An 80-year-old Mitochondrial Disease Patient with A3243G tRNA^{Leu (UUR)} Gene Presenting Cardiac Dysfunction as the Main Symptom

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Abstract

MELAS is characterized by mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes, but cardiac involvement also frequently occurs. An 80-year-old female patient had been suffering from insulin-dependent diabetes mellitus and neurosensory hearing loss. At the age of 79 she suffered metabolic acidosis with persistent drowsiness and was subsequently found to have severe cardiac dysfunction. Muscle biopsy disclosed the presence of abnormal mitochondria, and the MELAS gene mutation (A3243G of the tRNA^{Leu (UUR)}) was demonstrated. It is noteworthy that this mitochondrial disease patient has survived until a great age, which shows the wide clinical spectrum of MELAS, especially in the age of onset. (Internal Medicine 40: 405–408, 2001)

Key words: mitochondrial DNA, metabolic disorder, cardiomyopathy

Introduction

A significant number of human disease-causing mitochondrial DNA (mtDNA) mutations have been identified (1) and among them an A→G transition at nucleotide 3243 (A3243G) of the tRNA^{Leu (UUR)} gene is one common mutation (2). This mtDNA mutation clinically causes a unique syndrome called MELAS, which consists of mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes. Additionally, it has recently been noted that patients with this gene mutation show considerable variety in their clinical pictures (3).

In this report we describe a mitochondrial disease patient with an A3243G tRNA^{Leu (UUR)} gene who has been suffering from serious cardiac dysfunction but who has survived to age 80. The present patient might be the oldest among those reported with a MELAS gene mutation.

Case Report

The female patient had a long history (more than 40 years) of insulin-dependent diabetes mellitus, and at the age of 74 she began to use a hearing aid for bilateral marked hearing loss. At the age of 77 she noticed exertional dyspnea and easy fatigability, and these symptoms gradually worsened. When she was 79 she was admitted to another hospital, where cardiomegaly with pulmonary congestion was noted on the chest roentgenogram. Oral administration of furosemide (20 mg/day) was started. Three months later she was readmitted to the same hospital because of persistent drowsiness. Laboratory examinations revealed hyperglycemia (blood glucose 328 mg/dl), renal dysfunction (serum creatinine 4.4 mg/dl) and metabolic acidosis (pH 7.02, base excess –24.5, anion gap 23.8), but the urine was negative for ketone bodies. An intravenous drip of sodium bicarbonate was started and her symptoms soon improved. One week later she was referred to our hospital.

On physical examination, she was of short stature (135 cm tall), and weighed 30 kg. She had severe neurosensory hearing impairment, but she was alert and showed normal mental activity. There was no weakness in limb muscles. She had no history of hypertension, and brain magnetic resonance imaging (MRI) showed no abnormalities. Her 3 daughters, all of whom are of short stature, suffer from insulin-dependent diabetes mellitus. In addition, her one female grandchild was diagnosed as having hypertrophy of the left ventricle by echocardiography.

Laboratory examinations showed normocytic and normochromic anemia (red blood cell count $230 \times 10^4/\mu\text{l}$, hematocrit 20.4%, hemoglobin 7.1 g/dl) and renal dysfunction (blood urea nitrogen 67 mg/dl, serum creatinine 2.9 mg/dl). Serum levels of lactate and pyruvate were normal (9.1 mg/dl and 0.6 mg/dl) but both were elevated in the cerebral spinal fluid (lactate: 24.2 mg/dl, normal: 10–20 mg/dl; pyruvate: 1.4 mg/dl, normal: below 0.4 mg/dl). On chest roentgenogram an enlarged cardiac shadow without pulmonary congestion was seen (cardiothoracic ratio 65.5%) (Fig. 1). The electrocardiogram showed complete

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right bundle branch block, left anterior fascicular block and inverted T waves in leads V₄ to V₆. The echocardiogram disclosed symmetrical thickness of the interventricular septum and left ventricular wall with diffuse hypokinesis of wall motion (Fig. 2). Muscle biopsy specimens obtained from the left biceps brachii showed many ragged-red fibers on modified

Gomori-trichrome stain and electronmicroscopy revealed large aggregates of abnormal mitochondria with paracrystalline inclusions, mainly under the sarcolemma (Fig. 3). Total DNA was extracted from muscle biopsy specimens and the leukocytes which were collected from peripheral blood, and then a mtDNA fragment was amplified with polymerase chain reac-

Figure 1. Chest roentgenogram showing marked cardiomegaly.

Figure 2. Echocardiogram showing symmetrical hypertrophy of left ventricular wall. Interventricular septum: 15 mm, Left ventricular posterior wall: 17 mm, Diameter of ventricular cavity (diastolic phase): 47 mm, Diameter of ventricular cavity (systolic phase): 36 mm, Fractional shortening: 21% (normal>28%).

Figure 3. Electronmicrophotograph of abnormal mitochondria in the muscle fiber. Paracrystalline inclusions are present in the diseased mitochondria (×18,000).

Figure 4. Analysis pattern of the *ApaI*-digested mtDNA fragments. M: marker, Lane 1: normal control, 2: MELAS patient, 3 and 4: the present patient. Lanes 1, 2 and 3 showing DNA fragments obtained from muscle biopsy tissues and lane 4 showing those obtained from leukocytes. Two abnormal bands are seen in a MELAS patient and in the present patient, indicating the presence of an A→G transition at nucleotide 3243 of tRNA^{Leu(UUR)} gene. Additionally, this patient reveals that mutant mtDNA is more abundant in skeletal muscle than in leukocytes.

tion (PCR) (4). The restriction enzyme analysis of this PCR product (5) demonstrated the presence of an A3243G tRNA^{Leu(UUR)} gene (Fig. 4). She was discharged from our hospital without any specific treatment and still continues her activities of daily life at the age of 80.

Discussion

MELAS is one major clinical phenotype of human mitochondrial diseases and an A3243G tRNA^{Leu(UUR)} gene has been identified in approximately 80% of MELAS patients, but the patients with this gene mutation also comprise clinically heterogeneous subgroups: some patients show only diabetes mellitus and deafness with a maternally inherited pattern (so-called maternally inherited diabetes and deafness: MIDD) (6). Others suffer from hearing impairment, diabetes mellitus, short stature and ophthalmoplegia (3).

Cardiac involvement was reported to occur in about 38% of MELAS patients (7), but in practice clinically silent cardiomyopathy seems to be more frequent than is recognized in the literatures. The characteristic echocardiogram of cardiac involvement in MELAS usually shows symmetrical hypertrophy of the left ventricle with diffuse hypokinesis of wall motion (7–9). In the present patient the predominant clinical mani-

festation was cardiac dysfunction associated with the echocardiographic findings just mentioned, and she had no history of the hypertension which commonly leads to this cardiac abnormality. She was also demonstrated to have a MELAS gene mutation when she suffered from what was probably lactic acidosis at the age of 79. Her cardiac disorder was, therefore, considered to be causally related to mitochondrial disease although no myocardial biopsy was performed. Since she lacked any MELAS features such as encephalopathy, myopathy or stroke-like episodes, her clinical picture was surmised to coincide with the category of MIDD (6). In mitochondrial diseases the distribution and the amount of mutant mtDNA are considered to be an important factor in determining the variable phenotypes (10, 11): mutant mtDNA is widely distributed in systemic organs but the proportion of normal and abnormal mtDNA is different in various tissues, and the clinical severity of organ dysfunction correlates approximately with the amount of mutant mtDNA in the involved organ. The heteroplasmic mutation of mtDNA was demonstrated in the present patient and, considering her clinical manifestations, the percentage of mutant mtDNA might be higher in the myocardium than in skeletal muscles or brain.

Aging is known to be one risk factor for the development of mitochondrial diseases (12) and significant numbers of the MELAS patients with disease onset after the age of 60 have been described (13): their ages ranged from 69 to 75 and all patients shared the common feature of insidious moderate proximal muscle weakness, but cardiac dysfunction was not noted in them. It is noteworthy that our patient with a MELAS gene mutation could survive until the age of 80 and that even so she lacked clinically apparent myopathy. Finally, we emphasize that mitochondrial diseases should be considered when examining patients with cardiomyopathy of unknown etiology, even if they are very elderly.

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