Late-onset mitochondrial disease in a patient with MELAS and mitochondrial DNA T14487C mutation

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To the Editor: Mitochondrial encephalomyopathy with lactate acidosis and stroke-like episodes (MELAS) is one of the most common multisystem mitochondrial disorders with broad clinical manifestations.[1] It is usually caused by point mutations in the mitochondrial MT-TL1 gene, which accounts for approximately 80% of mutations in individuals with MELAS syndrome.[2] Pathogenic mitochondrial DNA (mtDNA) mutations were first described in 1988[3] and m.14487T>C is a known pathogenic mtDNA mutation,[4] which has been reported in patients with Leigh syndrome, optic neuropathy, ptosis, dystonia, and encephalomyopathy. We herein report a patient with late-onset MELAS syndrome with the m.14487T>C mutation for the first time.

The patient in this study is a 58-year-old male who had experienced recurrent stroke-like episodes and repeated attacks of dizziness since he was 46 years old. He visited a doctor for the first time at 46 years of age with complaints of dizziness and muscle weakness of both lower extremities and epileptic seizure. In the local hospital, he was diagnosed with ischaemic stroke and recovered without sequelae. There were three similar stroke-like episodes that he suffered during the following 10 years and he developed mild hearing loss. Brain magnetic resonance imaging (MRI) showed a small lesion in the occipital lobe when he was 56 years of age [Figure 1A]. At the age of 58 years, he was admitted to the local hospital due to the left lower limb numbness and defect of right field vision. Brain MRI revealed a subacute lesion in the bilateral parietal lobe and left occipital lobe [Figure 1B]. The symptoms were progressive, and he developed cognitive deficiencies, memory deterioration, and vomiting during hospitalization. Brain MRI indicated signal changes in the right cerebellar hemisphere and left hypothalamus and multiple lesions in bilateral parietal lobe, left occipital lobe and centrum semiovale [Figure 1C and 1D].

Physical examination indicated that he was of a normal stature and his deep tendon reflexes were normal, but his muscle strength and superficial sense of the left lower limb were mildly reduced. No abnormality was evident either serologically or in the cerebrospinal fluid (CSF), except for a moderately increased lactate level (2.3 mmol/L, normal<2.1 mmol/L) and slightly increased protein level (495 mg/L) in the CSF. Auditory-evoked responses were consistent with bilateral sensorineural hearing loss.

Muscle histopathological analysis showed no myopathic changes. However, we identified a T14487C mutation in the mtDNA, which causes an M63V substitution in the mitochondrial NADH dehydrogenase 6 (ND6) of complex I of the mitochondrial respiratory chain. The mutation was heteroplasmic in muscle and urine sediment with different mutation loads (97% in muscle and 48% in urine), and it was absent in the patient’s blood sample. The remarkable different distributions of mutant mtDNA in these tissues might explain the late onset and mild phenotype.

Muscle findings showed mild muscle hypertrophy, and there was no significant myopathic change on histological examination. The muscle weakness was consistent with the mitochondrial M63V mutation in complex I of the respiratory chain. The muscle strength was mildly reduced. No abnormality was evident either serologically or in the cerebrospinal fluid (CSF), except for a moderately increased lactate level (2.3 mmol/L, normal<2.1 mmol/L) and slightly increased protein level (495 mg/L) in the CSF. Auditory-evoked responses were consistent with bilateral sensorineural hearing loss.

We summarize the phenotypic presentations of 27 published cases (in 18 families) with this mutation [Table 1]. There was a wide range of clinical symptoms, and the age of onset ranged from early infancy to adulthood and was usually early infancy to childhood. Brain MRI anomalies were observed in the bilateral basal ganglia and brainstem lesions of most of these patients and substantianigral lesion, leukoencephalopathy and cortical atrophy were occasionally involved. Mutation loads varied in all these patients, irrespective of age at onset and the clinical phenotype. There was a successful preimplantation genetic diagnosis (PGD) treatment in a female m.14487T>C carrier.

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that resulted in the birth of a healthy boy.\textsuperscript{[5]} Although mitochondrial disease caused by mtDNA mutation is generally without treatment options, patients with PGD can achieve pregnancy with embryos that are either mutation-free or harbor heteroplasmic levels safely below the phenotypic threshold, and carriers of heteroplasmic mtDNA mutations have a fair chance of having healthy offspring.

In conclusion, although Leigh syndrome, which presents with ataxia, dystonia, and epilepsy, is a typical presentation of the m.14487T$>$C mutation and can present from birth to adolescence, this mutation also can manifest as late-onset MELAS syndrome without myopathic features or RRFs. We suggest that the m.14487T$>$C mutation should be analysed in patients with this clinical presentation, regardless of patient age.
Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

None.

Table 1: Summary of patients harboring the T14487C mutation in the mtDNA of 27 published cases (in 18 families).

| Characteristics                        | LS (n=23) | PME (n=2) | LHON (n=1) | PME and LHON (n=1) |
|----------------------------------------|-----------|-----------|------------|-------------------|
| Age of onset (years)                   | 0.5*      | 10 and 60 | 16         | 19                |
| Sex (female/male), n                   | 7/14      | 1/1       | 0/1        | 0/1               |
| Cardiomyopathy, n                      | 4         | 0         | 0          | 0                 |
| Ataxia, n                              | 5         | 1         | 0          | 0                 |
| Hypotonia, n                           | 9         | 0         | 0          | 0                 |
| Spasticity/hypertonia, n               | 7         | 2         | 0          | 1                 |
| Dystonia, n                            | 5         | 2         | 0          | 1                 |
| Epilepsy, n                            | 10        | 2         | 0          | 1                 |
| Swallowing difficulties/dysarthria, n  | 7         | 0         | 0          | 0                 |
| Developmental delay, n                 | 12        | 0         | 0          | 0                 |
| Optic atrophy, n                       | 7         | 0         | 1          | 1                 |
| Abnormal eye motility, n               | 3         | 0         | 0          | 0                 |
| Ptosis, n                              | 2         | 0         | 0          | 0                 |
| Hearing impairment, n                  | 2         | 0         | 0          | 0                 |
| Respiratory abnormalities, n           | 10        | 1         | 0          | 0                 |
| Gastrointestinal problems, n           | 4         | 0         | 0          | 0                 |
| Lactic acidosis¹, n                    | 8         | 0         | 0          | 0                 |
| Increased CSF lactate², n              | 5         | 0         | 0          | 0                 |
| Skeletal muscle morphology³, n         | 1         | 0         | 0          | 0                 |

*Median; ¹Eleven patients performed the examination; ²Six patients performed the examination; ³Eight patients performed the examination. CSF: Cerebrospinal fluid; LHON: Leber hereditary optic neuropathy; LS: Leigh syndrome; mtDNA: Mitochondrial DNA; PME: Progressive myoclonic epilepsy.

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