# Mitochondrial Encephalomyopathy Associated with Diabetes Mellitus, Cataract, and Corpus Callosum Atrophy

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### Abstract

A 44-year-old woman with mitochondrial encephalomyopathy noticed weakness of the lower extremities at the age of 30 years. She also has type 2 diabetes mellitus, posterior subcapsular cataracts in both eyes, and corpus callosum atrophy. Family history showed that a maternal cousin had a myopathy, 3 maternal aunts had diabetes mellitus, and her mother and 2 maternal aunts had cataracts. External ophthalmoplegia, proximal myopathy, and absent deep tendon reflexes were noted. The mitochondrial DNA 3243 point mutation was negative. Muscle biopsy showed ragged-red fibers, cytochrome c oxidase (COX)-positive fibers, and COX-negative fibers.

Key words: mitochondrial encephalomyopathy, diabetes mellitus, cataract, corpus callosum, diffusion tensor image

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## Introduction

Although mitochondrial disorders are increasingly being recognized, confirming a specific diagnosis remains a great challenge due to the genetic and clinical heterogeneity of the disease (1). Mitochondrial disorders preferentially affect the muscle and nervous systems (2) but they may also affect the endocrine glands, heart, ears, gastrointestinal tract, liver, kidneys, bone marrow, and dermis (3).

We encountered a case of mitochondrial encephalomyopathy associated with diabetes mellitus, cataract, and corpus callosum atrophy. Because this combination of manifestations has never been reported in the literature, we report the case here.

# **Case Report**

The patient is a 44-year-old woman who visited our clinic

with the chief complaint of dysarthria. She has never had problems in learning or motor skills in the primary, secondary, and high schools. She noticed weakness of the lower extremities at the age of 30 years. The weakness of the lower extremities progressed gradually and she began to use a wheelchair at the age of 41 years. She developed bilateral ptosis, diplopia, and dysarthria at the age of 43 years. She was admitted to our hospital for detailed examinations. Her past history was unremarkable. Family history showed that a maternal cousin died of a myopathy at the age of 50 years, 3 maternal aunts had diabetes mellitus, and her mother and 2 maternal aunts had cataracts (Fig. 1).

On physical and neurological examinations, she had myopathic face, bilateral ptosis (right palpebral fissure 7 mm, left palpebral fissure 3 mm), external ophthalmoplegia, diplopia, muscle weakness in the four extremities, and muscle hypotonia. Her voice was small and she had slurred speech. She could not walk and deep tendon reflexes were absent in the four extremities. She did not have myotonia

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Figure 1. The family tree of the present case.



Figure 3. The T1-weighted sagittal image of the head magnetic resonance imaging shows corpus callosum atrophy.



**Figure 2.** The left side of the figure shows her right eye and the right side of the figure shows her left eye. She has posterior subcapsular cataracts in both eyes.

nor Babinski signs. Ophthalmologists could not look at her ocular fundus because of bilateral posterior subcapsular cataracts (Fig. 2). She did not show any cognitive decline in Mini-mental state examination (29/30 points) and Hasegawa's dementia scale-revised (30/30 points).

Her blood tests were as follows: hemoglobin 10.3 g/dL (reference range: 11.3-15.2), alkaline phosphatase 596 IU/L (115-359), y-glutamyl transpeptidase 361 IU/L (<30), creatinine 0.24 mg/dL (0.47-0.79), potassium 5.4 mEq/L (3.6-5.0), total cholesterol 309 mg/dL (150-219), hemoglobin A<sub>1C</sub> 8.3% (4.3-5.8), angiotensin-converting enzyme 6.9 IU/L (8.3-21.4), creatinine phosphokinase 90 IU/L (32-180), aldolase 3.0 IU/L (2.1-6.1), myoglobin 79 ng/mL (<60), lactic acid 8.1 mg/dL (3.0-17.0), and pyruvic acid 0.55 mg/dL (0.30-0.94). Oral glucose tolerance test (75 g) was as follows: blood glucose 122 mg/dL, insulin 3.17 µU/mL before the test, 170 and 13.9 at 30 minutes, 219 and 27.4 at 60 minutes, 241 and 44.5 at 120 minutes. The thyroid function tests, cortisol, aldosterone, anti-nuclear antibody, antiacetylcholine receptor antibody, anti-mitochondria antibody, anti-mitochondria-M2 antibody, and anti-glutamate decarboxylase antibody were normal. The mitochondrial DNA 3243 point mutation was negative.

The cell count, protein, and glucose in the cerebrospinal fluid were normal but we did not examine the lactate level in the cerebrospinal fluid. The electroencephalogram showed gereralized increases in the amount of slow waves. The



Figure 4. The diffusion tensor images of the head magnetic resonance imaging in the present case (left) and in a healthy person (right). A decrease in the number of nerve fibers traveling through the corpus callosum (especially to the parietal lobe) is noted in the present case.

audiogram showed a slight hearing impairment in the high tone range. The electrocardiogram showed a left anterior fascicular block. The chest computerized tomography revealed a mild cardiac enlargement. The abdominal computerized tomography revealed a mild atrophy of the pancreas. The head magnetic resonance imaging (MRI) revealed diffuse atrophy of the brain and corpus callosum atrophy (Fig. 3). We made the diffusion tensor image (Fig. 4) using the magnetic resonance diffusion tensor analysis software "dTV", which was developed in the Department of Radiology, Tokyo University School of Medicine.

The muscle MRI revealed muscle atrophy. The needle electromyogram showed a decrease in the amplitude of motor unit potentials. Muscle biopsy showed marked fiber size variation, measuring from a few to 100  $\mu$ m in diameter. The modified Gomori trichrome stain showed ragged-red fibers (Fig. 5). The cytochrome *c* oxidase (COX) activity stain (Fig. 6) showed COX-positive fibers and COX-negative fibers. The succinate dehydrogenase (SDH) activity stain showed strongly SDH-reactive blood vessels. Direct sequence of total mitochondrial DNA (4) using the muscle



**Figure 5.** The modified Gomori trichrome stain of the biopsied biceps muscle shows ragged-red fibers.

specimen did not show any significant mutation and Southern blot analysis did not show any mitochondrial DNA deletion. She refused to use an artificial respirator and she died of respiratory failure. An autopsy was not performed.

#### Discussion

We made the diagnosis of mitochondrial encephalomyopathy because she had typical muscle biopsy findings and a diffuse atrophy of the brain. She had clinical features of chronic progressive external ophthalmoplegia and progressive proximal myopathy. Central nervous system manifestations of mitochondrial disorders include a diffuse atrophy of the brain (3). The corpus callosum atrophy has not been noted in mitochondrial encephalomyopathy but it may be noticed in cases with a diffuse atrophy of the brain if a sagittal view of MRI is taken. The corpus callosum atrophy in the present case may be nonspecific although the corpus callosum atrophy is more prominent than the diffuse atrophy of the brain in the present case. The diffusion tensor images of the brain were abnormal in the present case and they may be useful in detecting mitochondrial encephalomyopathy (5-7).

Mitochondrial disorders are caused by mutations in the mitochondrial DNA or nuclear DNA (1-3). Because we



Figure 6. The left side of the figure shows succinate dehydrogenase stain and the right side of the figure shows cytochrome c oxidase (COX) activity stain. The white arrow shows a COX-positive fiber and the black arrow shows a COX-negative fiber.

could not find any mitochondrial DNA mutation, the present case may have been caused by a nuclear DNA mutation or by an unidentified mutation in the mitochondrial DNA.

The oral glucose tolerance test indicates that diabetes mellitus in the present case is type 2. The association of mitochondrial encephalomyopathy and diabetes mellitus has been frequently reported in cases with the mitochondrial DNA 3243 point mutation (8-13), but other point mutations of mitochondrial transfer RNA genes as well as mitochondrial DNA deletions and duplications have also been associated with diabetes mellitus (14). In the present case, the mitochondrial DNA 3243 point mutation was negative but other point mutations were not examined.

The association of mitochondrial encephalomyopathy and cataract has been frequently reported in congenital cases (15-20), but it has also been reported in an adult case (21). The cataracts in the present case were considered to be not due to diabetes mellitus or aging because they were very prominent. Although the possibility of accidental association can not be ruled out, mitochondrial abnormalities may have been the cause of diabetes mellitus, cataract, and corpus callosum atrophy in the present case.

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