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Case Report

Left ventricular assist device implantation in an adult male with Danon disease

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ABSTRACT

Danon disease is an extremely rare inherited disorder characterized by cardiac involvement, myopathy, and intellectual disability. As patients with Danon disease die at an early age, mainly as a result of cardiac involvement, implantation of a left ventricular assist device (LVAD) and/or heart transplantation are essential options. However, various comorbidities associated with Danon disease should be assessed when these patients are being considered as potential heart transplant candidates. We report the case of an adult male patient with dilated-phase hypertrophic cardiomyopathy secondary to Danon disease, who received an LVAD as a bridge to transplantation.

<**Learning objective:** Some patients with Danon disease who underwent heart transplantation have been reported in Japan, but all were female. Male patients with Danon disease have more severe systemic comorbidities than females and heart failure progression is usually too rapid for them to be listed as heart transplant candidates. We present a rare case of an adult male with Danon disease who successfully underwent implantation of a left-ventricular assist device as a bridge to transplantation.>

Introduction

Danon disease was first described by Danon et al. as lysosomal glycogen storage disease with normal acid maltase [1]. This disease is one of the autophagic vacuolar myopathies caused by a primary deficiency of lysosome-associated membrane protein-2 (LAMP-2) and is known as an X-linked dominant disorder [2]. The clinical features of Danon disease differ between males and females, with males being more severely affected. Males with Danon disease are characterized by the triad of cardiomyopathy, myopathy, and intellectual disability, whereas female patients mainly present with cardiomyopathy. Various comorbidities, such as hepatic disorder, respiratory disorder, and retinopathy, have also been reported in patients with Danon disease [3,4]. As cardiac comorbidity is recognized as a prognostic factor for mortality, both implantation of a left ventricular assist device (LVAD) and heart transplantation (HTx) could be effective therapeutic options for Danon disease with severe cardiac involvement. However, as most adult male patients with Danon disease are deemed ineligible for both LVAD and HTx, because of various severe comorbidities other than cardiac disease, reports concerning LVAD and/or HTx therapies for adult male patients with Danon disease are lacking.

Here we report the case of an adult male patient with Danon disease who successfully underwent LVAD as a bridge to transplantation (BTT).

Case report

A 23-year-old male who had been genetically diagnosed with Danon disease at the age of 13 was referred to our institution for

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evaluation of his heart transplant candidacy. His mother died from suspected dilated cardiomyopathy at the age of 30 and his younger sister had also received medical treatments for dilated-phase hypertrophic cardiomyopathy.

At the age of 13, the patient underwent a medical workup because of short stature and elevation of both transaminase and creatine phosphokinase. After a series of examinations, Danon disease was strongly suspected from both histopathological and biochemical analysis of skeletal muscle biopsy specimens. Regarding cardiac involvement, the echocardiogram revealed hypertrophic cardiomyopathy with a preserved ejection fraction. The diagnosis of Danon disease was made on the basis of genetic testing (c.877C > T in exon 7).

The patient's clinical course was uneventful under outpatient care, except for persisting elevation of transaminase, total bilirubin, and creatine phosphokinase. He played tennis until he reached 15 years old, but stopped on doctor's orders. He worked as a part-time employee after graduating from regular community school and showed no problems with interpersonal relationships, though his intelligence quotient (IQ) was 64 points.

At the age of 23, the patient was hospitalized for his first episode of heart failure and was further referred to our institution. On admission, the patient was on a continuous infusion of milrinone 0.66 μg/kg/min. The echocardiogram revealed left ventricular dilation with severely reduced contraction (left ventricular diastolic dimension 61 mm, ejection fraction 13%) and the electrocardiogram showed an intraventricular conduction defect with first-degree atrioventricular block (Fig. 1). Pulmonary hypertension (mean pulmonary arterial pressure 42 mmHg) with severely elevated left ventricular filling pressure (pulmonary arterial wedge pressure 33 mmHg), together with low cardiac output (cardiac index 1.86 L/min/m^2), were also demonstrated by right heart catheterization. Based on these results, both dobutamine and milrinone were given, and the patient became dependent on inotropes with persistent elevations of transaminase and total bilirubin. Therefore, the patient was listed as a heart transplant candidate and underwent LVAD implantation (Jarvik 2000) as a BTT (Fig. 1). He was extubated on postoperative day 1 and was weaned from inotropic agents on postoperative day 2. The clinical course after LVAD implantation was almost satisfactory except for a stroke on postoperative day 3, which was completely recanalized by emergent catheter angioplasty without any neurological deficits. Echocardiography revealed a left ventricular diastolic dimension of 57 mm and ejection fraction 10% under Jarvik 2000 pump speed setting dial 2 and the patient's hemodynamics were almost compensated (mean pulmonary arterial pressure 18 mmHg, pulmonary arterial wedge pressure 4 mmHg, and cardiac index 2.46 L/min/m^2). His blood tests stabilized (Table 1). His younger sister and aunt would provide support in an emergency related to LVAD. The patient and his caregivers easily adapted to the presence of the LVAD and he was discharged 101 days after implantation.

Discussion

Danon disease is caused by mutation of the LAMP-2 gene, which codes for a major lysosomal membrane protein; LAMP-2 deficiency results in various organ disorders. As cardiac involvement can

Table 1 A series of examinations before LVAD implantation and at the time of discharge.

	Before LVAD	Before discharge
Blood test		
Total bilirubin (mg/dL)	2.6	2.4
Aspartate aminotransferase (IU/L)	182	200
Alanine aminotransferase (IU/L)	117	114
Creatine phosphokinase (IU/L)	497	436
Creatinine (mg/dL)	0.55	0.47
Brain natriuretic peptide (pg/mL)	1601.7	771.6
Echocardiography		
LVDD (mm)	61	55
LVSD (mm)	51	53
LVEF (%)	13	13
Hemodynamics		
MPAP (mmHg)	42	18
PAWP (mmHg)	33	4
RAP (mmHg)	11	6
CI (L/min/m^2)	1.86	2.46

LVAD, left ventricular assist device; LVDD, left ventricular diastolic dimension; LVSD, left ventricular systolic dimension; LVEF, left ventricular ejection fraction; MPAP, mean pulmonary arterial pressure; PAWP, pulmonary arterial wedge pressure; RAP, right atrial pressure; CI, cardiac index.

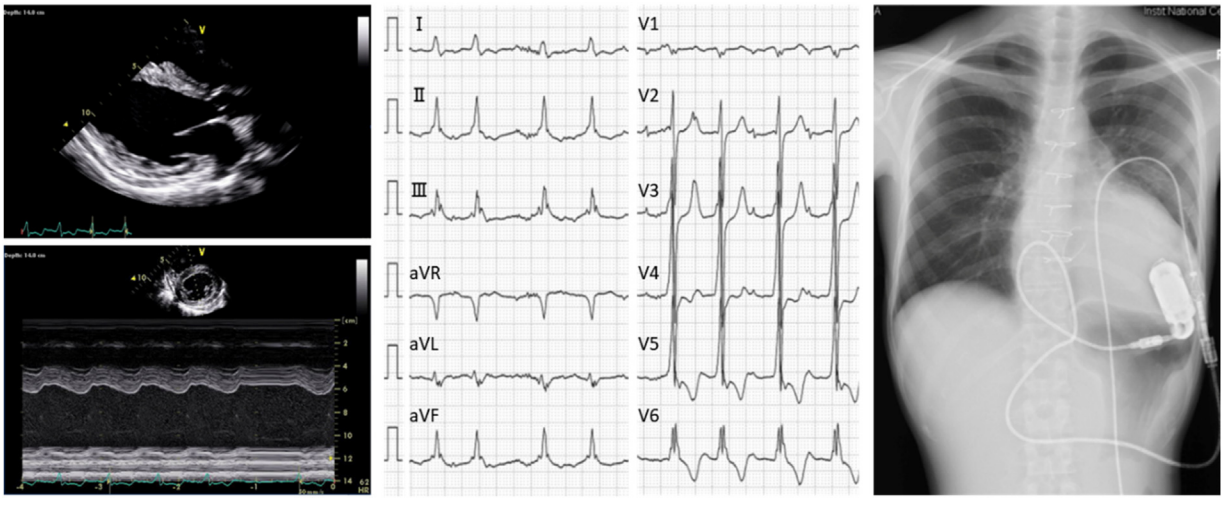

Fig. 1. Echocardiography (left) and electrocardiogram (middle) on admission, and chest X-ray after implantation of a left ventricular assist device (Jarvik 2000) (right). The left ventricle was dilated with reduced contraction, IVST 10 mm, LVPWT 7 mm, LVDD 61 mm, and LVEF 13%. An intraventricular conduction defect with first-degree atrioventricular block, high voltage in left precordial leads, and negative T-waves in V5-6 are shown.
IVST, interventricular septal thickness; LVPWT, left ventricular posterior wall thickness; LVDD, left ventricular diastolic dimension; LVEF, left ventricular ejection fraction.

cause a fatal outcome, advanced therapeutic options such as LVAD and/or HTx should be considered in patients with Danon disease. However, as male patients with Danon disease are prone to complications involving various severe systemic disorders and can die at an early age, they have generally been considered relatively ineligible for HTx. Because the implantable LVAD has only been approved for BTT use in our country, LVAD therapy has also been restricted to adult male patients with Danon disease suffering advanced heart failure. Our patient, who had several Danon disease-related comorbidities, managed to be approved as a transplant candidate and was also able to undergo LVAD implantation. Therefore, even adult male patients with Danon disease have a chance to be treated with advanced therapeutic options, such as LVAD and/or HTx. Here we have described the details of our patient's systemic comorbidities and how he was evaluated as a candidate for HTx.

Firstly, dilated or hypertrophic cardiomyopathy secondary to Danon disease can cause cardiac death from ventricular arrhythmia or heart failure, which has a poor prognosis, especially in male patients. Abnormal electrocardiogram findings related to cardiomyopathy are recognized in almost all patients with Danon disease, but Wolf–Parkinson–White syndrome is considered the most common abnormality. High voltage in precordial leads, a deep negative T-wave, and impaired atrioventricular conduction are also common [3,4]. To our knowledge, only one report from Japan has been published regarding implantable LVAD and HTx therapies in adult female patients [5]; our case is the first report of an adult male patient who underwent LVAD implantation for BTT (Table 2). As some male HTx cases with advanced cardiomyopathy had relatively stable courses after heart transplantation [6–8], advanced therapeutic options should always be considered for cardiac involvement with Danon disease.

Secondly, myopathy is usually mild and hardly progressive [4]. An elevation of creatine phosphokinase values is likely to be seen in male patients, but generally mild proximal limb and neck muscle weakness do not hinder daily activities. Myopathy associated with Danon disease is unlikely to be a contraindication for HTx. Disorders of respiratory function have been reported infrequently [3].

Thirdly, mild intellectual disability is present in approximately 70%–100% of male patients with Danon disease and their IQ scores tend to be within the range of 60–91 points [3,4]. However, most of them are capable of writing, reading, working, and building relationships with other people. Although mild electroencephalographic abnormalities and a decrease in cerebral glucose metabolism have been reported, no patients showed any structural brain abnormalities. Although our patient had a low IQ score without any organic abnormalities, he was able to form a good relationship with our medical staff and to completely understand how to operate the LVAD. He also passed the written test concerning the LVAD with a full score.

Fourthly, mild liver dysfunction with transaminase elevation to around 300 U/L is often seen, especially in male patients [3,4]. The etiology of liver dysfunction involves a decline in bile flow, with dilated bile canaliculi lacking in microvilli, and accumulation of bile acid in the liver that may result in mild liver injury [9]. Portal and central venous sclerotic lesions, vacuolated hepatocytes, and enlarged mitochondria with ragged crista have also been reported in pathological findings, and are considered to be primary disorders associated with Danon disease [10]. However, these mild liver dysfunctions in Danon disease have not been generally considered as a lethal comorbidity; we therefore recognized that our patient could be listed as a transplant candidate. Although elevations of transaminase and bilirubin continued after LVAD implantation in our case, the patient's hepatic function has not deteriorated but has remained stable.

Finally, round-the-clock caregivers are needed for patients with LVAD in Japan, and the patient's family may have to assume the role of caregiver. However, family members may have the same genetic disorder and may be incapable of providing care. A healthy aunt and sister with cardiomyopathy became caregivers for our patient, but at some point, it may be necessary for patients with LVAD to become caregivers for each other, with backup from at least one healthy person.

In conclusion, it is important for advanced treatment options such as LVAD and/or HTx to be considered even in male Danon disease. The further accumulation of cases with Danon disease and investigation of the mechanisms of their diverse symptoms are needed.

Table 2 Differences in clinical characteristics between male and female patients.

	This case	Boucek et al. [3]		Sugie et al. [4]		Kitahara et al. [5]		Maron et al. [6]		Lacoste-Collin et al. [8]
Sex	1 male	43 males	39 females	20 males	18 females	2 females		6 males	1 female	1 male
Age at onset	23	12.1 ± 6.5	28.1 ± 15	Until second decade	NA	12	NA	–	–	18
Age at diagnosis (age at evaluation)	13	13.5 ± 7.0	31.4 ± 15.4	(17 ± 7)	(38 ± 12)	18	(39)	12.7 ± 3.8	11	36
Cardiomyopathy	Yes	(100%)	(100%)	20 (100%)	18 (100%)	Yes	Yes	6 (100%)	Yes	Yes
WPW syndrome	No	(68.2%)	(26.7%)	6 (35.3%)	NA	Yes	NA	5 (83.3%)	Yes	Yes
Myopathy	Yes	(80%)	(50%)	18 (90.0%)	6 (33.3%)	No	No	NA	NA	Yes
Intellectual disability	Yes	(100%)	(46.6%)	14 (70.0%)	1 (5.6%)	No	No	2 (33.3%)	No	Yes
HTX	No (waiting)	13 (33.3%)	6 (17.6%)	1 (5.0%)	2 (11.0%)	No (waiting)	Yes	1 (16.7%)	No	Yes
LVAD	Yes	–	–	–	–	Yes	Yes	–	–	–
Age at HTX/LVAD	23 (LVAD)	18.1 ± 5.9	34.5 ± 15.7	25[a]	NA	19	LVAD at 39 years HTx 990 days after LVAD	NA	–	28
Death	No	16 (41.0%)	11 (32.4%)	7 (35.0%)	6 (33.3%)	No	No	5 (83.3%)[b]	No	No
Age at death	Alive	19.8 ± 7.1	36.0 ± 16.0	19 ± 6	40 ± 7	alive	alive	20.4 ± 3.5	alive	alive

Age is presented as mean (±standard deviation) for multiple cases. Symptomatic cases and outcomes are presented as a number (percentage) for multiple cases and Yes/No for individuals from the available data in each study.

WPW syndrome, Wolf–Parkinson–White syndrome; HTX, heart transplantation; LVAD, left ventricular assist device; NA, not available.

[a] A patient who underwent heart transplantation was reported by Dworzak et al. [7].

[b] The only survivor among 6 males was a transplanted patient.

Conflict of interest

The authors declare that there is no conflict of interest.

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