conduction abnormalities are equally common and present in almost all affected men.\textsuperscript{14,15} WPW syndrome is a common ECG abnormality in this disease.\textsuperscript{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.\textsuperscript{15} Congestive heart failure partly complicates progression of HCM to the dilated phenotype in later stages of this disease in young men.\textsuperscript{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.\textsuperscript{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.\textsuperscript{16} A heart transplant is the most effective form of treatment for this condition.\textsuperscript{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 programmed ventricular stimulation and techniques, such as MRI, for an individualized prevention strategy.\textsuperscript{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.\textsuperscript{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.

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