Hypertrophic Cardiomyopathy in Patients with Diabetes Mellitus Associated with Mitochondrial tRNA^{Leu(UUR)} Gene Mutation

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Left ventricular function and morphology were assessed using M-mode echocardiography in 3 patients with diabetes mellitus associated with mitochondrial tRNA^{Leu(UUR)} gene mutation, who were free of clinical, electrocardiographic, or thallium scan evidence of ischemic heart disease. Echocardiograms revealed hypertrophic cardiomyopathy in all 3 patients. Hypertrophy of the interventricular septum was mild in Cases 1 and 3 (12 and 13 mm, respectively) and severe in Case 2 (22 mm) (normal 7–10 mm). When they had neither signs nor symptoms suggestive of congestive heart failure, percentage fractional shortening (%FS), an index of wall motion of the left ventricle (normal >28%), was normal in Cases 2 and 3 (28 and 32%, respectively) whereas it was slightly decreased in Case 1 (22%). In Case 1 with mild hypertrophy, the development of congestive heart failure was associated with a marked decrease in %FS to 13%; this patient responded well to diuretics and captopril and %FS rose to 22%. However, a mild decrease in %FS to 21% caused congestive heart failure in Case 2 with severe hypertrophy. His response to treatment was marginal. The present study indicates that mitochondrial DNA analysis should be done in patients with diabetic cardiomyopathy, and that sequential echocardiography is invaluable for the detection of hypertrophic cardiomyopathy and the management of subsequent myocardial dysfunction in patients with mitochondrial diabetes mellitus and cardiomyopathy. (Internal Medicine 34: 953–958, 1995)

Key words: congestive heart failure, echocardiography, hearing loss

Introduction

Clinical, epidemiologic and pathologic data support the presence of specific cardiomyopathy related to diabetes mellitus (1, 2). The existence of diabetic cardiomyopathy was first suggested by Rubler et al (3) on the basis of postmortem findings in diabetic adults with congestive heart failure. The diagnosis of diabetic cardiomyopathy can be entertained only after the exclusion of coronary artery disease and other conditions such as hypertension, known to cause myocardial dysfunction. On the other hand, a striking increase in the incidence of congestive heart failure has been reported in patients with diabetes mellitus (4).

The present studies have demonstrated hypertrophic cardio-

myopathy in 3 patients with long-standing diabetes mellitus associated with a point mutation of mitochondrial DNA. We also describe their clinical course and the utility of echocardiography in the detection of subsequent myocardial dysfunction.

Patients and Methods

Patients

Clinical features and laboratory data are summarized in Tables 1 and 2. The 3 patients were short in stature, lean, hypolipidemic and were not hypertensive. In Cases 1 and 3, as previously reported (5), their mothers, but not fathers, were found to have diabetes. Despite long-standing diabetes mellitus

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and poor glycemic control in Cases 1 and 3, diabetic microvascular complication was not observed in 2 cases and was very mild in the other case. Bilateral sensorineural hearing loss was confirmed in all of them. However, they lacked symptoms and signs suggestive of mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS). As previously reported (5), Cases 1 and 3 had low responses not only of C-peptide to a glucagon injection but also of pancreatic glucagon to an arginine infusion, showing dysfunction of B cells as well as A cells.

Mitochondrial DNA analysis

This was done as previously reported (5). In brief, using mitochondrial DNA extracts from patients' platelets, we amplified the region encoding tRNAs by polymerase chain reaction and sequenced it. In Case 1, biopsy specimens were obtained,

after informed consent, from right ventricular endomyocardium during right heart catheterization. In addition, biopsy specimens were also obtained from mucosa of the stomach, rectum and urinary bladder, because he had polyposis of the gastrointestinal tract and benign prostate hypertrophy.

Echocardiography

M-mode echocardiograms of the left ventricle were obtained using an ultrasound system (Toshiba Corp., Tokyo, Japan) and a 3.5-MHz transducer. Those were performed at rest with the patient at a steady state in the left lateral position. We measured the thickness of the interventricular septum (IVS) and left ventricular posterior wall at the left ventricular minor axis at the level of the chordae tendinae just beyond the mitral leaflet tips, as recommended by the American Society of Echocardiography (6). Every effort was made to obtain optimal echocardiographic images, with the M-mode cursor perpendicular to the left ventricular long axis. End-diastolic and end-systolic dimensions of the left ventricle (LVDd and LVDs, respectively) were also measured. Percentage fractional shortening (%FS), an index of wall motion of the left ventricle, was calculated as follows:

$$\%FS = (LVDd - LVDs) / LVDs \times 100$$

Thallium-201 exercise myocardial perfusion scintigraphy. Thallium-201 (3 mCi) was injected i.v. at the time of maximal stress during a multistage treadmill test according to the Bruce protocol (7). Single photon emission computed tomography (SPECT) images were obtained with a wide-field-of-view rotating gamma camera equipped with a long-energy, high-resolution, parallel-hole collimator (Toshiba GC 90A, Tokyo, Japan). The SPECT images were acquired at the 80 KeV photopeak of thallium-201 with a symmetric 10% window. The early and delayed images were obtained 5 minutes and 3 hours after a thallium injection, respectively.

Table 1. Clinical Features of 3 Male Patients with Diabetes Mellitus Associated with the 3243 Mutation

	Case 1	Case 2	Case 3
Age (years)	59	77	43
Duration of diabetes (years)	10	27	26
Height (cm)	156	157	152
Body mass index (kg/m ²)	17.7	14.6	18.9
Family history:			
diabetes mellitus	Present	Present	Present
heart disease	Present	Absent	Absent
Diabetic therapy	Glibenclamide	Glibenclamide	Insulin
Hemoglobin A1c (%)	8.2	6.5	10.3
Overt proteinuria	Absent	Absent	Absent
Retinopathy	Absent	Absent	Simple
Hearing loss	Present	Present	Present
Hypertension	Absent	Absent	Absent

Table 2. Laboratory Data of the 3 Patients with Diabetes Mellitus and Hypertrophic Cardiomyopathy

	Case 1		Case 2		Case 3	Controls*
	1990 April	1993 December	1990 May	1993 June		
Fasting plasma glucose	253	114	125	106	315	92±2
Hemoglobin A1c (%)	10.5	9.1	7.6	6.5	10.3	<6.0
Total cholesterol	165	156	167	149	147	183±4
Triglycerides	136	105	80	64	55	90±5
HDL-cholesterol	26	32	61	63	42	49±2
Apolipoprotein AI	82	92	NA	NA	101	119±4
Apolipoprotein B	99	89	NA	NA	66	91±3

Unit is mg/dl unless otherwise stated. NA: data not available. *: mean (±SE) concentrations in 37 nondiabetic, normolipidemic males of an average age of 59±1 years. HDL: high density lipoprotein.

Results

An A-to-G transition at nucleotide 3243 was identified in mitochondrial DNA from platelets in all patients. In Case 1, the proportion of mutant mitochondrial DNA was 60% in right ventricular endomyocardial biopsy specimens, whereas it was 24% in platelets, 50% in the stomach, 54% in the rectum and 43% in the urinary bladder (Fig. 1). There was no mutation other than the transition at 3243 between position 3230 and 3304.

Case 1 underwent echocardiography because of systolic

Figure 1. Identification of the 3243 basepair (bp) mutation in Case 1. ^{32}P -labeled products (428 bp) of polymerase chain reaction were digested with Apa I. The presence of mutant mitochondrial DNA resulted in the formation of 218- and 210-bp fragments. C: control, Pl: platelets, H: heart (right-ventricular endomyocardial biopsy specimens), S: stomach, B: urinary bladder, R: rectum. The proportion of mutant mitochondrial DNA is indicated as heteroplasmy at the bottom of the figure.

murmur at age 56 (April 1990), when he received treatment for diabetes mellitus for the first time. Although he had neither signs nor symptoms suggestive of congestive heart failure, echocardiograms had revealed low %FS of 22%, thickening of the left-ventricular wall, and mild mitral regurgitation, the last of which was the cause of systolic murmur (Table 3). Exercise electrocardiogram (ECG) revealed no ischemic response and his chest radiograph was normal. He was diagnosed with diabetic cardiomyopathy. At age 59, he was admitted to the hospital because of congestive heart failure, which was associated with a further decrease of %FS and an increase of cardiothoracic ratio (CTR). Mitochondrial DNA analysis revealed the 3243 mutation. He responded well to treatment with diuretics and captopril. After 2 months of the treatment, his CTR decreased to 43% (Fig. 2), and his %FS rose to 22% (Fig. 3). Coronary angiography revealed no significant stenosis. Right ventricular endomyocardial biopsy revealed no remarkable findings except for vacuolation around the nucleus of myocytes.

Severe hypertrophic cardiomyopathy (Fig. 4) was detected, at age 74, in Case 2 with diabetes of 27 years' duration and taking an oral hypoglycemic agent. However, his %FS (28%), ECG and chest radiograph were normal. He was diagnosed as having idiopathic hypertrophic cardiomyopathy and/or diabetic cardiomyopathy. Three years later, he complained of exertional dyspnea. This was associated with cardiac enlargement with a CTR of 52% and a slight decrease of %FS to 21% from 28%. His CTR could not be restored with treatment with diuretics and inhibitors of angiotension converting enzymes. The 3243 mutation was demonstrated in his platelet DNA.

The third case was a 43-year-old man who was shown to have the 3243 mutation associated with diabetes of 26 years'

Table 3. Cardiac Examinations in 3 Patients with Diabetes Mellitus, Deafness and Hypertrophic Cardiomyopathy Associated with a Mitochondrial tRNA^{Leu(UUR)} Mutation

	Case 1			Case 2			Case 3	Normal range
	1990 April	1993 October	1993 December	1987	1991 March	1994 April		
Auscultation								
murmur	+	+	+	—	—	—	—	
moist rales	—	+	—	—	—	—	—	
CTR (%)	46	66	47	45	50	53	45	<50
ECG								
SV ₁ +RV ₅ (mm)	33	17	31	18	13	13	21	<35
Echocardiogram								
LVDd (mm)	54	54	54	N.D.	43	48	38	42–50
LVDs (mm)	42	47	42		31	38	26	26–34
%FS (%)	22	13	22		28	21	32	28–50
IVS (mm)	12	12	12		22	22	13	7–10
LVPW (mm)	12	12	12		12	12	13	9–10

CTR: cardiothoracic ratio, LVDd and LVDs: end-diastolic and end-systolic left ventricular dimension, respectively, %FS: percentage fractional shortening, IVS: interventricular septum, LVPW: left ventricular posterior wall, N.D.: not done.

Figure 2. Chest radiographs in a 59-year-old male (Case 1) with diabetes mellitus, deafness, and hypertrophic cardiomyopathy associated with a point mutation of mitochondrial DNA. Cardiac enlargement with a CTR of 66% and pleural effusion was found in October 1993 (left), at the time of complaints of orthostatic dyspnea and edema, and disappeared after 2 months of treatment with diuretics and captopril (December 1993, right). He lost 13 kg body weight and his CTR decreased to 47%.

duration on insulin. He showed mild cardiac hypertrophy on echocardiograms, although his ECG, chest radiograph and %FS of 32% were normal. He never had signs or symptoms suggestive of congestive heart failure.

Exercise myocardial perfusion scintigraphy with thallium-201 showed no defects in Cases 1 and 3. Case 2 refused it.

Discussion

An A-to-G transition at position 3243 in the mitochondrial tRNA^{Leu(UUR)} gene was originally identified in patients with MELAS syndrome (8). This mutation was subsequently found in patients with diabetes mellitus and deafness (9, 10) as well as in those with cardiomyopathy (11, 12). The present study employing echocardiography, demonstrated hypertrophic cardiomyopathy in 3 patients with diabetes mellitus and deafness associated with the 3243 mutation. This observation may be consistent with a recent finding that cardiomyopathy was found in 4 patients with MELAS, whose age ranged from 10 to 19 years old (13). Because different point mutations and deletions of mitochondrial DNA have been reported in patients with hypertrophic cardiomyopathy (11, 14, 15), genetic mitochondrial dysfunction may be of pathogenic importance in the development of myocardial hypertrophy.

The presence of specific cardiomyopathy related to diabetes mellitus, diabetic cardiomyopathy, is supported by epidemiologic, clinical and pathologic data (1, 2). The diagnosis of diabetic cardiomyopathy should be made only after the exclusion of atherosclerotic and hypertensive heart disease and other conditions known to cause myocardial dysfunction. When

hypertrophic cardiomyopathy was disclosed by means of echocardiography in Cases 1 and 2 on their respective first occasion, they were free of clinical heart disease, except for systolic murmur in Case 1. They were neither hypertensive, obese nor hypercholesterolemic. In addition, their exercise ECG revealed no ischemic response. Furthermore, they had no conditions other than long-standing diabetes mellitus, such as alcohol abuse, valvular disease, congenital heart disease, pericardial disease, thyroid disorders, or pericarditis, known to cause myocardial dysfunction. Therefore, they had been diagnosed as having diabetic cardiomyopathy. Three years later, mitochondrial DNA analysis became available for clinical use and an A-to-G transition at position 3243 in the mitochondrial tRNA^{Leu(UUR)} was subsequently identified in these 2 patients. These observations indicate that mitochondrial DNA mutation should be examined in diabetic patients with cardiomyopathy.

The Framingham Heart Study suggests a causal role of diabetes mellitus in the development of congestive heart failure (4). In this prospective study over an 18-year-follow-up period, the frequency of congestive heart failure was more than twice as high in diabetic men than in the nondiabetic cohort. This excessive risk persisted even when taking into account age, hypertension, obesity and hypercholesterolemia, factors which commonly coexist with long-standing diabetes mellitus. The excessive risk of congestive heart failure was confined to diabetic individuals with hyperglycemia severe enough to warrant insulin therapy, whereas patients treated with diet therapy or oral hypoglycemic agents had no increased risk of congestive heart failure (4). In the present studies, 2 diabetic patients with congestive heart failure were lean, hypo-

Figure 3. Echocardiograms in Case 1 taken in October (A) and December (B), 1993. Although end-diastolic left ventricular dimension was the same (54 mm) on both occasions, end-systolic left ventricular dimension decreased from 47 to 42 mm. Therefore, %FS rose to 22% from 13%.

cholesterolemic and not hypertensive and have been treated with an oral hypoglycemic agent. These findings suggest that congestive heart failure found in these 2 patients was not secondary to diabetic cardiomyopathy but was associated with hypertrophic cardiomyopathy due to an A-to-G transition in the mitochondrial tRNA^{Leu(UUR)}.

It is noted that ultrasound examination of the heart in Case 1 revealed cardiac hypertrophy and left ventricular dysfunction indicated by low %FS, even when his ECG and chest radiograph were normal. Three years later, he developed congestive

Figure 4. Echocardiograms showing severe hypertrophy in Case 2 with diabetes of 27 years' duration and taking an oral hypoglycemic agent. He was diagnosed as having idiopathic and/or diabetic hypertrophic cardiomyopathy when mitochondrial DNA analysis was not available.

heart failure. This was associated with a 9% decrease in %FS (from 22 to 13%) and an increase in CTR. His ECG and chest radiograph, however, were normal after 2 months of treatment with diuretics and captopril; %FS rose to 22% and CTR restored to normal. These findings, coupled with the observation that, as mentioned earlier, myocardial hypertrophy is found in patients with various forms of genetic mitochondrial dysfunction, suggest that patients with mitochondrial DNA mutation should undergo echocardiography even if the ECG and chest radiograph are normal.

A portion of this work has been described in Letters to the Lancet (16).

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