REVIEW

Danon disease: focusing on heart

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Danon disease is a rare X-linked dominant lysosomal disease due to the primary deficiency of lysosome-associated membrane protein 2 (LAMP2) gene. Cardiomyopathy, skeletal myopathy and mental retardation are the typical triad of Danon disease. More than 60 LAMP2 mutations have been reported. The molecular mechanism is defects in LAMP2 protein (due to LAMP2 mutation) which causes insidious glycogen accumulation in cardiac muscle cells and resulting in cardiac hypertrophy and electrophysiological abnormalities. However, there are significant differences between the male and female Danon disease patients with regard to clinical features and cardiac manifestations. The clinical symptoms are variable, from asymptomatic to sudden cardiac death. Wolff–Parkinson–White syndrome is more common in male than female patients. Hypertrophic cardiomyopathy is predominant in male patients, whereas the similar prevalence of hypertrophic and dilated cardiomyopathy in female patients. Male patients are diagnosed usually at teenage, whereas the diagnosis and events occurred approximately 15 years later in female than male patients. Heart transplantation is the reliable treatment once the occurrence of heart failure and should be considered as early as possible due to its rapid progression.

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Danon disease is an X-linked dominant lysosomal disease¹ due to the primary deficiency of lysosome-associated membrane protein 2 (LAMP2) gene.² Although apparently rare, the geographic distribution of Danon disease is wide, reported from the USA, Italy, Australia, Sweden, the UK, Japan and China.^{3–11} The pathological hallmark of the disease is intracytoplasmic vacuoles containing autophagic material and glycogen in cardiac (Figure 1) and skeletal muscle cells.^{1,12} The final diagnosis is based on the genetic analysis of LAMP2 gene. LAMP2 gene is located on Xq24, including nine exons (1–9a) and intron–exon junctions.¹³ More than 60 mutations of LAMP2 gene have been reported. The reported LAMP2 mutations in the past 10 years are summarized in Table 1. Cardiomyopathy, skeletal myopathy and mental retardation are the typical triad of Danon disease.^{5,14,15} The article will focus on heart, from molecular mechanism, clinical features to characteristics of electrocardiography and echocardiography as well as treatment.

MOLECULAR MECHANISM

Glucose enters cardiac muscle cells through transport proteins and undergoes phosphorylation by hexokinase, after which it is targeted for glycolysis or glycogen (a branched glucose polymer containing 93 percent 1–4 glucose bonds and 7 percent branched 1–6 glucose bonds, is a dynamic reservoir of energy for cardiac muscles) synthesis by glycogen synthase. Defects in glycogen degradation pathways (including lysosome activity) result in glycogen accumulation in

cardiac muscle cells. Therefore, defects in LAMP2 protein (due to LAMP2 mutation) cause insidious glycogen accumulation, resulting in cardiac hypertrophy and electrophysiological abnormalities.

Figure 1 Electron microscopic examinations revealed the autophagic vacuole (arrow indicated) containing glycogen particles in cardiac muscle cells in one patient who underwent endomyocardial biopsy (magnification $\times 15\,000$).

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Table 1 Reported mutations of *LAMP2* gene in past 10 years^a

Authors	Mutation	Location	Mutation type
Cheng <i>et al.</i> ³	c.808_809 insG	Exon 6	Frameshift
	c.320_321 insCATC	Exon 3	Frameshift
	c.257_258delCC	Exon 3	Frameshift
Cottinet <i>et al.</i> ⁴	c.864 + 1delG	IVS-6	Splicing
Boucek <i>et al.</i> ⁵	c.-22_30delCGCCGCCGT	Promoter	-
	c.1-?_64 + ?	Exon 1	Large deletion
	c.64 + 1G>A	IVS-1	Splicing
	c.183 + 1G>A	IVS-2	Splicing
	c.247C>T	Exon 3	Stop codon
	c.398-?_1233 + ?del	Exons 4–10	Large deletion
	c.507 G>A	Exon 4	Stop codon
	c.865-1 G>C	IVS-6	Splicing
	c. 1082 delA	Exon 8	Frameshift
	c.-1137-1140 del TATA/ins GCTGGTCCAAT	Exon 9B	Insertion/deletion
Kim <i>et al.</i> ⁶	c.241delG	Exon 3	Frameshift
Yang <i>et al.</i> ⁷	(TA) _n simple repeat	5'UTR and exon 1	microdeletion
Toib <i>et al.</i> ⁸	c.293 G>A	Exon 3	Stop codon
Sabourdy <i>et al.</i> ⁹	c.716delT	Exon 5	Frameshift
Regelsberger <i>et al.</i> ¹⁰	c.179 delC	Exon 2	Frameshift
Dougu <i>et al.</i> ¹¹	c.573 delA	Exon 5	Frameshift
Di Blasi <i>et al.</i> ¹⁷	c.1093 + 1G>C	IVS-8	Splicing
Iascone <i>et al.</i> ¹⁸	c.877 C>T	Exon 7	Stop codon
van der Kooi <i>et al.</i> ¹⁹	c.1150G>C	Exon 9B	Missense
Bui <i>et al.</i> ²⁰	c.864 + 3-6delGAGT	IVS-6	Splicing
Nadeau <i>et al.</i> ²¹	c.865-3C>A	IVS-6	Splicing
Tunon <i>et al.</i> ²²	c.1093 + 2 T>A	IVS-8	Splicing
Taylor <i>et al.</i> ²³	c.1219delA	Exon 8	Frameshift
Fanin <i>et al.</i> ²⁴	c.680_701del	Exon 5	Frameshift
	c.796_797insC	Exon 6	Frameshift
	c.294 G>A	Exon 3	Stop codon
Echaniz-Laguna <i>et al.</i> ²⁵	c.102_103 delAG	Exon 2	Frameshift
Yang <i>et al.</i> ²⁶	c.467 T>G	Exon 4	Stop codon
	c.1075 C>T	Exon 8	Stop codon
Balmer <i>et al.</i> ²⁷	c.138 G>A	Exon 2	Stop codon
Lobrinus <i>et al.</i> ²⁸	c.470 C>G	Exon 4	Stop codon
Musumeci <i>et al.</i> ²⁹	c.961 T>C	Exon 8	Nonsynonymous
Arad <i>et al.</i> ¹⁵	c.64 + 1G>T	IVS-1	Splicing
	c.65_2A>G	IVS-1	Frameshift
	c.864 + 1-4 del GTGA	IVS-6	Splicing
	c.865_2A>G	IVS-6	Frameshift
	c.928 G>A	Exon 7	Missense
	c.327T>A	Exon 3	Stop codon
Charron <i>et al.</i> ³⁰	c.36_42delAGGGCTC	Exon 1	Frameshift
	c.520 C>T	Exon 4	Stop codon
Horváth <i>et al.</i> ³¹	c.929_1G>A	IVS-7	Splicing
Lacoste-Collin <i>et al.</i> ³²	c.874_897del AACCGATTTATCTGAAGGAAGTG	Exon 7	Large deletion
Takahashi <i>et al.</i> ³³	c.883_884 insT	Exon 7	Frameshift

^aOnly the first report of the same mutation was listed.

CLINICAL FEATURES

The prevalence is significantly higher in men than women.⁵ Men are severely affected, and heart is involved in 88% male patients with the predominance of hypertrophic cardiomyopathy.⁵ Men have a high morbidity and are unlikely to reach the age of 25 years without a cardiac transplantation.¹⁴ Women are less severely affected, with an equal prevalence of dilated cardiomyopathy and hypertrophic cardiomyopathy.⁵ The average ages of first symptom, cardiac transplantation, and death are 12.1, 17.9 and 19.0 years in men and

27.9, 33.7 and 34.6 years in women, respectively; occurrence of events was 15 years later in female than male patients.⁵ Symptoms are variable, from asymptomatic to sudden cardiac death (SCD). Palpitations and chest pain are the most common symptoms. Maron *et al.*¹⁴ reported seven Danon disease patients (six male) were classified New York Heart Association class I at cardiac diagnosis and recognized by virtue of heart murmur, family screening, abnormal electrocardiography or symptoms (chest pain and syncope); all the seven patients experienced serious adverse events

during 8.6 ± 2.6 years follow-up, including death of acute or progressive heart failure in four, SCD in two and heart transplantation in one. All the seven patients developed marked left ventricular (LV) systolic dysfunction (LV ejection fraction $25\% \pm 7\%$) with rapid deterioration with time interval from clinical stability to end stage of heart failure as brief as 6 months.

However, female patients have a different clinical course. Miani *et al.*¹⁶ reported six female patients showing a severe arrhythmogenic phenotype, including four patients who died suddenly (one aborted) at 37–54 years of age, and the other two patients underwent heart transplantation. Gene dosage probably accounts for the different clinical consequences of X-linked LAMP2 mutations in men as compared with women.¹⁵ Gene dosage also contributed to different clinical expression in men with different LAMP2 mutations, the partial function of mutant LAMP2 proteins may be preserved resulting from different LAMP2 mutations.¹⁵

CHARACTERISTICS OF ELECTROCARDIOGRAPHY AND ECHOCARDIOGRAPHY

Conduction abnormalities are very common in male patients, Cheng *et al.*³ reported two of three and Maron *et al.*¹⁴ reported five of six male patients having Wolff–Parkinson–White (WPW) syndrome with maximal LV voltage of 1.5–14.5 mV as well as T-wave inversion. Toib *et al.*⁸ reported only one of seven and Miani *et al.*¹⁶ reported only two of six female patients with WPW syndrome. Boucek *et al.*⁵ summarized a total of 145 Danon disease patients, 68% male and 27% female patients had a WPW pattern on electrocardiography.

The findings on echocardiography are different in male and female patients, male patients predominantly are having hypertrophic cardiomyopathy, Maron *et al.*¹⁴ reported the maximal LV thickness of 29–65 mm with normal LV ejection fraction and LV cavity dimensions at diagnosis, and evolved into dilated or enlarged during the follow-up. Cheng *et al.*³ reported all the three male patients with concentric LV hypertrophy with maximal LV thickness of 14–34 mm, normal LV ejection fraction and LV cavity dimensions at diagnosis. However, female patients had the equal prevalence of hypertrophic and dilated cardiomyopathy.

TREATMENT

Catheter ablation is an effective method for the abolishment of WPW syndrome. Boucek *et al.*⁵ reported half of the male and one third of the female patients underwent catheter ablation.

SCD is common in patients with Danon disease, especially in female patients.¹⁶ Implantable cardioverter defibrillator (ICD) implantation is one preventive treatment for SCD. Boucek *et al.*⁵ reported 41% male and 31% female patients received ICDs. However, ICD was less effective in patients with Danon disease than other cardiac disease (such as ischemic heart disease). Maron *et al.*¹⁴ reported that all the seven patients had received ICDs, which ultimately failed to terminate lethal ventricular tachyarrhythmias in five. Heart transplantation significantly enhances the survival of patients with Danon disease, although only 17.6% patients underwent heart transplantation.⁵ Therefore, physicians should consider early intervention with heart transplantation once LV dysfunction occurs owing to the rapid progression of the disease.^{5,14}

In conclusion, there are significant differences between male and female Danon disease patients with regard to clinical features and cardiac manifestations. WPW syndrome is more common in male than female patients. Hypertrophic cardiomyopathy is predominant in male patients, whereas the similar prevalence of hypertrophic and dilated cardiomyopathy in female patients. However, the clinical

symptoms and events occurred approximately 15 years later in female than male patients. Heart transplantation is the reliable treatment once the occurrence of heart failure and should be considered as early as possible due to its rapid progression.

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