Rapid Progression of Cardiomyopathy in Mitochondrial Diabetes

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Cardiac involvement and its clinical course in a diabetic patient with a mitochondrial tRNA_{Leu(UUR)} mutation at position 3243 is reported in a 54-year-old man with no history of hypertension. At age 46, an electrocardiogram showed just T wave abnormalities. At age 49, it fulfilled SV_{1} + RV_{5,6} >35 mm with strain pattern. At age 52, echocardiography revealed definite left ventricular (LV) hypertrophy, and abnormally increased mitochondria were shown in biopsied endomyocardial specimens. He was diagnosed as having developed hypertrophic cardiomyopathy associated with the mutation. However, at age 54, SV_{1} and RV_{5,6} voltages were decreased, and echocardiography showed diffuse decreased LV wall motion and LV dilatation. Because he had mitochondrial diabetes, the patient’s heart rapidly developed hypertrophic cardiomyopathy, and then it seemed to be changing to a dilated LV with systolic dysfunction. Rapid progression of cardiomyopathy can occur in mitochondrial diabetes. (Jpn Circ J 1999; 63: 130-132)

Key Words: Cardiomyopathy; Diabetes mellitus; Mitochondria

Case Report

The case presented is a 54-year-old man who had had non-insulin-dependent diabetes mellitus for 25 years, during which time he had been on insulin. His hemoglobin A1c level was usually around 8.0%, and he had diabetic retinopathy (background) and neuropathy. His mother had also had diabetes and died of myocardial infarction at age 62. His elder and younger brothers were not diabetic but both died suddenly at age 25 and 19, respectively. At age 50, a molecular test using a restriction endonuclease Apa I diagnosed him as having the 3243 mutation in blood leuko-

Fig 1. (A) Serial electrocardiograms (ECG) and (B) M-mode echocardiographic data. At age 46, ECG showed T-wave abnormalities. At age 49, the ECG fulfilled the criterion for LV hypertrophy (SV_{1} + RV_{5,6} >35 mm) with strain pattern. At age 52, SV_{1} and RV_{5,6} voltages became much higher, and M-mode data indicated LV hypertrophy (LV posterior wall thickness >11 mm). At age 54, a decrease in SV_{1} and RV_{5,6} voltages was found, and M-mode data indicated LV systolic dysfunction (fractional shortening <28%). LVIDd, LV end-diastolic internal dimension.

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He had no clinical signs of MELAS, but had a severe hearing impairment that required a hearing aid. He was lean (body height 158 cm and body weight 42 kg) and had no history of hypertension. Blood pressures were usually around 125/85 mmHg. At age 46, his electrocardiogram (ECG) showed just T wave abnormalities (Fig 1). Three years later (age 49), his ECG fulfilled the LVH criterion of $SV_1 + RV_5 \geq 35$ mm with strain pattern. However, on echocardiography the left ventricular (LV) posterior wall thickness was 9.5 mm, which was within the normal limits (<11 mm) (Fig 1,2). At age 52, his ECG showed much deeper $SV_1$ and higher $RV_5,6$ voltages than before. Echocardiography revealed the development of LVH (posterior wall thickness 12.0 mm and LV mass$^9$ 284 g). LV systolic function was still within the normal limits (fractional shortening 31%, normal $>28\%$) (Fig 1). However, the pulsed Doppler analysis of LV inflow velocities showed a high A/E velocity ratio and a prolonged deceleration time of the E wave, indicating impaired LV diastolic function (Table 1).

Cardiac catheterization was performed. Coronary arteriography revealed no significant stenosis, and the LV ejec-
tion fraction was 56%. In the endomyocardial biopsy specimens, light microscopy showed myocyte hypertrophy and severe vacuolar degeneration of myocytes. Electron microscopy revealed markedly increased mitochondria with abnormal configuration of cristae (Fig 3). He was diagnosed as having developed HCM associated with the 3243 mutation. Two years later (age 54), decreases in the SV1 and RV56 voltages were found, as shown in Fig 1. He had no clinical signs of heart failure, but echocardiography demonstrated diffuse decreased LV wall motion (fractional shortening 21%) and LV dilatation (Figs 1,2). There was no change in LV wall thickness compared with 2 years before. His heart was seen to be changing to a dilated LV with LV systolic dysfunction. However, the pulsed Doppler analysis showed a lower A/E velocity ratio and shorter deceleration time of the E wave than before, suggesting pseudonormalization of an abnormal LV filling pattern (Table 1).

Discussion

The 3243 mutation was originally found in MELAS2 and LVH and HCM are often reported in patients with MELAS3–6 Ito et al reviewed 21 patients with MELAS and found LVH in 8 patients7 Anan et al performed echocardiography in 5 patients with MELAS and found LVH in 2 patients8 Of the 2 patients with LVH, I showed LV systolic dysfunction. Hence, LVH with or without systolic dysfunction is a recognized clinical feature of cardiac involvement in MELAS. However, the precise mechanism of LVH in MELAS has not been clarified. In patients with MELAS who developed HCM, markedly increased mitochondria with an abnormal configuration of cristae were reported in their heart tissue9,10 These abnormalities of the cardiac mitochondria are considered to be a compensatory reaction to its metabolic alterations3,10 A morphometric study of myocardium in a patient with mitochondrial myopathy and HCM showed that the LVH was mainly due to cellular hypertrophy, which was attributed to increased mitochondrial mass11 Therefore, mitochondrial metabolic alterations due to the 3243 mutation would cause a compensatory increase in cardiac mitochondria, which leads to LVH.

Mitochondrial diabetes associated with the 3243 mutation is known to be characterized by maternal transmission of diabetes and hearing impairment12 The present patient had both these characteristics. As in MELAS, there have been 7 reported cases with mitochondrial diabetes who developed HCM13–18 In 1992, Obayashi et al first detected the 3243 mutation in the autosomal heart of a diabetic patient with HCM19 Yoshida et al reported 2 patients with mitochondrial diabetes and HCM who had a much higher proportion of mutant mitochondrial DNA in their heart tissue than in blood20 Recently, abnormally increased mitochondria, as reported in MELAS, were demonstrated in biopsied myocardium of patients with HCM associated with mitochondrial diabetes15,16 The present case with mitochondrial diabetes also developed HCM and showed abnormally increased mitochondria in his myocardium. Hence, LVH and HCM also seem to be the features of cardiac involvement in mitochondrial diabetes. Of the 7 reported cases with mitochondrial diabetes who developed HCM, 3 were described as having LV systolic dysfunction15–16 Moreover, Shiotani et al reported one patient with mitochondrial diabetes who had a dilated LV with LV systolic dysfunction similar to dilated cardiomyopathy15 Therefore, patients with mitochondrial diabetes occasionally have LV systolic dysfunction, and rapid progression from HCM to dilated cardiomyopathy may occur.

In the patient reported here, his heart rapidly developed HCM associated with abnormally increased mitochondria, and then seemed to be changing to a dilated LV with LV systolic dysfunction.

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References


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