Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes

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Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) is one of the mitochondrial cytopathies caused by defects in the mitochondrial genome. The MELAS syndrome affects multiple systems, particularly the nervous system and muscles. Due to the heterogeneity of the clinical symptoms, MELAS syndrome is often misdiagnosed. The outcomes of the clinical treatments are usually very poor, and the disease is progressive and fatal. Here, we report our diagnosis of MELAS syndrome in an 11-year-old boy with excellent therapeutic outcome with supplement treatments. The case indicates that early correct diagnosis and treatments can eliminate the clinical symptoms of MELAS syndrome.

An 11-year-old boy was admitted to our hospital with a history of recurrent headache, vomiting, generalized seizures, and visual disturbance for 30 months, and muscle weakness of the limbs for 8 months. Symptoms deteriorated with bilateral sensorineural deafness and difficulty in standing and walking for 10 days. He had been admitted in other hospitals several times, and the diagnoses were 'viral encephalitis,' 'epilepsy,' and 'demyelination disease.' He had been treated with anti-viral and anti-epileptic drugs. There was no other medical history except a cyst excision on the right parietal lobe. There was no abnormal family medical history. His mother and young sister (aged 3 months) appeared to be healthy. Physical examination showed a short-stature (135 cm) boy. He demonstrated loss of consciousness (unresponsive). Eye movements were normal, without trembling. His cardio-respiratory examinations turned out to be normal. Although his muscle tone and the deep tendon reflexes were normal, he presented difficulty in standing and walking and muscle atrophy of the limbs. Muscular tremor was found in the left limbs. Laboratory evaluations, including peripheral blood cell counts, serum electrolytes, C-reactive protein, CSF routine, muscle enzyme, electrocardiogram, heart color ultrasonics, chest x-rays, and electromyogram, were within the normal reference ranges, except marked lactic acidosis of the arterial blood level - serum lactate 6.7 mmol/L (normal value: <1.5 mmol/L). The EEG revealed increased bilateral and symmetrical slow waves. One year before admission, an MRI performed in another hospital revealed abnormal signals in the left occipital, parietal, and temporal cortical lobes, and a cyst in the right parietal lobe. Thus, we carried out another MRI and found abnormal signals in the occipital, parietal, and temporal cortical lobes in the right hemisphere instead, as well as symmetrical lesions at the lenticular nucleus. The above findings suggested a hereditary disease that appeared to be a mitochondrial disorder. A biopsy of the biceps brachii muscle was ordered, and studies using electron microscopy showed that some muscle fibers contained excessive numbers of mitochondria in abnormal shapes, huge mitochondria, and inclusion bodies in the mitochondria. These results suggested a diagnosis of MELAS syndrome.

To confirm the diagnosis, we investigated the mitochondrial DNA of the patient, his young sister, and his mother by polymerase chain reaction/restriction fragment length polymorphism analysis, followed by confirmation with sequence analysis. The A3243G mutation was identified in all 3 individuals. Quantitative analyses of the mutation showed higher loads in the patient (59.7% in urine, 34% in blood) and his sister (75.3% in urine, 52.5% in blood), but a lower level in his mother (36.5% in urine, 3.8% in blood) (**Figure 1**). After the diagnosis of MELAS syndrome was confirmed by the mutation analysis, we treated the patient with high doses of coenzyme Q10 (40 mg/d), ATP (140 mg/d), coenzyme A (200 U/d), and vitamin supplementation (vitamin B1 and vitamin B2, 40-60 mg/d each) and stopped the treatment with valproic acid. His symptoms were partially relieved within a week of treatment. After one week, no more seizure episodes occurred, and he was conscious. His vision and listening also improved. After 3 weeks, he could walk by himself. One month after the treatment, an MRI revealed a dramatic decrease in the abnormal signals of the right cerebrum and in the symmetrical lesions at the lenticular nuclei. His symptoms disappeared

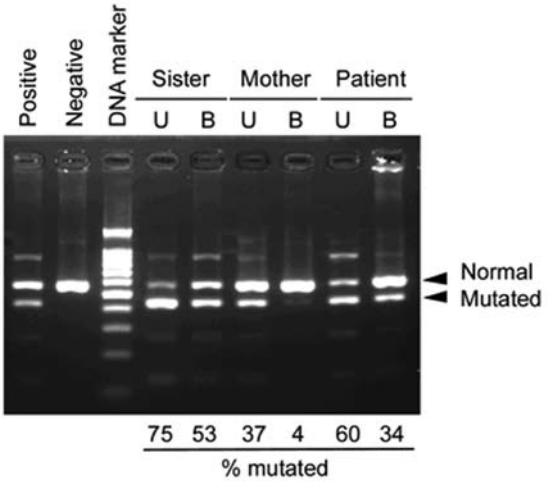

Figure 1 - Quantitation of the A3243G mutation of mitochondrial DNA (mDNA). Mitochondrial DNA of the urine sediment cells (U) and blood cells (B) was amplified by using 5'-CCTCCCTGTACGAAAGGACA-3' (forward) and 5'-GCCTAGGTTGAGGTTGACCA-3' (reverse), and the polymerase chain reaction products were analyzed by agarose gel electrophoresis after incubation with the endonuclease Apa I. The percentages of the A3243G mDNA over the total DNA are listed under each lane.

completely, except for the weakness of his physical strength, 2 months after the treatments. There were no systemic symptoms at the one-year follow-up.

Mitochondrial diseases, such as MELAS syndrome, are a clinically heterogeneous group of disorders that result from dysfunction of the mitochondrial respiratory chain. There are many clinical phenotypes of the mitochondrial diseases, ranging from asymptomatic to oligosymptomatic (milder or isolated symptoms) and to fully symptomatic. The case reported here was a typically and fully symptomatic MELAS case. This case had headaches, seizures, sensorineural disorders, astasia-abasia, unconsciousness, and blood lactic acidosis. Those symptoms can easily lead to misdiagnosis for a long time. Occurrence of seizures is usually diagnosed as epilepsies, with the consequent use of anti-epileptic drugs for many years. Canafoglia et al[1] reported that 53% of his 31 cases of mitochondrial diseases started with epilepsies. A higher percentage (67.7%) of the MELAS patients were reported to have epileptic symptoms, even status epileptics. Seizures are considered the most frequent manifestations of stroke-like episodes. The stroke-like episodes and seizures are likely caused by neuronal vulnerability and hyperexcitability in MELAS syndrome.

The MELAS syndrome is also usually misdiagnosed as viral encephalitis, which can be easily excluded by routine CSF test. Atypical MRI and neuromuscular symptoms of MELAS syndrome sometimes lead to misdiagnosis as demyelination diseases, but this can be easily excluded by blood lactic acidosis and muscle biopsy. Our diagnosis of this case was confirmed by mitochondrial abnormalities of the muscle biopsy samples and mitochondrial DNA mutation analysis. Many mitochondrial DNA mutations have been identified as a cause of mitochondrial diseases. Approximately, 30 point mutations have been demonstrated to underlie MELAS syndrome. The A3243G mutation (an adenine is replaced by guanine at point 3243 of the mitochondrial DNA) has been shown to associate with MELAS syndrome most often. However, this mutation occurs in the general population at a prevalence of 0.06%, or 60 per 100,000 individuals.[2] Approximately 80% of individuals with the clinical characteristics of MELAS syndrome have a heteroplasmic A-to-G point mutation in the dihydrouridine loop of the tRNALEU(UUR) gene at position 3243. Our sequence analysis indicated that the case reported in this study also carried this A3243G mutation. The G13513A mutation in the ND5 gene of mitochondrial DNA has also been reported to be a common cause of MELAS syndrome. Other MELAS-causing mutations include 2 mitochondrial DNA mutations in the ND3 and ND5 genes.[3] Intergenomic signaling defects (nDNA) also can underlie MELAS syndrome and other mitochondrial diseases. The MELAS syndrome may represent the complex genetics and diverse manifestations of mitochondrial diseases.

There is no cure for MELAS syndrome and other mitochondrial diseases,[4] and effective treatments are few to date. Most treatment regimens are cocktail treatments involving a combination of creatine, carnitine, coenzyme Q10, lipoic acid, vitamin supplementation, and, recently, L-arginine. We used the cocktail treatment and obtained a 'miraculous' effect. As similar cocktail treatments have been widely used and because the MELAS syndrome is very heterogenic, our 'miraculous' therapeutic achievement might be attributed to the right doses of each supplement for the case. Nevertheless, the efficacy of this case indicates that the MELAS syndrome can be managed to a symptom-free status for at least one year.

Symptomatic management is fundamental in addition to the cocktail treatment. Epilepsy and fever need to be controlled, because the increase of cerebral metabolism can increase stroke-like episodes. Valproic acid was an important drug for tonic seizure, but it can increase the epileptic episode in MELAS instead.[5] Valproic acid can change the structure of the mitochondrial membrane, decrease the respiratory function of mitochondria by decreased cytochrome aa3, and restrain the proton pump of complex IV. Valproic acid also can lead to an obstructed absorption of carnitine. In this case, the epileptic episodes were decreased and stopped after we stopped the treatment with sodium valproate.

In conclusion, our successful management of this MELAS syndrome case indicates that timely correct diagnosis and early treatments with supplements can eliminate the clinical symptoms for at least one year.

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