

Evaluation of Myocardial Changes in Familial Amyloid Polyneuropathy after Liver Transplantation

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Abstract

Objective The progression of cardiac amyloidosis is a prognostic factor after liver transplantation (LT) in familial amyloid polyneuropathy (FAP). The aim of this study was to assess myocardial changes in FAP amyloidogenic transthyretin (ATTR) Val30Met after LT.

Patients and Methods Twelve Japanese FAP ATTR Val30Met patients who underwent LT and were followed for more than 2 years, were examined with serial echocardiography after LT. Serum BNP levels were measured in 9 patients.

Results A significant increase in mean left atrial diameter and interventricular septal thickness was observed after LT. The increase in left atrial diameter was correlated with the presence of granular sparkling echo (GSE) at preoperative examination. Serum brain natriuretic peptide (BNP) levels in patients with left atrial diameter dilation (152.0 ± 157.6 pg/mL) were higher than in those without left atrial diameter dilation (32.0 ± 30.0 pg/mL).

Conclusion LAD and IVS were significantly increased after LT compared with preoperative examinations in Japanese FAP ATTR Val30Met patients. BNP is an important biochemical indicator of myocardial dysfunction in FAP patients. GSE is a useful echocardiographic marker to predict cardiac amyloidosis after LT.

Key words: familial amyloid polyneuropathy, echocardiogram, cardiac amyloidosis, liver transplantation

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Introduction

Liver transplantation (LT) for familial amyloid polyneuropathy (FAP) amyloidogenic transthyretin (ATTR) Val30Met has been widely performed to halt the progression of clinical manifestations of FAP, because the liver synthesizes more than 90% of circulating transthyretin (TTR) in blood (1-3). A long-term follow-up study of abdominal fat tissue biopsy indicated that the amount of amyloid deposition in transplanted FAP patients is markedly decreased (4).

However, ocular amyloid deposits can not be prevented by LT because TTR is synthesized by the retina. In addition, cardiomyopathy also deteriorates in several non-Val30Met types of patients, although the mechanism remains to be elucidated (5, 6). In addition, recently such a change was also

even observed in several Swedish FAP ATTR Val30Met patients who had later onset than Portuguese and Japanese patients. However, this complication has not been well examined in early FAP ATTR Val30Met patients (7).

Concerning the evaluation of cardiomyopathy in FAP, no appropriate biochemical markers are applicable. It has been well documented that the quantitative measurement of brain natriuretic peptide (BNP) is a sensitive tool for diagnosing ventricular dysfunction and heart failure (8-10). The BNP gene is an acutely responsive cardiac gene for ventricular overload (11). The expressions of BNP and its gene are augmented in the ventricular myocytes of patients with cardiac amyloidosis (12).

The aim of this study was to assess cardiac amyloidosis of transplanted FAP patients with ATTR Val30Met in Kumamoto University Hospital. Changes in echocardiographic

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findings and serum BNP levels as cardiac biochemical markers were evaluated in these patients.

Abbreviations: FAP: familial amyloid polyneuropathy, ATTR: amyloidogenic transthyretin, BNP: brain natriuretic peptide

Patients and Methods

Thirty-four FAP ATTR patients, including 30 ATTR Val30Met, 1 ATTR Ser50Ile and 3 ATTR Tyr114Cys referred to Kumamoto University Hospital from 1994 to 2007 underwent LT. All patients were diagnosed with FAP by typical clinical findings, amyloid deposits in biopsy samples, and/or genetic testing. Twelve FAP Val30Met patients (7 men and 5 women, aged 30 to 66 years) who were evaluated with serial echocardiography after LT and were followed for more

than postoperative 2 years, out of the 30 FAP Val30Met patients were examined in this study. Nine of the 12 patients were also examined with echocardiography before LT.

Patients were studied with two-dimensional and M-mode echocardiography. Cardiac appearance was obtained from the parasternal, apical, and subcostal positions. Aortic diameter (Ao), mean left atrial diameter (LAD), left ventricular end-diastolic diameter (LVD), interventricular septal thickness (IVS), posterior wall thickness (PWT), and fractional shortening (FS) were measured. Granular sparkling echo (GSE) findings were defined as distinct and bright echoes that could be visualized from different projections or angulations, and persisted at a gain setting low enough to eliminate echoes from the surrounding the endocardium and myocardium (Fig. 1) (7). The peak velocity of early (E) and late filling (A) waves, E/A ratio and deceleration time of E wave in transmitral flow were measured in the latest examination. Serum BNP levels were measured with a chemiluminescent enzyme immunoassay by a commercial laboratory (SRL, Tokyo, Japan). The results are expressed as the mean±standard deviation. Relationships were tested using paired t test, unpaired t test, and Fisher's exact probability test. P-values less than 0.05 were considered significant.

Abbreviation: GSE: granular sparkling echo

Results

The outcome of the clinical findings is summarized in Table 1. Mean (±standard deviation) duration was 3.0±2.4 years before LT and 7.5±3.0 years after LT. Symptoms of cardiac failure were noted in one patient who died ten years after LT (Table 1, patient 3). Ten patients have resumed their normal life, and none have been hospitalized, except for the patient mentioned above. The longest survival after LT is 12 years (Table 1, patient 1). Electrocardiogram of

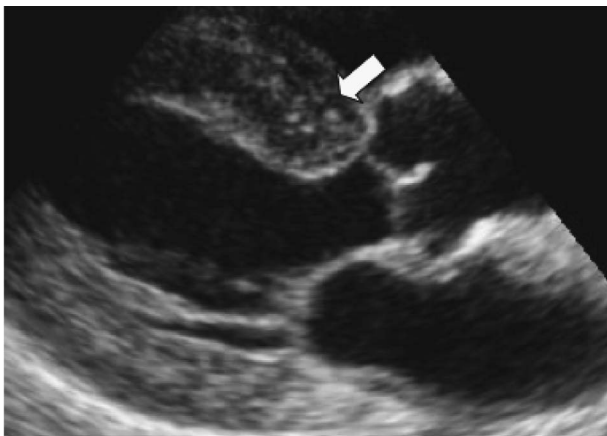


Figure 1. Echocardiography in a familial amyloid polyneuropathy (FAP) amyloidogenic transthyretin (ATTR) Val30Met patient. Granular sparkling echo (GSE) can be visualized from the longitudinal view from the surrounding endo- and myocardium (arrow).

Table 1. Patient's Characteristics

No	Sex	Age at onset of initial symptoms (years)	Age at LT (years)	Duration after LT (years)	Condition	Symptoms of heart failure	Arrhythmias	QS pattern in ECG	Pacemaker	HT	HLP	Liver injury	Renal dysfunction	LAD (mm)		IVS (mm)		Granular sparkling echo	Comment
														before LT	after LT	before LT	after LT		
1	M	25	28	12	full	no	III	no	yes	no	no	no	no	24.2	39.9	10.4	13.8	yes	Comment 1
2	F	37	41	11	full	no	I	no	no	no	yes	no	no	32.0	32.0	13.0	14.7	no	
3	F	40	47	11	dead	yes	II	yes	yes	no	no	yes	yes	27.4	41.5	11.3	11.2	yes	Comment 2
4	M	24	29	10	full	no	III	yes	yes	no	no	no	no	32.5		15.1		yes	Comment 3
5	F	35	36	8	full	no	no	no	no	no	no	no	no	42.7		8.9		yes	
6	M	28	30	8	full	no	I	no	yes	no	no	no	no	18.0	33.5	13.0	17.1	yes	Comment 4
7	F	29	31	8	full	no	I	yes	yes	no	no	no	no	26.0		11.0		no	Comment 4
8	M	57	58	7	full	no	no	no	no	no	no	no	no	35.3	40.6	11.2	18.4	no	
9	M	38	40	6	full	no	no	yes	no	no	no	no	no	27.1	29.6	9.2	7.1	no	
10	M	47	49	6	stay home	no	trifascicular block	yes	yes	no	no	no	yes	29.3	34.7	13.0	26.1	yes	Comment 5
11	F	29	30	4	full	no	no	no	no	no	no	no	no	33.0	35.0	8.0	8.1	no	
12	M	27	28	2	full	no	no	no	no	no	no	no	no	32.1	34.3	6.2	10.7	no	

full: fully active

Arrhythmias: I, first-degree atrioventricular block; II, second-degree atrioventricular block (Wenckebach);

III, third-degree atrioventricular block (complete AV block)

ECG, electrocardiogram; HT, hypertension; HLP, hyperlipidemia

Comment 1: pacemaker: 12 years after LT, 2: cause of death: heart failure pacemaker: 8 years after LT, 3: pacemaker: 6 years after LT, 4: pacemaker: before LT,

5: nephrotic syndrome pacemaker: 6 years after LT

Table 2. Changes in Echocardiographic Findings before and after Liver Transplantation

Measurements	Before LT (n=9)	After LT (6.8±3.4 years) (n=9)	p
Ao (mm)	27.6±4.6	30.4±7.0	0.11
LAD (mm)	28.7±5.3	35.7±4.1	0.01
LVD(D) (mm)	41.6±7.3	42.0±4.5	0.8
IVS (mm)	11.6±1.5	15.5±6.0	0.048
PWT (mm)	10.8±2.5	13.0±5.7	0.19
FS (%)	49.1±6.2	44.6±7.5	0.46
GSE (n) (%)	3 (33)	4 (44)	

Ao, aortic diameter; LAD, mean left atrial diameter; LVD (D), left ventricular end-diastolic diameter; IVS, interventricular septal thickness; PWT, posterior wall thickness; FS, fractional shortening; GSE, granular sparkling echo. Differences between groups were tested using paired t test. Data are expressed as the mean ± SD.

chest leads before LT revealed QS pattern in 5 of 12 patients. Complications before and after LT, such as liver injury, mild renal dysfunction, and mild hyperlipidemia, which may influence cardiac function, are shown in Table 1. Liver injury and hyperlipidemia were observed in one patient each. Renal injury was observed in two patients. No patients had hypertension, obstructive vascular diseases, or a history of previous myocardial infarction.

The echocardiographic findings of 9 patients examined before and after LT are presented in Table 2. A statistically significant increase in LAD and IVS was observed after LT compared with those before LT. GSE was found in 3 patients at examination before LT and in 4 patients at follow-up examination after LT.

Figure 2 shows serial echocardiographic findings in LAD and IVS of 12 patients. In 11 of 12 patients, LAD remained within the normal range before LT. However, 6 patients showed gradual increases in LAD after LT (≥ 5.0 mm). In 4 of 6 patients, the latest findings of LAD were above the normal range. IVS was within the normal range in 8 of 12 patients, and gradually increased (≥ 1.0 mm) in 6 patients after LT. In 5 of 6 patients, the latest findings of IVS were above normal range. There was no correlation between LAD dilatation and IVS thickness. In serial echocardiographic findings of Ao, LVD, PWT, and FS, no increase was observed after LT.

Table 3 indicates the patients' profile with or without LAD dilatation. There was no statistically significant difference in duration of symptomatic disease before LT and duration after LT between patients with LAD dilatation and those without LAD dilatation. Although there was no statistically significant difference in age at onset and age at LT between the 2 groups, they tended to be higher in the patients with increased LAD. GSE was found in 5 of 6 patients with LAD dilatation, whereas in only 1 of 6 patients without LAD dilatation. Although 3 of the 6 patients with GSE had not undergone echocardiography before LT, GSE was detected at the first echocardiography performed 12, 36 and 41 months after transplantation. The ratio of GSE-positive patients in patients with LAD dilatation was significantly higher than in those without LAD dilatation. There was no

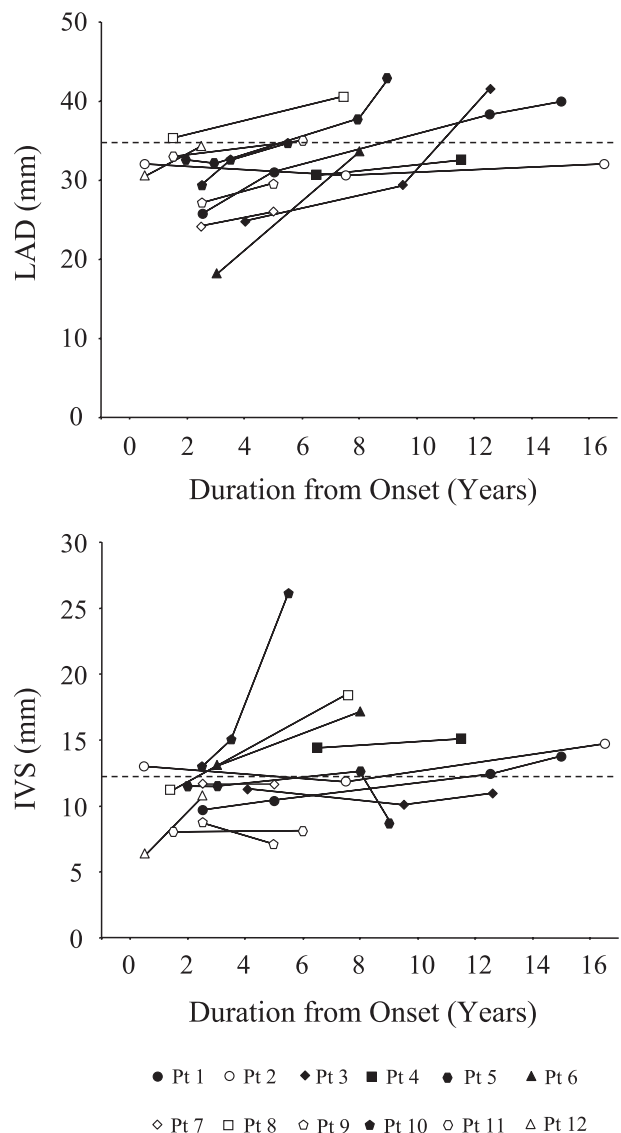


Figure 2. Changes in LAD and IVS after LT in FAP Val30 Met patients. Serial echocardiographic data were plotted. Data from the same patient were expressed with the same symbols. Open and closed symbols represent data from FAP patients with GSE and without GSE before or just after LT. Those under the dotted line are in the normal range.

Table 3. Patients' Profile with or without LAD

	No LAD dilation <5.0 mm (n=6)	LAD dilation ≥5.0 mm (n=6)	p
Age at onset (years)	30.7±5.6	38.7±12.0	0.17
Age at LT (years)	33.2±5.8	41.3±11.9	0.16
Duration of disease at LT (years)	2.5±1.6	2.7±2.3	0.89
Duration after LT (years)	6.6±3.5	8.7±2.3	0.31
serum BNP (pg/mL)	32±30.0 (n=3)	152.0±157.6 (n=6)	0.25
GSE (%)	1 (17%)	5 (83%)	0.04

Differences between groups were tested using unpaired t test and Fisher's exact probability test.

Data are expressed as the mean ± SD.

significant difference between the ratio of GSE-positive patients with IVS thickness and those without IVS thickness. There was no correlation among age at symptom development, age at LT, and year of follow-up after LT.

E/A ratio and deceleration time were measured in 9 of 12 patients. In patients with LAD dilation and without LAD dilation, mean E/A ratios were 1.61±0.84 and 1.04±0.15 ($p=0.23$) and mean deceleration times were 198.3±47.3 and 214±28.3 msec ($p=0.57$), respectively. The mean E/A ratio tended to be higher and mean deceleration time tended to be lower in the LAD dilation group than in those without LAD dilation.

Serum BNP levels were examined in 9 of 12 patients. BNP levels in 2 patients without LAD dilation were below the normal value (<18.4 pg/mL). BNP levels in patients with LAD dilation tended to be higher than in those without LAD dilation (Table 3). Mean BNP levels were 108.8±145.7 and 39.3±28.5 pg/mL in GSE-positive and GSE-negative groups, respectively. BNP levels in the GSE-positive group tended to be higher than those in the GSE-negative group.

In our study, 4 patients underwent pacemaker implantation after LT. The mean duration from LT to pacemaker implantation was 5.5 years (6-12 years). In those patients, electrocardiogram at LT did not show conduction abnormalities except for in one patient (Patient 3). At the time of pacemaker treatment, the electrocardiogram revealed complete A-V block in two patients, second-degree A-V block (Wenckebach type) in one, and trifascicular block in one. LAD dilatation developed in 3 of the patients who received pacemaker treatment after LT. Moreover, all the patients showed GSE.

Discussion

Echocardiographic analysis revealed that LAD and IVS were significantly increased after LT compared with preoperative examinations in Japanese FAP ATTR Val30Met pa-

tients. The rate of GSE in FAP patients with increased LAD was significantly higher than in those without increased LAD. This finding suggests that GSE may be a factor predicting the progression of cardiac amyloidosis after LT in FAP Val30Met patients. Moreover, as shown in Table 3, age at onset and age at LT in FAP patients with increased LAD tended to be higher than in those without increased LAD. Serum BNP levels in FAP patients with cardiomyopathy also tended to be higher than in those without cardiomyopathy providing evidence that the serum BNP level is a useful biomarker to evaluate heart failure by cardiac amyloidosis of FAP patients after LT.

This echocardiographic study found the progression of cardiac amyloidosis in some Japanese FAP Val30Met patients after LT. For FAP Val30Met patients, no increase in heart wall thickness was described in these reports (5, 6). However, IVS and PWT were increased in several Swedish FAP ATTR Val30Met patients with later onset compared with Portuguese and Japanese patients (7). A similar finding was reported from a French group (13). Late-onset FAP Val30Met patients older than 50 years had a risk of amyloid cardiomyopathy after LT (14). The present study also revealed increases in IVS and LAD in Japanese FAP Val30Met patients after LT, indicating that some early-onset FAP patients show cardiac amyloidosis progression.

The mean E/A ratio tended to be higher and mean deceleration time tended to be lower in the LAD dilation group than in those without LAD dilation. Therefore, it has been assumed that restriction of left ventricular dilatation might induce increased intra-atrial pressure, resulting in enlargement of left atrium.

Our analysis also demonstrated that the presence of GSE on the echocardiogram before LT was a risk factor for the progression of cardiac amyloidosis after LT. It has been well documented that echo brightness increases by amyloid deposition in the heart, and that GSE indicates early-stage cardiac amyloidosis. In FAP patients with a small amount of

amyloid deposition in the heart, cardiac amyloidosis might continue to progress even after LT (15). In our study, we did not investigate GSE with quantitative methods (16). Further studies should be performed with acoustic quantification analysis to evaluate GSE more precisely.

As demonstrated in Table 3, serum BNP levels in patients with LAD dilatation tended to be higher than in patients without LAD dilatation. For follow-up amyloid cardiomyopathy in FAP patients, serum BNP levels should be measured after LT. BNP is a peptide secreted from cardiac ventricles in cases of heart failure, and has been clinically used for the evaluation of heart failure. Light chain-associated (AL) amyloidosis patients often present with cardiac amyloidosis, and serum BNP levels are used to evaluate heart failure and the effect of therapy. The level of NT-pro-BNP is a prognostic indicator of survival in AL amyloidosis patients (17). A Swedish group reported that BNP is a sensitive marker for cardiomyopathy in FAP patients (18). Measurement of BNP for the evaluation of cardiac amyloidosis should be widely performed to predict cardiac function in

FAP.

Although there was no correlation between LAD dilatation and IVS thickness, it seems that increased thickness of IVS, LAD dilatation and elevated serum BNP levels, and GSE are causally related to severity of TTR-derived amyloid deposition on myocardium. Further studies are needed to clarify the relationship among them.

In summary, cardiac amyloidosis progressed in some Japanese FAP Val30Met patients after LT. The presence of GSE and high levels of serum BNP may become important markers to predict cardiac amyloidosis after LT in FAP Val 30Met patients. In addition, transplanted FAP patients should undergo serial echocardiographic examinations and measurement of serum BNP levels to identify heart failure in the early stage. Long-term prospective study by echocardiography and measurement of serum BNP levels is needed to compare consecutive series of transplanted patients with non-transplanted FAP patients.

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