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Danon disease as a cause of concentric left ventricular hypertrophy in patients who underwent endomyocardial biopsy

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Background Danon disease is an X-linked dominant disorder; concentric left ventricular hypertrophy (LVH) is one of its manifestations. In this study, we investigated the prevalence of Danon disease in patients with concentric LVH who underwent endomyocardial biopsy (EMB).

Methods and results A total of 50 patients with concentric LVH underwent EMB from January 2008 to December 2010. Cardiac amyloidosis was diagnosed in 14 patients; genetic analysis of lysosome-associated membrane protein 2 (LAMP2) was done in the remaining 36 patients. Three novel LAMP2 frameshift mutations were found. They were c.808_809 insG in exon 6, c.320_321 insCATC in exon 3, and c.257_258delCC in exon 3, leading to a premature stop codon on cDNA analysis. The prevalence of Danon disease was seen in 6% (3 of 50) of unselected concentric LVH patients who underwent EMB, or 8% (3 of 36) after excluding cardiac amyloidosis through EMB. All the three patients were male teenagers with a mean age of 15 ± 1 years, and had mild mental retardation, two of the three with Wolff–Parkinson–White (WPW) syndrome and markedly increased left ventricular voltage. All the three patients had increased serum hepatic enzymes and creatine kinase (CK) concentrations. There was no death or cardiovascular hospitalization during 20 ± 15 months of follow-up.

Conclusions Danon disease may account for a number of patients with concentric LVH who underwent EMB. Danon disease should be suspected in the male teenager with concentric LVH, especially with elevated serum hepatic enzymes and CK concentrations, and/or WPW syndrome with markedly increased voltage of the left ventricle. Genetic analysis of LAMP2 can help make the diagnosis.

Keywords Danon disease • LAMP2 • Genetics • Left ventricular hypertrophy • Endomyocardial biopsy

Introduction

Concentric left ventricular hypertrophy (LVH) is a common finding, the majority of which is due to long-term severe hypertension or aortic stenosis. Endomyocardial biopsy (EMB) could help make the diagnosis for unexplained concentric LVH, because for a part of the patients the cause found to be infiltrative cardiomyopathy. However, there are still many unexplained cases of concentric left ventricular hypertrophy for which one make the diagnosis. Previous studies[1–3] showed that glycogen storage disease, such as Danon disease, could be the cause of hypertrophic cardiomyopathy (HCM). Danon disease is an X-linked dominant lysosomal disease[4] due to a primary deficiency of lysosome-associated membrane protein 2 (LAMP2).[3] The pathological hallmark of the disease is intracytoplasmic vacuoles containing autophagic material and glycogen in cardiac and skeletal muscle cells.[2,4] The phenotype typically associated with mutations in the LAMP2 gene is characterized by cardiomyopathy, skeletal myopathy, and mental retardation[2,3]; Wolff–Parkinson–White (WPW) syndrome is very common. The phenotypic expression of Danon

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disease is, however, variable.[2] The objective of the present study was to identify Danon disease from patients with unknown concentric LVH at discharge after EMB. Therefore, we decided systematically to screen the LAMP2 gene in consecutive patients with unexplained concentric LVH after EMB.

Methods

Study population

A total of 50 consecutive patients with concentric LVH [maximum left ventricular wall thickness >13 mm and the ratio between maximum thickness of interventricular septum (IVS) and left ventricular posterior wall (LVPW) <1.3], who underwent EMB in Peking Union Medical College Hospital from January 2008 to December 2010, were enrolled. Fourteen patients were diagnosed as cardiac amyloidosis with positive Congo red staining with demonstration of apple-green birefringence under a polarizing microscope. LAMP2 genetic analysis was done for the remaining 36 consecutive unknown patients through EMB after obtaining written informed consent. A total of three patients with positive LAMP2 mutation constituted the study patients (Danon disease group). The remaining 33 patients with unknown concentric LVH constituted the non-Danon disease group (*Figure 1*), including diastolic heart failure in 14 patients, arrhythmia referred for catheter ablation or pacemaker implantation in 11 patients (concealed atrioventricular accessory pathways in 3 patients, atrioventricular nodal re-entrant tachycardia in 5 patients, and third degree atrioventricular block in 3 patients), and left bundle branch block in 8 patients.

Data collection

We performed a detailed examination of the medical records of the 36 patients after obtaining the approval from the Institutional Review Board of Peking Union Medical College Hospital. The following information was reviewed and recorded: demographic data including mental retardation, New York Heart Association (NYHA) heart failure class at the time of EMB, ECGs, and ECHOs findings, serum hepatic enzymes [including alanine aminotransferase (ALT), aspartate aminotransferase (AST), and lactate dehydrogenase (LDH)], creatine kinase (CK), cardiac tropoin I (cTnI), and N-terminal pro-B-type brain natriuretic peptide (NT-proBNP) concentrations as well as isoenzyme electrophoresis of CK. The ECGs were analysed for the following characteristics: rhythm, PR interval, conduction abnormalities (i.e. WPW syndrome), and the voltage of the left ventricle (defined by sum of the voltages of S_{V1} and $R_{V5/6}$). The ECHOs were analysed for the following characteristics: left atrial (LA) dimension, IVS thickness, LVPW thickness, left ventricular end of diastolic dimension (LVEDD), left ventricular end of systolic dimension (LVESD), left ventricular ejection fraction (LVEF), and E/A ratio. Trans-thoracic ECHO was performed using commercially available GE Vivid 7 Ultrasound machines. Interventricular septal and LVPW thicknesses were measured in standard fashion according to American Society of Echocardiography guidelines.[5] Also, LA dimension and LVEDD as well as LVESD were measured in standard fashion. The left ventricular ejection fraction was assessed using the biplane Simpson's equation from apical two-chamber views. Mitral inflow peak velocities of E- and A-waves, were measured in patients in normal sinus rhythm, the E/A-wave ratio was calculated in standard fashion.

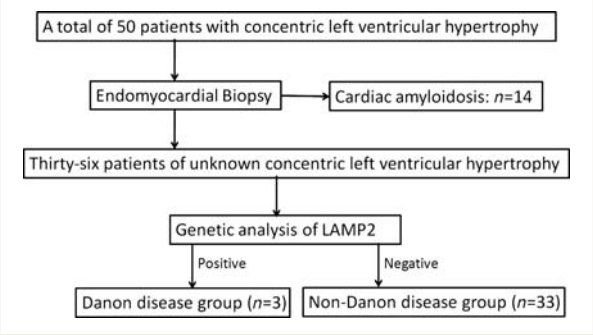

Figure 1 Population evaluated in the study. LAMP2, lysosome-associated membrane protein 2.

Molecular genetics

Genomic DNA was extracted from white blood cells of the 36 patients. We directly sequenced the entire coding regions of the LAMP2 gene, located on Xq24,[6] including the nine exons (1–9a) and intron–exon junctions, with primers previously described.[3] Sequencing reactions were performed with an ABI 3730xl DNA Analyzer (Applied Biosystems, Foster City, CA, USA). Sequence variants were confirmed by re-amplifying and re-sequencing.

Endomyocardial biopsy and electron microscopic examination

Right ventricular biopsy was performed after obtaining the patients' informed consent. Access was by the right internal jugular venous system and fluoroscopic guidance was used to obtain four to six samples of myocardium. Biopsies for the pathological examination were immediately fixed in buffered formaldehyde solution (10%) and embedded in paraffin within 1 day after fixation. These sections were analysed with standard haematoxylin–eosin, Periodic Acid-Schiff (PAS), and Congo red staining in standard fashion. The biopsies were fixed in 2.5% glutaraldehyde and processed for electron microscopic examination. All biopsies were examined by a single, experienced pathologist who was blinded to all other study data.

Follow-up

All the patients were followed up by telephone. The primary outcome was death from any cause. The secondary outcome was cardiovascular hospitalization.

Statistical analysis

Data were reported as mean ± standard deviation (SD) for continuous variables or percentage for categorical variables. Differences in baseline characteristics between the two groups were evaluated with the Mann–Whitney *U* test for all continuous variables, all categorical variables were compared using Fisher's exact test and *P*-values were not adjusted for the issue of multiple testing. All *P*-values were two-sided and the results were considered statistically significant at the level of $P < 0.05$. SPSS statistical software of version 13.0 for windows was used for all statistical analyses.

Results

Clinical features, serum biomarkers, electrocardiographic, and echocardiographic characteristics of the study population

The Danon disease patients were younger than the non-Danon disease patients (15 ± 1 vs. 40 ± 17 years, $P = 0.007$). The percentage of age ≤20 years was higher in the Danon disease group than the non-Danon disease group (100 vs. 15%, $P = 0.008$). The Danon disease group had more NYHA class I at EMB (100 vs. 31%, $P = 0.04$) and mental retardation (100 vs. 3%, $P = 0.001$) than the non-Danon disease group. The percentages of ALT more than three times of the upper limit of normal range (ULN, 100 vs. 12%, $P = 0.005$), AST more than three times of the ULN (100 vs. 3%, $P = 0.001$), LDH more than three times of ULN (100 vs. 0, $P < 0.001$), and CK less than three times of the ULN (100 vs. 12%, $P = 0.005$) were more common in the Danon disease group than the non-Danon disease group. The WPW syndrome on ECG was more common in the Danon disease group than the non-Danon disease group (67 vs. 0, $P = 0.005$). The LVEF (76 ± 3 vs. 53 ± 14%, $P = 0.011$) was higher, and the LVEDD (42 ± 1 vs. 50 ±

Table 1 Clinical features, serum biomarkers, and electrocardiographic and echocardiographic characteristics of the study population

	Danon disease ($n = 3$)	Non-Danon disease ($n = 33$)	*P*-value
Clinical features			
Age (years)	15 ± 1	40 ± 17	0.007
Age ≤20 years	3 (100%)	5 (15%)	0.008
Male	3 (100%)	22 (67%)	0.538
Follow-up (months)	20 ± 15	20 ± 16	0.886
NYHA Class I at EMB	3 (100%)	10 (31%)	0.040
NYHA Class II at EMB	0	18 (55%)	0.229
NYHA Class III at EMB	0	5 (15%)	1.000
Mental retardation	3 (100%)	1 (3%)	0.001
Primary outcome	0	2 (6%)	1.000
Secondary outcome	0	3 (9%)	1.000
Serum biomarkers			
ALT more than three times of ULN	3 (100%)	4 (12%)	0.005
AST more than three times of ULN	3 (100%)	1 (3%)	0.001
LDH more than three times of ULN	3 (100%)	0	<0.001
Serum CK more than three times of ULN	3 (100%)	4 (12%)	0.005
cTnI less than three times of ULN	3 (100%)	27 (82%)	1.000
NT-proBNP more than three times of ULN	3 (100%)	15 (46%)	0.229
Electrocardiography			
Sinus rhythm	3 (100%)	29 (88%)	1.000
WPW	2 (67%)	0	0.005
High voltage of LV[a]	3 (100%)	28 (85%)	1.000
Echocardiography			
Maximum LVPW thickness (mm)	24 ± 10	18 ± 2	0.236
Maximum septum thickness (mm)	24 ± 9	18 ± 2	0.297
Left ventricular ejection fraction	76 ± 3%	53 ± 14%	0.011
LV end of diastolic dimension (mm)	42 ± 1	50 ± 7	0.029
LV end of systolic dimension (mm)	24 ± 1	35 ± 8	0.014
Left atrial dimension (mm)	37 ± 9	39 ± 7	0.709
E/A ratio	1.7 ± 0.7	1.9 ± 1.3	0.855
Reduced LV compliance	2 (67%)	19 (58%)	1.000
Pericardial effusion	1 (33%)	8 (24%)	1.000

NYHA, New York Heart Association; EMB, endomyocardial biopsy; ALT, alanine transpeptidase; ULN, upper limit of normal range; AST, glutamic–oxalacetic transaminase; LDH, lactic dehydrogenase; CK, creatine kinase; cTnI, cardiac tropoin I; NT-proBNP, N-terminal pro-B-type brain natriuretic peptide; WPW, Wolff–Parkinson–White; LV, left ventricular; LVPW, left ventricular posterior wall.

[a]Sum of the voltages of S_{V1} and $R_{V5/6} > 3.5$ mV.

Table 2 Detailed clinical features, serum biomarkers, and molecular genetics of the three Danon disease patients

	Patient 1	Patient 2	Patient 3	Mean ± SD
Age (years)	15	16	14	15 ± 1
Gender	Male	Male	Male	
Follow-up (months)	18	36	6	20 ± 15
Presentation	Progressive activity intolerance	Abnormal hepatic enzymes and CK	Intermittent palpitation and syncope	
NYHA Class	I	I	I	
Mental retardation	Mild	Mild	Mild	
Serum hepatic enzymes				
ALT (U/L)	175	271	299	248 ± 65
AST (U/L)	255	182	275	237 ± 49
LDH (U/L)	1015	1081	873	990 ± 106
Serum CK (U/L)	1414	1540	2167	1707 ± 403
CK-MM (%)	100	100	100	
cTnI	Negative	Negative	Negative	
NT-proBNP (pg/mL)	3583	2100	1012	2232 ± 1291
Molecular genetics	c.808_809 insG in exon 6	c.320_321 insCATC in exon 3	c.257_258delCC in exon 3	

SD, standard deviation; CK, creatine kinase; NYHA, New York Heart Association; ALT, alanine transpeptidase; AST, glutamic-oxalacetic transaminase; LDH, lactic dehydrogenase; cTnI, cardiac tropoin I; NT-proBNP, N-terminal pro-B-type brain natriuretic peptide.

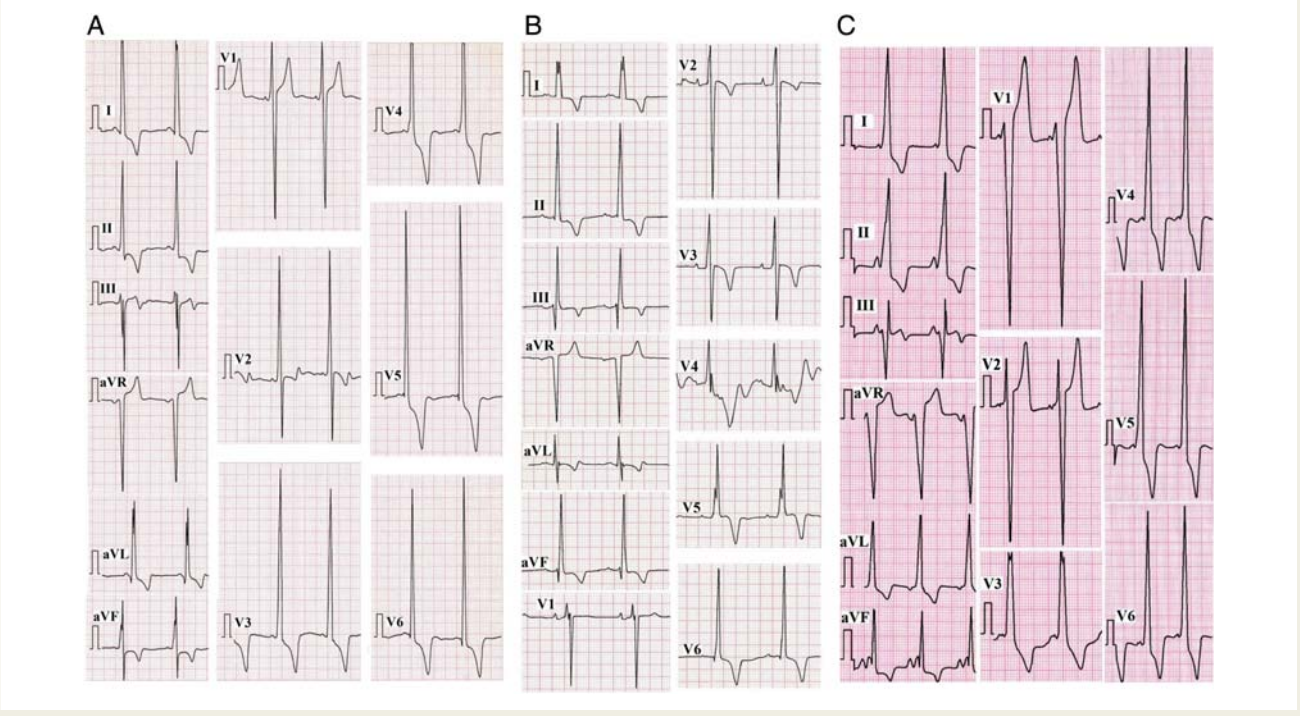

Figure 2 ECGs of the three Danon disease patients. ECG of Patient 1 showed Wolff–Parkinson–White syndrome with very high voltage of the left ventricule ($S_{V1} + R_{V5} = 13.4$ mV) and inverted T-waves (*A*). ECG of Patient 2 showed normal PR interval (200 ms) with high voltage of the left ventricule ($S_{V1} + R_{V6} = 6.5$ mV) and inverted T-wave (*B*). ECG of Patient 3 showed Wolff–Parkinson–White syndrome with very high voltage of the left ventricule ($S_{V1} + R_{V5} = 13.2$ mV) and inverted T-wave (*C*). WPW, Wolff–Parkinson–White.

7 mm, $P = 0.029$) as well as the LVESD (24 ± 1 vs. 35 ± 8 mm, $P = 0.014$) were lower in the Danon disease group than the non-Danon disease group. However, the primary (0 vs. 6%, $P = 1$) and secondary (0 vs. 9%, $P = 1$) outcomes in the Danon and non-Danon disease groups were similar during the follow-up of 20 ± 15 and 20 ± 16 months, respectively. *Table 1* summarized the

clinical features, serum biomarkers, and electrocardiographic and echocardiographic characteristics of the study population.

Detailed clinical features and serum biomarkers of the three Danon disease patients

All the three patients were male, mean age 15 ± 1 years (14–16 years) at diagnosis. The prevalence was 6% (3 of 50) of the total patients with concentric LVH underwent EMB or 8% (3 of 36) of the patients with concentric LVH excluding cardiac amyloidosis. All the three patients had mild mental retardation, mainly involving learning difficulties, and were classified in NYHA functional class I at diagnosis. The presentations of the three patients at diagnosis were variable, from asymptomatic to progressive activity intolerance and syncope. The serum hepatic enzymes, including ALT [248 ± 65 (range 175–299) U/L, normal: 5–40 U/L], AST [237 ± 49 (range 182–275) U/L, normal: 5–37 U/L], LDH [990 ± 106 (range 873–1081) U/L, normal: 97–270 U/L], and CK [1707 ± 403 (range 1414–2167) U/L, normal: 18–198 U/L] as well as NT-proBNP [2232 ± 1291 (range 1012–3583) pg/mL, normal: 0–125 pg/mL] concentrations, were elevated. CK-MM was 100% by isozyme electrophoresis of CK in the three patients. Cardiac tropoin I was negative in the three patients. *Table 2* summarized the detailed clinical features, serum biomarkers, and molecular genetics of the three Danon disease patients. There was no death or cardiovascular hospitalization during 20 ± 15(6–36) months of follow-up.

Table 3 Detailed electrocardiographic and echocardiographic characteristics of the three Danon disease patients

	Patient 1	Patient 2	Patient 3	Mean ± SD
Electrocardiography				
Rhythm	Sinus	Sinus	Sinus	
WPW	Yes	No	Yes	
PR interval (ms)	100	200	80	127 ± 64
Maximum LV voltage (mV)[a]	13.4	6.5	13.2	11 ± 4
Others	Inverted T-waves	Inverted T-waves	Inverted T-waves	
Echocardiography				
LV outflow gradient (rest, mmHg)	0	0	0	
Maximum LVPW thickness (mm)	24	34	15	24 ± 10
Maximum septum thickness (mm)	30	27	14	24 ± 9
Left ventricular ejection fraction (%)	78	73	78	76 ± 3
LV end of diastolic dimension (mm)	43	42	41	42 ± 1
LV end of systolic dimension (mm)	23	24	25	24 ± 1
Left atrial dimension (mm)	32	32	47	37 ± 9
E/A ratio	2.5	1.2	1.5	1.7 ± 0.7
LV compliance	Restrictive	Normal	Decreased	
Pericardial effusion	No	Mild	No	

SD, standard deviation; WPW, Wolff–Parkinson–White; LV, left ventricular; LVPW, left ventricular posterior wall.
[a]Sum of the voltages of S_{V1} and $R_{V5/6}$.

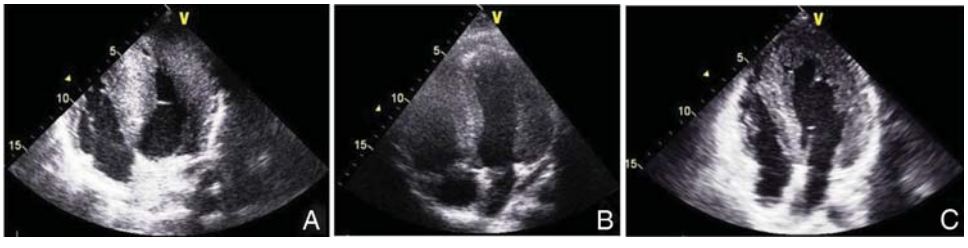

Figure 3 Apical four-chamber views of ECHO of the three Danon disease patients. ECHOs demonstrated concentric left ventricular hypertrophy in the three patients, the thickness of left ventricular posterior wall and interventricular septum were 24 and 30 mm in Patient 1 (*A*), 34 and 27 mm in Patient 2 (*B*), and 15 and 14 mm in Patient 3 (*C*), respectively.

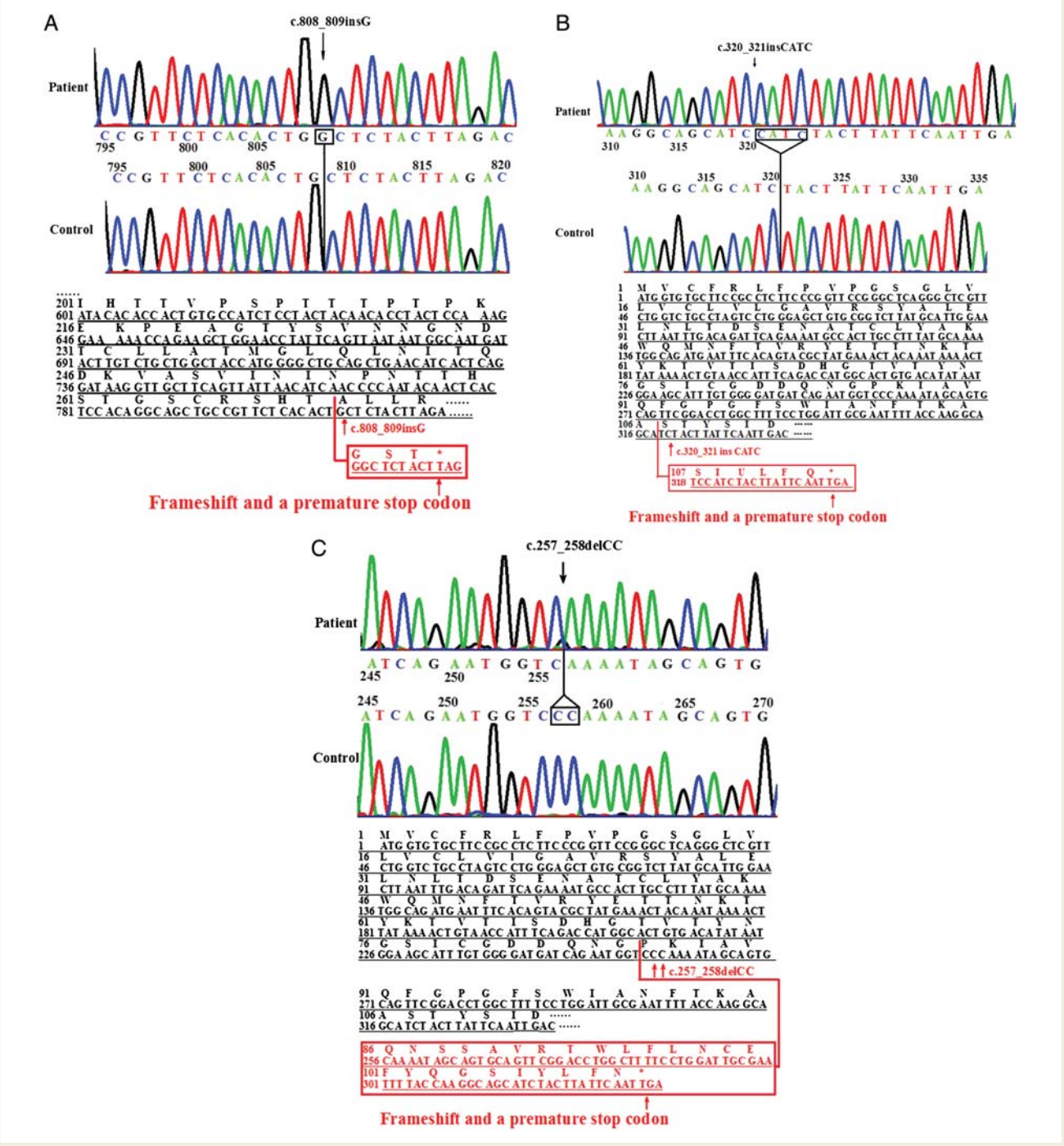

Figure 4 Molecular genetics and cDNA analysis of the lysosome-associated membrane protein 2 gene of the three Danon disease patients. The 1 bp insertion (808_809 insG) in exon 6 of Patient 1, leading to frameshift mutation of lysosome-associated membrane protein 2 and a premature stop codon on cDNA analysis [see red box (*A*)]. The 4 bp insertion (320_321 insCATC) in exon 3 of Patient 2, leading to frameshift mutation of lysosome-associated membrane protein 2 and a premature stop codon on cDNA analysis [see red box (*B*)]. The 2 bp deletion (257_258 delCC) in exon 3, leading to frameshift mutation of lysosome-associated membrane protein 2 and a premature stop codon on cDNA analysis [see red box (*C*)]. Asterisk indicated the stop codon.

Detailed electrocardiographic and echocardiographic characteristics of the three Danon disease patients

All the three patients were in sinus rhythm at diagnosis, two of the three patients with typical WPW syndrome. Patient 3 underwent successful ablation for WPW syndrome. The PR interval was 127 ± 64 (80–200) ms. All the three patients' ECGs showed high voltage of the left ventricle; the sums of the voltages of S_{V1} and $R_{V5/6}$ were 13.4, 6.5, and 13.2 mV. All the three patients' ECGs showed inverted T-waves. *Figure 2* was the ECGs of the three Danon disease patients.

There was no left ventricular outflow gradient at rest in the three patients. The maximum LVPW and IVS thickness were 24 ± 10 (15–34) mm and 24 ± 9 (14–30) mm, respectively. The LVEF and the LVEDD as well as the LVESD were normal. Patient 3 had enlarged LA dimension and Patient 2 had mild pericardial effusion. Two of the three patients had abnormal left ventricular compliance, one with mildly decreased and another with restrictive left ventricular compliance with the E/A ratio of 2.5. *Table 3* summarized the detailed ECG and ECHO characteristics of the three Danon disease patients. *Figure 3* was the apical four-chamber views of the three Danon disease patients.

Molecular genetics and cDNA analysis of the three Danon disease patients

Three novel frameshift mutations of LAMP2 gene were identified in the three patients. They were a 1 bp insertion (808_809 insG) in exon 6 (Patient 1), a 4 bp insertion (320_321 insCATC) in exon 3 (Patient 2), and a 2 bp deletion (257_258 delCC) in exon 3, resulting in frameshift mutations and a premature stop codon on cDNA analysis (*Figure 4*).

Endomyocardial biopsy and electron microscopic examinations

All the three biopsies were positive PAS and negative Congo red staining. Light microscope examinations revealed the demonstrations of autophagosome-like vesicle. Biopsies from Patients 1 and 3 also had electron microscopic examinations, which revealed some autophagic vacuoles containing glycogen particles (*Figure 5*).

Discussion

This study is the first attempt to evaluate the prevalence of Danon disease among a large population of patients with concentric LVH who underwent EMB. The prevalence in the total patients with concentric LVH was 6% (3 of 50), or 8% (3 of 36) of the patients excluding cardiac amyloidosis through EMB. The prevalence of 6–8% in the present study was higher than 1–4% in previous studies[1,7,8] probably because of the selection of the study population; previous studies included all HCM patients; however, the present study only included the patients with concentric LVH. The Danon disease patients were younger; significantly elevated serum hepatic enzymes and CK as well as WPW syndrome on ECG were more common than the non-Danon disease patients, and they constituted a very specific entity.

All the three Danon disease patients were male teenagers. The mean age was 15 ± 1 years, two of the three were with WPW syndrome with greatly increased voltages of the left ventricle. All the three patients had inverted T-waves, and were classified into NYHA functional class I at diagnosis, consistent with previous studies.[1,9] Arad *et al.*[1] reported that five of six Danon disease patients were boys with mean age of 15 years, and five patients were with WPW syndrome and markedly increased left ventricular voltage. Maron *et al.*[9] reported that six of seven Danon disease patients were boys with a median age of 14 years, and six patients were with WPW syndrome and deeply inverted T-waves at diagnosis. Furthermore, all the three patients had markedly elevated serum hepatic enzymes and CK concentrations, consistent with previous studies by Yang *et al.*,[7] Maron *et al.*,[9] Cottinet *et al.*,[10] Balmer *et al.*,[11] and Morisawa *et al.*[12]

Another important finding of the present study was three novel frameshift mutations of the LAMP2 gene. They were c.808_809 insG in exon 6, c.320_321 insCATC in exon 3, and c.257_258 delCC in exon 3; all the frameshift mutations led to a premature stop codon on cDNA analysis.

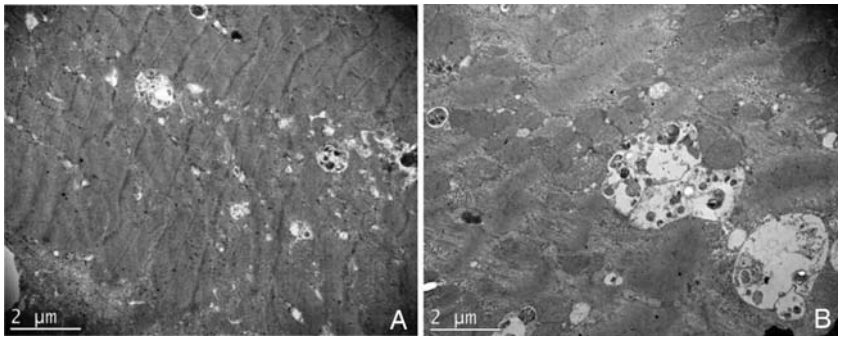

Figure 5 Electron microscopic examinations of Patients 1 (*A*) and 3 (*B*). Electron microscopic examinations revealed some autophagic vacuoles containing glycogen particles in both patients (magnification × 15 000).

The cardiac phenotype of Danon disease is severe with early onset and poor prognosis. In a study of 20 male patients, the mean age at onset was 17 years (range from 10 months to 19 years), and all patients except one died before the age of 30 years.[2] Maron *et al.*[9] reported that each of the seven Danon disease patients experienced serious adverse clinical consequences by 14–24 years of age (mean: 21 years), four patients died of acute or progressive heart failure, and one patient underwent heart transplantation; all seven patients had received implantable cardioverter defibrillators (ICDs), which ultimately failed to terminate lethal ventricular tachyarrthymias in five. Therefore, physicians should consider early intervention with heart transplantation[2,13] once left ventricular dysfunction occurs, despite the possibility of extracardiac organ involvement of this disease.[2,8]

To distinguish HCM from Danon disease is important, as there are some Danon disease patients with asymmetric septal hypertrophy,[9] resembling HCM. First, majority of Danon disease patients are male teenagers with a very poor prognosis. Deaths are due to heart failure or sudden cardiac death. This is in contrast to HCM, in which cardiac death is only ~1–2% per year and of which only 10% develop heart failure.[14,15] Second, clinical manifestations of Danon disease are broad[16–18] with additional cardiac or extracardiac features.[19] The abnormal ECG, especially revealing WPW syndrome[20] with very high voltage of the left ventricle, is very common in Danon disease. Mental retardation was reported in 70% of cases of Danon disease.[2] Third, there is no specific treatment for Danon disease except heart transplantation. Implantable cardioverter defibrillators failed to terminate lethal ventricular tachyarrhythmias in most Danon disease patients.[9] Fourth, Danon disease is an X-linked dominant disorder, and different from HCM. The differential diagnosis between HCM and Danon disease may be achieved by genetic analysis of LAMP2.

In conclusion, 6–8% patients with concentric LVH who underwent EMB were diagnosed with Danon disease. Danon disease should be suspected in the male teenager with concentric LVH, especially with WPW syndrome and very high voltage of the left ventricle or unknown markedly increased serum hepatic enzymes and CK concentrations. Genetic analysis of the LAMP2 gene can yield the diagnosis.

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Conflict of interest: none declared.

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