Mitochondria, distinct organelles present in most cells in our body, play an essential role in the maintenance of glucose homeostasis. On the mitochondrial inner membrane, the burning of hydrogen produces an electrochemical gradient, which is used to generate chemical energy in the form of ATP(1). Abnormalities in the mitochondrial DNA (mtDNA) cause diseases due to defects in the oxidative production of energy.

Maternally inherited diabetes and deafness (MIDD) is a subtype of diabetes, caused by a mutation of mtDNA (2, 3). Common clinical features of MIDD are diabetes, neurosensory hearing loss, a normal or low body mass index (BMI), short stature, and the presence of macular dystrophy.

The A3243G mutation in the mitochondrial tRNALeu (UUR) gene are known to cause mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) in some pedigrees (4).

The clinical characteristics of the MELAS are episodic vomiting, seizures, and recurrent cerebral insults resembling strokes and causing hemiparesis, hemianopsia, or cortical blindness. The most frequent symptoms are episodic sudden headache with vomiting and convulsions. The characteristics of headache of MELAS patients are similar to migraine headache and successful treatment of headache by sumatriptan has been reported (5).

The latest version of the international classification of headache disorders (ICHD-II) categorized headache in patients with MELAS into a subform of “headache attributed to cranial or cervical vascular disorder” (6).

Mutations in mtDNA have been identified in other subgroups of mitochondrial encephalomyopathies, e.g., long deletions of different lengths in various locations in Kearns-Sayre syndrome, and point mutations in mitochondrial tRNA-lys in the MERRF syndrome (myoclonus epilepsy associated with ragged-red fibers). These mitochondrial syndromes share some common encephalomyopathic features and show unique symptoms for each syndrome. These syndromes are caused by different mutations in mtDNA. The A3243G MELAS mutation in the mitochondrial tRNALeu (UUR) gene was also found to cause MIDD. In the earlier reports, MELAS and MIDD are regarded as different clinical entities and the differences between the two syndromes caused by the same mtDNA mutation have been emphasized.

There are multiple mtDNA copies per cell and the situation that mutations are present in only a fraction of the total mtDNA population, can be encounterd. This situation is called heteroplasmy. Differences in heteroplasmy, the fraction of the total mtDNA carrying the mutation, in different tissues could explain part of the phenotypic variations in a entity and between entities.

On the other hand, recent studies have suggested a clinically wider spectrum than previously recognized. In a multicenter study conducted in France (7), 43% of MIDD patients with A3243G mutation had myopathy, 15% had cardiomyopathy, and 18% had neuropsychiatric symptoms.

MIDD patients with myopathic symptoms reported painful muscle weakness that affected the lower limbs during prolonged walking or running. Muscle biopsy showed ragged-red fibers, typical of mitochondrial myopathy in some of these MIDD patients.

Ocular motor palsy was present in 2 patients and cerebellar ataxia with cerebellar atrophy on nuclear magnetic resonance imaging was seen in another patient. Atrophic changes in the brain were observed in the 4 other patients. Neuropsychiatric disturbances included aggressive and unstable behavior (1 patient), impaired memory and concentration (3 patients), mental retardation of varying severity (4 patients), and psychotic behavior with auditory hallucinations (1 patient).

In the current issue of this journal, Kobayashi et al (8) reported a mother and child with MIDD bearing the A3243G mutation showing brain atrophy.

These unusual and interesting cases can be understood in the clinical spectrum of MIDD and MELAS due to A3243G mutation. Seeking better management, we should pay attention to the possibility of muscle and brain involvements among MIDD patients in our routine clinical practice. Accumulation of such cases will reveal the mechanism of phenotype differences in identical mtDNA mutations and may provide some clues to solve the pathophysiology of mitochondrial diseases.

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