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Cardiac Dysfunction in Patients with Chronic Progressive External Ophthalmoplegia

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Summary

Background: Chronic progressive external ophthalmoplegia (CPEO), which includes Kearns-Sayre syndrome, is a mitochondrial disorder with large deletions of mitochondrial DNA. Recently, mtDNA deletions in cardiac muscle cells were thought to be a cause of dilated cardiomyopathy. However, the cardiac involvement in patients with CPEO is generally considered to be limited to the cardiac conduction system.

Hypothesis: The purpose of this study was to evaluate left ventricular function in patients with CPEO.

Methods: We evaluated the cardiac function of five patients with CPEO by means of carotid pulse recording and Doppler echocardiography.

Results: The ratio of the pre-ejection period to ejection time was increased to 0.67 in one patient and to 0.50 in another. Echocardiography showed left ventricular dilatation and diffuse hypokinetic wall motion in both cases. Left ventricular fractional shortening was decreased to 5 and 19%, respectively, and the mean rate of circumferential shortening was decreased to 0.12 and 0.63 circ/s, respectively. One of the two patients died of congestive heart failure 2 months after the study. The Doppler pattern of left ventricular filling in the three remaining patients showed a decrease in the ratio of peak flow velocity in early diastole to that in late diastole, with an increase in deceleration time.

Conclusion: Although cardiac involvement in patients with CPEO is generally considered to be limited to the cardiac conduction system, left ventricular dysfunction may be present and should receive more attention in the management of patients with CPEO.

Key words: chronic progressive external ophthalmoplegia, mitochondrial myopathy, cardiac dysfunction

Introduction

Chronic progressive external ophthalmoplegia (CPEO), which includes Kearns-Sayre syndrome (KSS),[1] is a mitochondrial disorder with large deletions of mitochondrial DNA (mtDNA).[2–5] Recently, mtDNA deletions in cardiac muscle cells were thought to be a cause of dilated cardiomyopathy.[6,7] However, cardiac involvement in patients with CPEO is generally considered to be limited to the cardiac conduction system.[8–10] In this paper, we report on left ventricular (LV) function in five patients with CPEO using carotid pulse recording and Doppler echocardiography.

Methods

Study Population

We evaluated the cardiac function in five Japanese patients with CPEO, two men and three women ranging in age from 20 to 64 years (mean 48 years), by carotid pulse recording and Doppler echocardiography. As controls, we evaluated 40 normal subjects without cardiac or neuromuscular disease, 18 men and 22 women ranging in age from 20 to 65 years [46 ± 10, mean ± standard deviation (SD)].

A biopsy of the deltoid muscle was obtained in the five patients with CPEO. Specimens were examined by an evaluation of modified Gomori-trichrome staining and histochem-

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istry for cytochrome oxidase. Muscle tissue was also examined by electron microscopy. Analysis of mtDNA was performed as described previously.[11] In brief, mtDNA from the skeletal muscle specimens was examined by Southern blotting using the restriction enzyme, PvuII, and probes for human mtDNA (map position nt 3,153–3,551), and by the primer shift polymerase chain reaction (PCR) using primers that were designed on widely separated regions of mtDNA. To determine the deletion sites of mtDNA, the PCR products that contained breakpoints were sequenced by the dideoxy method using 7-deaza sequenase.[11]

Carotid Pulse Recording

Electrocardiogram (ECG), phonocardiogram and carotid pulse were recorded simultaneously. Left ventricular ejection time (ET) was measured as the interval from the beginning of the upstroke to the onset of the dicrotic notch on the carotid pulse tracing. QRS to the second sound interval (Q-2) was measured as the interval from the onset of the QRS complex to the earliest high-frequency vibrations of the aortic component of the second heart sound. Pre-ejection period (PEP) was calculated by subtracting ET from Q-2. The ratio of PEP to ET (PEP/ET) was calculated to evaluate LV systolic function.[12]

Doppler Echocardiography

Two-dimensional (2-D), M-mode, and pulsed Doppler echocardiographic examinations were performed with an ultrasound system (Toshiba, SSH-160A) using mechanical and phased-array sector scanners with a 2.5 or 3.5 MHz transducer. The interventricular septal thickness (IVS), LV posterior wall thickness (LVPW), LV end-diastolic dimension (LVDd), and LV end-systolic dimension (LVDs) were measured according to the recommendations of the American Society of Echocardiography.[13] Fractional shortening (FS) was calculated as (LVDd−LVDs)/LVDd. The mean rate of circumferential shortening (mVcf) was calculated as (LVDd−LVDs)/LVDd·ET.

Left ventricular inflow velocities were recorded by pulsed Doppler echocardiography. The Doppler sample volume was placed at the level of the leaflet tips of the mitral valve using the apical long-axis view. Peak flow velocities of the LV inflow in early diastole (peak-E) and late diastole with atrial contraction (peak-A) were measured from the baseline to the maximum flow velocity, and the ratio of peak E to peak A (E/A) was calculated. Mitral deceleration time (Mdt) was measured as the time required for peak E velocity to decline to baseline.[14] Values were the mean of eight beats.

Statistical Analysis

Data are expressed as mean ± SD. The upper and lower 95% confidence limits of the measurements in carotid pulse recording and Doppler echocardiography are the mean ± 1.645 SD values obtained in normal subjects.

Results

Clinical Features of Patients with Chronic Progressive External Ophthalmoplegia

The clinical features of the five patients with CPEO are summarized in Table I. None had a family history of CPEO or cardiomyopathy. None had a medical history of hypertension, diabetes mellitus, hyperlipidemia, smoking, or alcohol abuse. Patient No. 1 experienced exertional dyspnea at the age of 19. His routine ECG showed QS in leads V_{1-3}, T inversion in leads V_{4-6}, and a normal PQ interval. He died of congestive heart failure at the age of 20, 2 months after the present study. Patient No. 2 experienced exertional dyspnea at the age of 55. The ECG in this patient showed first-degree atrioventricular block. A His-bundle electrogram showed that the His-Purkinje interval was prolonged to 90 ms. No symptoms of heart failure were observed in the other three patients. Their ECGs revealed no cardiac conduction disturbance. Skeletal muscle biopsy in the five patients revealed the presence of 1.0 to 9.7% scattered ragged red fibers lacking cytochrome oxidase activity. Electron microscopic examination of the skeletal muscle in all patients showed variations in the size and structural abnormalities of the mitochondria with paracrystalline inclusions and abnormal cristae. Southern blot analysis showed mtDNA deletions of 10 kb in Patient No. 1, and of 5 kb in Patients No. 2 and 3. Southern blot analysis in Patients No. 4 and 5 did not detect deletions, but primer shift PCR showed mtDNA deletions of 5.4 kb and 5.7 kb, respectively. Sequencing of the deleted mtDNA showed that the mtDNA deletions ranged from 5,920 nucleotides (nt) to nt 16,012 in Patient No. 1; from nt 8,483 to nt 13,459 in Patient No. 2; from around nt 8,260 to nt 13,613 in Patient No. 3; from nt 8,139 to nt 13,577 in Patient No. 4; and from around nt 7,897 to nt 13,613 in Patient No. 5.

TABLE I Clinical features of five patients with chronic progressive external ophthalmoplegia

	Patient No.				
	1	2	3	4	5
Age (years)	20	57	61	38	64
Sex	M	M	F	F	F
Clinical symptoms					
Dementia	−	−	−	+	−
Short stature	−	+	+	−	−
Ophthalmoplegia	+	+	+	+	+
Retinal degeneration	−	+	−	−	−
Hearing loss	+	+	−	−	+
Limb weakness	+	+	−	−	+
Ataxia	−	−	−	−	+
Heart block	−	+	−	−	−
Dilated cardiomyopathy	+	+	−	−	−

Abbreviations: M = male, F = female, + = present, − = absent.

Findings of Carotid Pulse Recording

The PEP/ET in the normal subjects was 0.27 ± 0.03 (mean ± SD). This ratio was abnormally high in Patients No. 1 (0.67) and No. 2 (0.5) (Fig. 1).

M-Mode and Two-Dimensional Echocardiographic Findings

M-mode echocardiographic measurements in normal subjects were as follows: IVS 8.9 ± 1.1 mm, LVPW 8.8 ± 0.9 mm, LVDd 45.0 ± 3.0 mm, LVDs 30.1 ± 3.2 mm, FS 35.0 ± 4.8, and mVcf 1.4 ± 0.3 circ/s. The IVS in Patient No. 1 was slightly decreased to 6 mm, but was within normal limits in the remaining four patients, as was the LVPW in all five patients with CPEO. The LVDd and LVDs were enlarged to 63 mm and 60 mm, respectively, in Patient No. 1, and enlarged to 53 mm and 43 mm, respectively, in Patient No. 2. The FS was decreased to 5% in Patient No. 1 and to 19% in Patient No. 2. The mVcf was decreased to 0.12 circ/s in Patient No. 1 and to 0.63 circ/s in Patient No. 2 (Fig. 1). In these two patients, 2-D echocardiography showed an enlarged LV dimension with diffuse hypokinesis of the LV wall (Fig. 2).

Pulsed Doppler Echocardiographic Findings

In the normal subjects, peak E was 69 ± 10 cm/s, peak A was 37 ± 4.7 cm/s, E/A was 1.9 ± 0.4, and Mdt was 117 ± 13 ms. In the patients with CPEO, peak E was decreased to 43 cm/s in Patient No. 3, to 45 cm/s in Patient No. 4, and to 48 cm/s in Patient No. 5. Peak A was increased to 57 cm/s in Patient No. 3, to 58 cm/s in Patient No. 4, and to 60 cm/s in Patient No. 5. Peak E to peak A ratio was decreased to 0.75 in Patient No. 3, to 0.78 in Patient No. 4, and to 0.80 in Patient No. 5. In Patient No. 1, peak A was decreased to 21 cm/s, and E/A was increased to 3.3. Mitral deceleration time was increased to 160 ms in Patient No. 2, to 162 ms in Patient No. 3, to 167 ms in Patient No. 4, and to 200 ms in Patient No. 5, and was decreased to 80 ms in Patient No. 1 (Fig. 3).

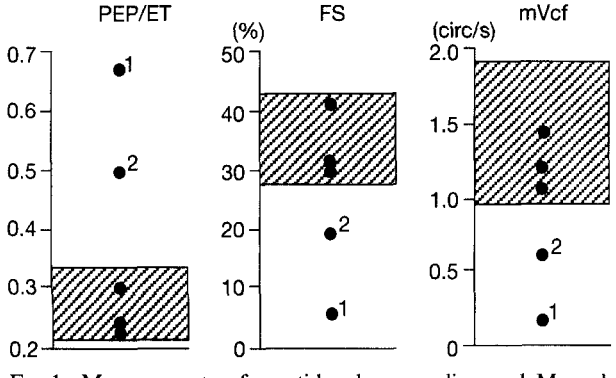

FIG. 1 Measurements of carotid pulse recording and M-mode echocardiography in five patients with chronic progressive external ophthalmoplegia/Kearns-Sayre syndrome. PEP/ET = ratio of pre-ejection period to ejection time, FS = fractional shortening, mVcf = mean rate of circumferential shortening. ●1 = Patient No. 1. ●2 = Patient No. 2. Shaded areas indicate the 95% confidence limits of normal values.

Discussion

Patients with mitochondrial disease related to the point mutation in mtDNA commonly exhibit cardiac involvement such as cardiomyopathy. Hypertrophic cardiomyopathy is frequently found in patients with mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS).[15] The A-to-G transition at position 3,243 in the $tRNA^{LEU(UUR)}$ gene, which is found in the majority of patients with MELAS, is reportedly associated with hypertrophic cardiomyopathy.[16] Mitochondrial myopathy with an A-to-G transition at position 3,260 in the $tRNA^{LEU(UUR)}$ gene is also complicated by hypertrophic cardiomyopathy.[17] An A-to-G transition at position 4,269 in the $tRNA^{Ile}$ gene is complicated with dilated cardiomyopathy.[18] On the other hand, cardiac conduction disturbance has been identified in patients with CPEO including KSS, which had mtDNA deletions.[8–11] Although the ultrastructural investigation has revealed mitochondrial abnormalities in the heart muscle,[19] LV dysfunction has been considered to be very rare in previous studies of the heart of patients with CPEO including KSS.[8–11] Only three patients with KSS that was associated with dilated

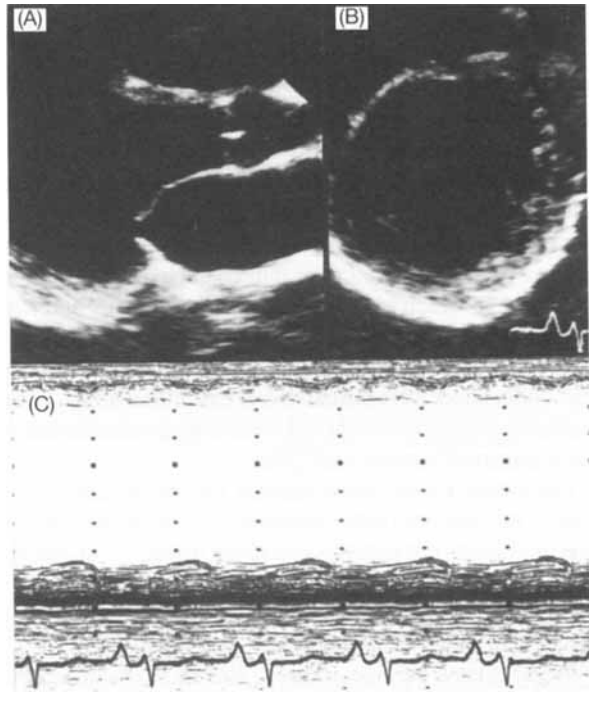

FIG. 2 Two-dimensional echocardiogram obtained in the parasternal long-axis view (A) and short-axis view (B), and M-mode echocardiogram (C) in Patient No. 1. The left ventricular (LV) dimension is markedly enlarged and the LV wall is thin. Motion of the interventricular septum and of the LV posterior wall is severely reduced.

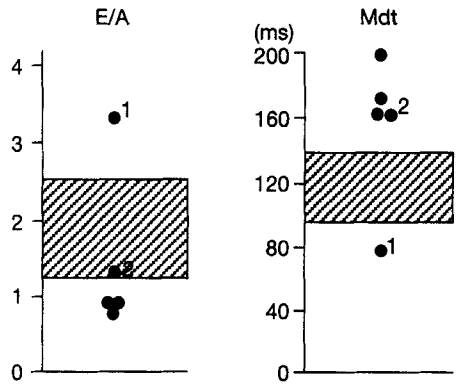

FIG. 3 Doppler echocardiographic measurements in five patients with chronic progressive external ophthalmoplegia/Kearns-Sayre syndrome. E/A = the ratio of peak flow velocity of the left ventricular inflow in early diastole to that in late diastole with atrial contraction, Mdt = mitral deceleration time. ● 1 = Patient No. 1. ● 2 = Patient No. 2. Shaded areas indicate the 95% confidence limits of normal values.

cardiomyopathy have been reported.[20–22] There are few detailed reports about the mechanocardiographic and Doppler echocardiographic findings in patients with CPEO.

The increase in PEP/ET and the decrease in FS and mVcf in Patients No. 1 and 2 indicates a reduction in their LV systolic function. The transmitral flow observed in Patient No. 1 could be explained as a pseudo-normalized pattern,[14] which suggested that the diastolic pressures of the left ventricle and the left atrium were markedly increased by the presence of severe LV dysfunction. These results and the 2-D echocardiographic findings showed that both patients had dilated cardiomyopathy. The decreased E/A and the increased Mdt in the remaining three patients indicated a reduction in LV diastolic function with preservation of systolic function. Using Doppler echocardiography, Suzuki *et al.*[23] observed a decrease in diastolic LV function in patients with MELAS who had no symptoms of heart failure. The myocardial involvement of patients in an early phase of CPEO was thus characterized by diastolic dysfunction, which led to dilated cardiomyopathy at the advanced stage. In addition, four of the five patients studied showed LV dysfunction with no apparent disturbance in cardiac conduction. Myocardial involvement as well as cardiac conduction disturbance should receive more attention in the management of patients with CPEO.

Phenotypic expression in patients with mitochondrial myopathy is considered to be determined by the relative proportion of mutant-type mtDNA in a given tissue.[4, 24] In addition to the threshold effect,[4, 24] it is not known whether the deleted regions of mtDNA are related to cardiac function. Two patients, a previously reported case[20, 25] and our Patient No. 2, who had dilated cardiomyopathy, shared a "common deletion" of mtDNA.[26] This deletion has been observed in many patients with CPEO,[3] and it is not specific for cardiomyopathy. The mtDNA deletion in Patient No. 1 was large and involved the major part of non-D-loop region. Besides the threshold effect, the site of mtDNA deletion in Patient No. 1 may have been related to the development of fatal dilated cardiomyopathy. Further investigations are needed to elucidate the relationship between the deleted region of mtDNA and cardiac function.

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Association between Psychiatric Disorders and Marfan's Syndrome in a Large Sardinian Family with a High Prevalence of Cardiac Abnormalities

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Summary

Background: Marfan's syndrome is an inherited disorder of connective tissue associated with characteristic abnormalities of the skeletal, ocular, and cardiovascular systems. Marked clinical variability and age dependency of all manifestations of Marfan's syndrome may render the unequivocal diagnosis difficult in mildly affected, young subjects.

Hypothesis: The study and care of a 32-year-old woman with evidence of Manfan's syndrome, several cardiac abnormalities, and paranoid schizophrenia led to an investigation of her consenting relatives to verify the penetrance of Marfan's syndrome and the degree of comorbidity between the disease and psychiatric disorders.

Methods: The patient and 12 subjects belonging to three generations of her family underwent cardiovascular, skeletal, ophthalmologic, and psychiatric examinations. Two-dimensional and Doppler echocardiography were performed.

Results: One female index patient and six of her first-degree relatives were found to be affected by Marfan's syndrome. All seven patients were found to have mitral valve prolapse associated with other cardiac abnormalities. Four of these patients were affected by the following psychiatric disorders: generalized anxiety disorder, major depressive disorder, paranoid schizophrenia (two cases). Six more relatives without Marfan's syndrome showed mitral valve prolapse in association with other echocardiographic features. Two of these were found to be affected by a major depressive disorder.

Conclusions: The present data support the hypothesis that a psychiatric condition, associated with a significantly high frequency of cardiac involvement, may be part of the phenotype of Marfan's syndrome.

Key words: connective tissue disease, cardiovascular findings, neuropsychiatric symptoms, schizophrenia

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Introduction

Marfan's syndrome is an inherited disorder of connective tissue associated with characteristic abnormalities of the skeletal, ocular, and cardiovascular systems.[1] The gene of fib-