A Case of Mitochondrial Encephalomyopathy, Lactic Acidosis and Stroke-like Episodes Associated With Diabetes Mellitus and Hypothalamo-Pituitary Dysfunction

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Abstract. A 45-year-old woman with mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS) had muscular atrophy, severe cerebral and cerebellar atrophy, and cardiac hypertrophy. She also had diabetes mellitus treated with insulin, and sensorineural hearing loss. Ragged-red fibers were observed on muscle biopsy and an adenine to guanine transition mutation at position 3243 of her mitochondrial DNA was confirmed. Further investigations revealed that she also had hypothalamo-pituitary dysfunction. It appears that diabetes mellitus, hypothalamo-pituitary dysfunction, and the other abnormalities are all associated with mitochondrial dysfunction in this patient.

Key words: Mitochondrial dysfunction, Endocrine abnormalities, Position 3243 mitochondrial mutation, MELAS, Diabetes mellitus

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MITOCHONDRIAL encephalomyopathies are increasingly recognized as a group of multi-system disorders, often associated with ragged red fibers on muscle biopsy and ultrastructural abnormalities of the mitochondria. These diseases have been grouped into syndromes such as mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS), myoclonus epilepsy with ragged-red fibers (MERRF), Kearns-Sayre syndrome (KSS), and chronic progressive external ophthalmoplegia (CPEO). MELAS patients are usually normal at birth and during the first year of life, but then show stunted growth, episodic vomiting, seizures and recurrent cerebral insults resembling strokes that cause hemiparesis, hemianopia or cortical blindness [1]. The MELAS syndrome has been shown to be associated with an adenine to guanine transition mutation at nucleotide 3243 in the dihydrouridine loop of mitochondrial tRNALeu(UUR) [2]. Recent reports have suggested that this mitochondrial gene mutation is also associated with diabetes and sensorineural hearing loss [3–6]. Furthermore, the reported endocrinological abnormalities are not limited to diabetes but also include hypogonadism [7] as well as hypoparathyroidism [8]. Here we report a case of MELAS associated with both diabetes and hypothalamo-pituitary dysfunction.

Case Report

A 45-year-old woman had a history of normal
birth and development except for short stature. Her first menstruation was observed at the age of 14 years, and she subsequently married and delivered a child at the age of 27. She was diagnosed as having diabetes at the age of 28 and started insulin therapy 1 year later. Sensorineural hearing loss and rapid, brief myoclonic jerks appeared at the age of 35 and 45 years, respectively. One year before admission her menstruation became irregular and was not observed during admission (3 months). She was admitted to our hospital in April, 1995 with disturbance of consciousness.

Physical examination revealed her to be emaciated, with a weight of 27 kg and a height of 147 cm. Skeletal abnormalities were absent. Her intelligence was below normal limits, with an IQ of 48. Funduscopic examination showed diabetic retinopathy. An ejection systolic murmur (Lev II/VI) was audible. Muscle atrophy and weakness were generalized, but were more severe in the proximal limb muscles. Rapid, brief myoclonic jerks were noted and her gait was ataxic. Examination of the cranial nerves showed sensorineural hearing loss. The deep tendon reflexes were decreased and vibration sense was impaired. We informed the patient and her family of the necessity of the following examinations including muscle biopsy and they consented to our performance of these examinations.

Routine laboratory tests on admission are shown in Table 1. Plasma glucose (253 mg/dl) and hemoglobin A1C (8.6%) levels were high. The C-peptide immunoreactivity (CPR) response to glucagon stimulation was decreased and urinary 24-h excretion of CPR was noticeably reduced. Serum lactate and pyruvate levels were moderately increased, and the former was noticeably increased in the cerebrospinal fluid (CSF). Echocardiography indicated left ventricular hypertrophy. Magnetic resonance imaging demonstrated severe cerebral and cerebellar atrophy with dilatation of the lateral and fourth ventricles. The pituitary gland seemed normal on this imaging study. Light microscopy of a biopsy from the left biceps muscle showed some "ragged red fibers" on modified Gomori trichrome staining (Fig. 1).

DNA isolated from peripheral leukocytes and skeletal muscle was analyzed for the point mutation associated with MELAS. A 322 base pair (bp) fragment encompassing the mutation site at nucleotide 3243 was therefore amplified by the polymerase chain reaction (PCR) and digested with Apa I. The forward primer was 5'GGACAAG-ADAAATAAGGCCT3', and reverse primer was 5'AAAGGTTGTAGTAGCCGTA3'. PCR reaction was performed in a final volume of 50 µl containing 25 pmol sense and antisense primers, 0.1 µg DNA, 7.5 pmol of each deoxyribonucleoside triphosphate, 10 mM Tris-HCl (pH 8.3), 50 mM KCl, 1.5 mM MgCl2, 1.25 U Taq polymerase. The reaction
conditions were: initial denaturation for 3 min at 94 °C then 33 cycles of denaturation for 30 sec, annealing at 55 °C for 20 sec and extension at 72 °C for 40 sec, with final extension at 72 °C for 1 min. The PCR product of our patient was cleaved by Apa I to give three fragments (Fig. 2), suggesting the presence of an adenine to guanine nucleotide transition at position 3243 in the dihydrouridine loop of mitochondrial tRNALeu(UUR). These findings were compatible with a diagnosis of MELAS.

Hormonal studies showed low basal levels of TSH, FSH, LH, GH and somatomedin C, normal basal levels of ACTH, and high basal levels of cortisol and PRL (Table 1). Moreover, as shown in Fig. 3, there were abnormal responses of pituitary hormones to hypothalamic releasing factors, i.e., no responses of ACTH to corticotropin-releasing factor (CRF), TSH to TRH, or LH to LH-RH, as well as a delayed response of FSH to LH-RH, and an increased response of GH to GH-releasing factor (GRF) and PRL to TRH. These data indicated that hypothalamo-pituitary function was abnormal in our patient.

Discussion

Mitochondrial encephalomyopathy is characteristic of mitochondrial disorders. Many studies have demonstrated that MELAS patients are also prone to develop diabetes mellitus, and insulin secretion is reported to be decreased in these patients [6]. Current evidence indicates that pancreatic B cells secrete insulin in response to a rise in the ATP level caused by glucose oxidation. Our patient was diagnosed as having diabetes in her twenties and started insulin therapy about 1 year later. Her insulin response to glucose stimulation was noticeably decreased, indicating that energy production in the pancreatic B cells was impaired. Although we did not analyze mitochondrial DNA from pancreatic B cells, an abnormality of the B cell mitochondria is suspected to underlie such decreased energy production.

She also had other endocrinological abnormalities related to the hypothalmo-pituitary axis. To our knowledge, there have been 9 patients...
reported who had hypothalamo-pituitary hypofunction associated with mitochondrial encephalomyopathy (Table 2) [9–15]. The features of these patients were: short stature (130–140 cm), female predominance, and failure of GH, LH and FSH secretion which frequently occurs in panhypopituitarism. The short stature of these patients was probably due to GH deficiency. Hypothalamo-pituitary hypofunction can be seen in all of the mitochondrial encephalomyopathies, including KSS, CPEO, MERRF and MELAS. Since hormone secretion is an energy dependent process, a defect of mitochondrial oxidative phosphorylation may lead to the failure of hormone secretion. Alternatively, abnormalities in the mitochondria of the blood vessels may cause ischemic damage to the endocrine organs. Indeed, Hasegawa et al. have reported abnormal mitochondria in the smooth muscle cells of small arteries obtained from a MELAS patient [16]. In our patient, imaging studies excluded tumors of the pituitary gland or hypothalamus, suggesting that hypothalamo-pituitary dysfunction was associated with mitochondrial abnormalities affecting her endocrine organs, but the precise mechanism of such dysfunction in the mitochondrial encephalomyopathies remains to be clarified.

Table 2. Cases of mitochondrial encephalomyopathy associated with hypothalamo-pituitary dysfunction

<table>
<thead>
<tr>
<th>Reference</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>Height (cm)</th>
<th>Deficient hormones</th>
</tr>
</thead>
<tbody>
<tr>
<td>Petty (1986) [14]</td>
<td>32</td>
<td>male</td>
<td>CPEO</td>
<td>149</td>
<td>GH</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>female</td>
<td>MELAS</td>
<td>124</td>
<td>GH, LH, FSH</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>female</td>
<td>MELAS</td>
<td>119</td>
<td>GH</td>
</tr>
<tr>
<td>Joko (present report)</td>
<td>46</td>
<td>female</td>
<td>MELAS</td>
<td>147</td>
<td>TSH, LH, FSH</td>
</tr>
</tbody>
</table>

KSS, Kearns-Sayre syndrome; MERRF, myoclonus epilepsy with ragged-red fibers; CPEO, chronic progressive external ophthalmoplegia; MELAS, mitochondrial encephalomyopathy, lactic acidosis and stroke like episodes.

References


