

Case Report

Transition from Leigh syndrome to MELAS syndrome in a patient with heteroplasmic MT-ND3 m.10158T>C

Atsuko Kori^a, Ikumi Hori^a, Tatsushi Tanaka^a, Kohei Aoyama^a, Koichi Ito^a,
Ayako Hattori^a, Kyoko Ban^b, Yasushi Okazaki^c, Kei Murayama^d, Shinji Saitoh^{a,*}^a Department of Pediatrics and Neonatology, Nagoya City University Graduate School of Medical Sciences, Japan^b Department of Pediatrics, Yokkaichi Municipal Hospital, Japan^c Intractable Disease Research Center, Juntendo University, Japan^d Department of Metabolism, Chiba Children's Hospital, Japan

Received 7 March 2019; received in revised form 16 May 2019; accepted 22 May 2019

Abstract

An m.10158T>C mutation in MT-ND3, encoding a subunit of respiratory complex I, causes early-onset Leigh syndrome (LS), mitochondrial encephalomyopathy with lactic acid and stroke-like episodes (MELAS) syndrome, and LS and MELAS overlapping syndrome, presumably dependent on the ratio of heteroplasmy. Herein, we report a 4-year-old girl with heteroplasmic m.10158T>C mutation, showing an evolving age-dependent phenotype from LS to MELAS syndromes. She showed mild developmental delay during infancy, which was associated with magnetic resonance imaging lesions in the brain stem and basal ganglia. At the age of 4 years, she developed rapid neurological deterioration and intractable seizures, which was associated with recurrent multiple cerebral lesions as well as basal ganglia lesions. Her cerebral lesions were located predominantly in white matter and appeared at multiple areas simultaneously, unique characteristics that are distinct from typical MELAS. Two patients with LS-MELAS overlapping syndrome with m.10158T>C have been previously reported, however, this is the first patient with m.10158T>C showing significant age-dependent changes in clinical features and neuro-images, implying an age-dependent role of complex I in the developing brain. © 2019 The Japanese Society of Child Neurology. Published by Elsevier B.V. All rights reserved.

Keywords: mitochondrial disease; respiratory complex I; neuroimaging

1. Introduction

Respiratory complex I is the largest multiprotein enzyme complex of the respiratory chain, and its main function is the transport of electrons from NADH to ubiquinone with simultaneous shunting of protons. Complex I consists of at least 46 distinct subunits, seven

of which are encoded by mitochondrial DNA (mtDNA), such as NADH dehydrogenase subunit 3 (ND3) [1]. An m.10158T>C mutation in the MT-ND3 gene was first reported in 2003 [2], and 17 patients with an m.10158T>C mutation have been reported to date. Initially, the m.10158T>C mutation was identified in patients with Leigh syndrome with poor prognosis [1–6]. These patients demonstrated an early onset, very rapid disease progression, and lethal consequences in early childhood [4]. Indeed, nine of ten LS patients died within one year of life [1–6]. It is of note that these LS patients are associated with homoplasmy or a very high

* Corresponding author at: Department of Pediatrics and Neonatology, Nagoya City University Graduate School of Medical Sciences, 1-Kawasumi, Mizuho-cho, Mizuho-ku, Nagoya 467-8601, Japan.

E-mail address: ss11@med.nagoya-cu.ac.jp (S. Saitoh).

ratio of heteroplasmy (>83%) of the m.10158T>C mutation in muscle. Additionally, two patients with LS and mitochondrial encephalomyopathy with lactic acid and stroke-like episodes (MELAS) overlapping syndrome [7,8], and three patients with MELAS have been reported [6,9]. The non-LS patients tend to exhibit a lower ratio of heteroplasmy in muscle or blood and an older age of onset, but the small number of patients precludes any definite conclusions. Herein, we describe a 4-year-old girl carrying an m.10158T>C mutation in MT-ND3 with 82% heteroplasmy in blood, who showed motor development delay at 1 year and 6 months, and rapid neurological deterioration and intractable seizures at 4 years. Magnetic resonance imaging (MRI), initially involving only the brain stem and basal ganglia, found multiple cerebral lesions of predominantly white matter, indicating a transition from LS to a MELAS phenotype.

2. Case report

The proband was a 4-year-old girl. She was born at 38 weeks and 6 days of gestation, with a birth weight of 2790 g, by normal delivery. Her elder sister was healthy and there is no family history of neuromuscular diseases. Her parents were healthy and unrelated. She presented to our hospital at 2 years and 1 month because she was not able to walk alone. Neurological examination was normal except for a mild decrease in muscle tone. Laboratory examination showed increased venous lactic acid (61.1 mg/dl) and lactate/pyruvate ratio (30.5). The lactic acid and lactate/pyruvate ratio of cerebrospinal fluid was also increased (48.9 mg/dl and 23.7, respectively). MRI revealed FLAIR/T2WI high signal and T1WI low signal lesions in bilateral globus pallidus, periaqueductal gray matter of midbrain, cerebral peduncles, and superior colliculi (Fig. 1A, B), which are typical findings in LS. Respiratory chain enzyme activity of skin fibroblasts was low only at complex I (19%; citrate synthase ratio). To identify the pathogenic mutation in this patient, we performed targeted gene panel sequencing (panel information available on request). The targeted regions including nuclear-encoded mitochondrial disease genes and whole mitochondrial genome were captured using the Agilent SureSelect custom target enrichment kit (Agilent Technologies) following Agilent protocols. The paired-end reads sequencing was performed on an Illumina MiSeq according to the manufacturer's protocols. We finally identified a pathogenic mutation m.10158T>C (618 of 754 reads; 81.96% in blood). This mutation was not detectable with Sanger sequencing from parents blood DNA whereas the patient had high ratio of heteroplasmy (data not shown). Although focal aware seizures of limbs appeared at 2 years and 4 months, seizures were well controlled by levetiracetam (30 mg/kg/day) and the patient had been in a stable condition for approximately

two years. At 4 years, recurrent focal aware seizures of the right upper limb followed by loss of consciousness and apneic attack occurred. MRI showed new lesions in the cortex as well as in bilateral basal ganglia (Fig. 1C). Administration of multi-vitamin, carbamazepine, clonazepam, and L-arginine failed to control seizures, and the patient exhibited rapid functional decline and neurodegenerative regression over four months. She became less able to assume a sitting position, swallowing function declined, and tube feeding was introduced. Her speech gradually regressed, and she became less able to turn over. She showed various seizure types including generalized clonic seizures, clusters of focal seizures of various origins, and apneic attacks. Sometimes, the patient displayed epilepsy partialis continua such as twitching of the corners of the mouth or right thumb, that continued almost an entire day. Her seizures tended to appear in cluster, and the seizure frequency fluctuated. Each time a seizure cluster occurred, new MRI lesions were identified in various areas of cerebral cortex and white matter (Fig. 1D–F).

Diagnostic study was approved by the ethics committee of Juntendo University and Chiba Children's Hospital, and was performed after receiving written informed consent from the parents of the patient.

The parents of the patient assented to be reported in this literature.

3. Discussion

Characteristic brain MRI findings in LS are bilateral and symmetrical lesions in the basal ganglia and brainstem, while characteristic brain MRI findings in MELAS are asymmetrical lesions in the cortex and subcortical white matter of the occipital, temporal, and frontal lobes. In terms of clinical features, LS develops in infancy and is characterized by developmental delay, seizures, and hypotonia, while MELAS develops in childhood and is characterized by stroke-like symptoms and hyperlactatemia. Our case exhibited developmental delay during infancy, and brain MRI revealed lesions in the brainstem and basal ganglia, which is consistent with LS. However, at the age of four, rapid neurological regression with refractory seizures was observed that was associated with new cerebral lesions, resembling the stroke-like symptoms of MELAS. Therefore, we concluded the phenotype had changed from LS to MELAS in an age-dependent manner.

The clinical features of previously reported cases with an m.10158T>C mutation in MT-ND3 and the case presented here are summarized in Table 1. Previous reports have reported a significant correlation between phenotype and the age of onset (Table. 1) [1–9]. The median age of onset in LS cases was 3 months, while the median age of onset in MELAS cases was 26 years. Two patients with m.10158T>C were reported to develop LS and

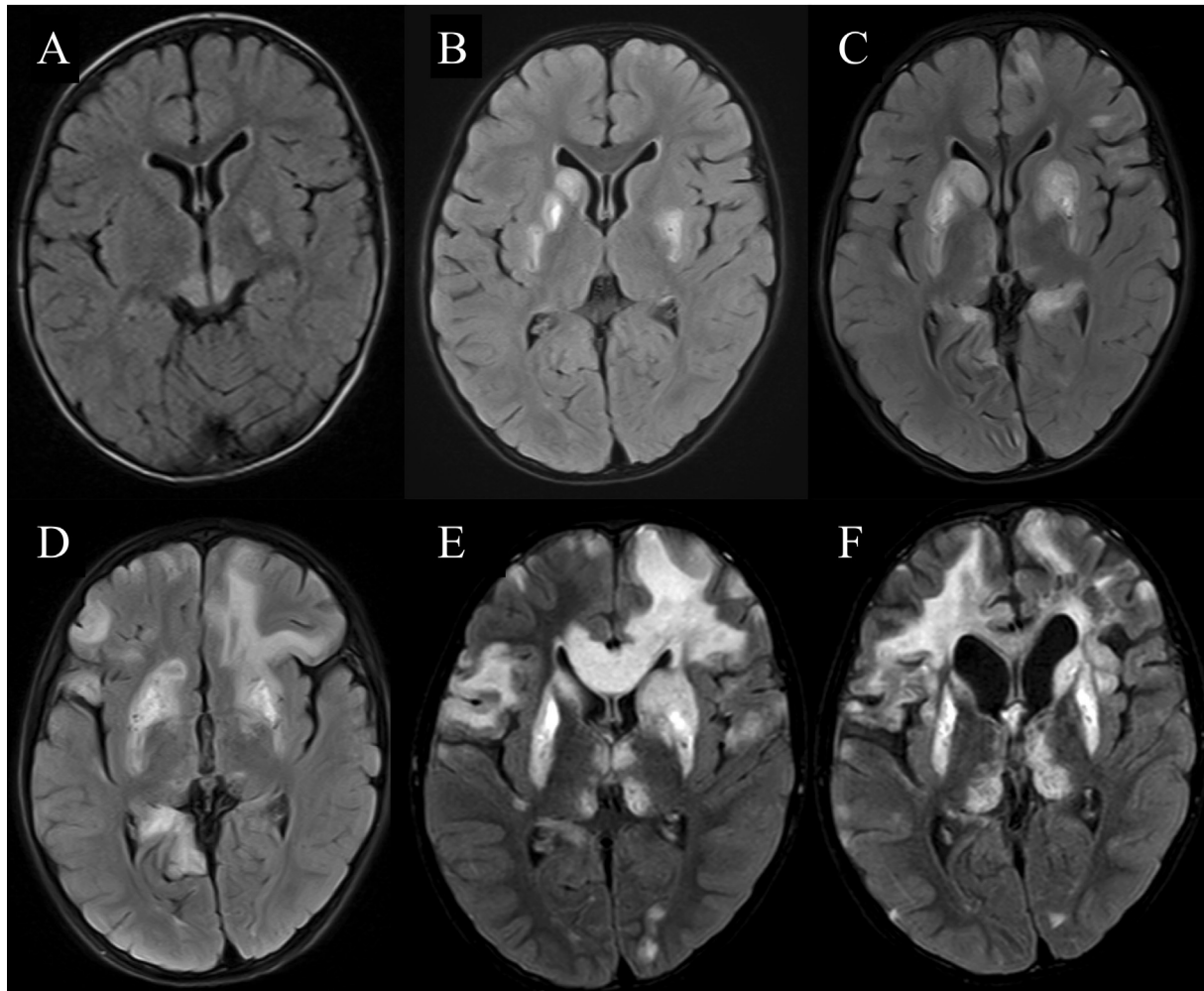


Fig. 1. Age-dependent changes in brain magnetic resonance imaging (FLAIR image): (A) MRI showed high signal lesions in the left globus pallidus and bilateral superior colliculi at the age of 2 years and 1 month. (B) High intensity of the bilateral basal ganglia at 3 years and 6 months. The new lesions identified in (C) the cortex of the frontal and bilateral occipital lobes at 4 years; (D) the frontal cortex, subcortical white matter and right occipital cortex at 4 years and 2 months, (E) the corpus callosum and left frontal cortex at 4 years and 3 months, and (F) the bilateral frontal lobes at 4 years and 5 months.

MELAS simultaneously [7,8], with a median age of onset of 8.5 years, which is between the median ages of onset of LS and MELAS, respectively. There is no published account of a phenotype changing over time in patients with m.10158T>C, such as we report here with our patient. Yet, it is possible that in the two previously reported patients with overlapping syndrome, LS symptoms in infancy were present but not observed. The age-dependent changes have been reported in MELAS/LS overlap syndrome with other mitochondrial DNA mutations. Therefore, we should be aware that a patient with a mitochondrial DNA mutation including m.10158T>C may show age-dependent phenotype changes. The medians of heteroplasmy ratio in blood and muscle were higher in LS than MELAS cases, while homoplasmy was not shown in patients with MELAS phenotype (Table. 1). It has been suggested that heteroplasmy ratio may correlate with clinical

presentation and brain image findings in patients with an m.10158T>C mutation [10]. Our patient is unique because she showed transition from LS to MELAS. Her heteroplasmy ratio in blood was 82% and comparable to that of the LS and overlap syndrome, but not MELAS. Therefore, her intermediate phenotype would support the correlation between heteroplasmy ratio and clinical severity in patients with an m.10158T>C mutation.

In MRI of patients with an m.10158T>C mutation, 38% of LS cases had cerebral lesions, 33% of MELAS cases had basal ganglion lesions, and 100% of cases with overlapping LS and MELAS had both cerebral lesions and basal ganglion lesions (Table. 1). These MRI findings imply overlapping brain involvement irrespective of clinical presentation. In our patient, brain MRI showed the T2WI/FLAIR high signal lesions with brainstem and basal ganglia at 2 years and 1 month,

Table 1
Current and previous reported patients with an MT-ND3 mt.10158T>C mutation.

Phenotype	Number of cases	Median age of onset	Survival rate (Median age of death)	Cerebral lesion	Basal ganglion lesion	Heteroplasmy ratio in blood, median (range, n) [*]	Heteroplasmy ratio in muscle, median (range, n) [*]	Percentage of cases of homoplasmy in blood	Percentage of cases of homoplasmy in muscle
LS	12	3 months (neonatal-1 year)	11% (6.5 months)	38%	100%	96% (48–100%, 5)	88% (83–100%, 6)	40%	17%
LS/MELAS	2	8.5 years (7–10 years)	100%	100%	100%	70% (n = 1)	98% (95–100%, 2)	0%	50%
MELAS	3	26 years (20–63 years)	100%	100%	33%	4.2% (3–5.3%, 2)	80% (69.5–89.5%, 3)	0%	0%
Present case	1	1.5 years	Alive	+	+	82%	NA	NA	NA

NA: Not applicable.

^{*} Homoplasmy is treated as 100%.

which is typical for LS. At the age of 4, brain MRI showed multiple recurrent cerebral lesions predominantly in the white matter, which is not typical for MELAS. Three previously reported patients with an m.10158T>C mutation also showed MRI high signal intensity in the white matter. Two are LS cases; one had high signal in the basal ganglia and the cortex-subcortex of gyrus of cingulum and central region [2], and the other had high signal in the supratentorial white matter, cerebral peduncles, periaqueductal gray matter, and medulla [3]. The third case is a MELAS-like encephalopathy case, whose MRI showed bilateral cortical and subcortical high-intensity lesions, with red nuclei, mesencephalic tectum, vermis and cerebellar flocculus also involved [9]. Thus, it may be characteristic of the m.10158 T > C mutation that white matter lesions are observed in addition to cortex lesions.

In conclusion, to our knowledge, this is the first report to show a patient with an MT-ND3 m.10158T>C mutation exhibiting an age-dependent transition from LS to MELAS, which suggests an age-dependent role of complex I in the developing brain.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.braindev.2019.05.006>.

References

- [1] Crimi M, Papadimitriou A, Galbiati S, Palamidou P, Fortunato F, Bordonni A, et al. A new mitochondrial DNA mutation in ND3 gene causing severe Leigh syndrome with early lethality. *Pediatr Res* 2004;55:842–6.
- [2] Lebon S, Chol M, Benit P, Mugnier C, Chretien D, Giurgea I, et al. Recurrent de novo mitochondrial DNA mutations in respiratory chain deficiency. *J Med Genet* 2003;40:896–9.
- [3] McFarland R, Kirby DM, Fowler KJ, Ohtake A, Ryan MT, Amor DJ, et al. De novo mutations in the mitochondrial ND3 gene as a cause of infantile mitochondrial encephalopathy and complex I deficiency. *Ann Neurol* 2004;55:58–64.
- [4] Kouga T, Takagi M, Miyauchi A, Shimbo H, Iai M, Yamashita S, et al. Japanese Leigh syndrome case treated with EPI-743. *Brain Dev* 2018;40:145–9.
- [5] Fang F, Liu Z, Fang H, Wu J, Shen D, Sun S, et al. The clinical and genetic characteristics in children with mitochondrial disease in China. *Sci China Life Sci* 2017;60:746–57.
- [6] Vodopivec I, Cho TA, Rizzo 3rd JF, Frosch MP, Sims KB. Mitochondrial encephalopathy and optic neuropathy due to m.10158 MT-ND3 complex I mutation presenting in an adult patient: case report and review of the literature. *Neurologist* 2016;21:61–5.
- [7] Grosso S, Carluccio MA, Cardaioli E, Cerase A, Maladrini A, Romano C, et al. Complex I deficiency related to T10158C mutation ND3 gene: a further definition of the clinical spectrum. *Brain Dev* 2017;39:261–5.
- [8] Werner KG, Morel CF, Kirton A, Benseler SM, Shoffner JM, Addis JB, et al. Rolandic mitochondrial encephalomyelopathy and MT-ND3 mutations. *Pediatr Neurol* 2009;41:27–33.

- [9] Mukai M, Nagata E, Mizuma A, Yamano M, Sugaya K, Nishino I, et al. Adult-onset mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke (MELAS)-like encephalopathy diagnosed based on the complete sequencing of mitochondrial DNA extracted from biopsied muscle without any myopathic changes. *Intern Med* 2017;56:95–9.
- [10] Lebre AS, Rio M, Faivre d’Arcier L, Vernerey D, Landrieu P, Slama A, et al. A common pattern of brain MRI imaging in mitochondrial diseases with complex I deficiency. *J Med Genet* 2011;48:16–23.