CASE REPORT

MELAS syndrome associated with a new mitochondrial tRNA-Val gene mutation (m.1616A>G)

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SUMMARY

We describe the case of a 40-year-old-man with mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes (MELAS) syndrome, with cardiomyopathy and severe heart failure. He had a mitochondrial transfer RNA (tRNA) mutation (m.1616A>G) of the (tRNA-Val) gene, and it was not found in MELAS syndrome ever before. The presence of this newly observed tRNA-Val mutation (m.1616A>G) may induce multiple respiratory chain enzyme deficiencies and contribute to MELAS syndrome symptoms that are associated with mitochondrial DNA (mtDNA) mutations. We report that the pathognomonic symptom in MELAS syndrome caused by this newly observed mtDNA mutation may be rapid progression of cardiomyopathy and severe heart failure.

syndrome is a characteristic mitochondrial disorder. Most patients with MELAS syndrome have the leucine transfer RNA (tRNA) point mutation (m.3243A>G) in their mitochondrial DNA (mtDNA),¹ but other mtDNA point mutations are also associated with MELAS. We herein report a Japanese man with MELAS syndrome, with cardiomyopathy, severe heart failure and a mitochondrial tRNA mutation (m.1616A>G) of the (tRNA-Val) gene.

CASE PRESENTATION

Our patient was a 40-year-old-man with delayed mental development, epilepsy, bilateral cataracts and deafness first recognised when he was in elementary school. The patient hardly consulted a hospital afterwards. The patient had headache with vomiting and seizure occasionally. The patient had a brother with an intellectual disability. At 40 years of age, the patient was admitted to our hospital because he experienced dyspnoea on

BACKGROUND

Mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes (MELAS)

Figure 1 A muscle biopsy. (1) H&E; (2) SDH activity; (3) COX; (4) modified Gomori trichrome. A muscle biopsy revealed mild variation in fibre size, as well as SDH-reactive vessels and decreased COX activity in many fibres and ragged-red fibre. COX, cytochrome-c oxidase; SDH, succinate dehydrogenase.

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Mitochondrial respiratory chain activity / complex II activity			Mitochondrial respiratory chain activity / CS activity	
	This case	Control (n=5) Range (mean±SD)	This case	Control (n=5) Range (mean±SD)
I	0.14 (18%)	0.26 - 1.20 (0.76 ± 0.39)	0.24 (13%)	0.58 - 4.70 (1.90 ± 1.60)
II	-	-	1.80 (75%)	1.20 - 3.90 (2.40 ± 1.10)
III	0.54 (59%)	0.72 - 1.80 (0.91 ± 0.41)	1.00 (43%)	1.90 - 3.70 (2.30 ± 0.80)
IV	0.19 (22%)	0.42 - 1.30 (0.88 ± 0.36)	0.30 (16%)	1.20 - 3.20 (1.90 ± 0.80)
V	2.00 (200%)	0.69 - 1.20 (1.00 ± 0.19)	3.50 (117%)	2.70 - 3.50 (3.00 ± 0.33)

Figure 2 Genetic testing and a biochemical assay. Genetic testing revealed a homoplasmic point mutation (m.1616A>G) in mitochondrial transfer RNA-Val. A biochemical assay using muscle homogenates demonstrated reduced activity in complexes I, III and IV of the mitochondrial respiratory chain.

effort and could therefore not walk unassisted. The neck vein distention, rales, tachycardia and bilateral ankle oedema were noted. Neurological examination revealed mental retardation, muscle weakness (manual muscle testing 3–4 of the extremities), muscle hypotonia and atrophy of the extremities, diminished tendon reflexes and astasia.

INVESTIGATIONS

A chest X-ray revealed the heart enlargement (cardiothoracic ratio: 69%) and pleural effusions. Delta waves were observed on his ECG, and both diminished wall motion of the left ventricle and depressed left ventricular ejection fraction (21%) were observed by ultrasonic cardiography, without ischaemic change. Serological tests indicated elevated serum creatine kinase levels (hyperCKemia) (3891 IU/L; reference

range, 62–287 IU/L), elevated blood lactate (18.6 mg/dL; reference range, 3.0–17.0 mg/dL) and pyruvate (1.14 mg/dL; reference range, 0.30–0.94 mg/dL). Endocrinological examination showed elevated brain natriuretic peptide (1639 pg/mL; reference range, 0.0–18.4 pg/mL). Cerebrospinal fluid testing revealed elevated lactate (34.8 mg/dL; reference range, 3.0–17.0 mg/dL) and pyruvate (1.29 mg/dL; reference range, 0.30–0.94 mg/dL). Brain CT indicated whole brain atrophy. Chest CT showed the heart enlargement and pleural effusions. CT of the whole body indicated muscle atrophy and fatty degeneration of the body trunk and extremities. A muscle biopsy revealed mild variation in fibre size, as well as succinate dehydrogenase-reactive vessels, decreased cytochrome-c oxidase activity in many fibres and ragged-red fibre (figure 1). Genetic testing revealed a homoplasmic point mutation (m.1616A>G)

in mitochondrial tRNA-Val. A biochemical assay using muscle homogenates demonstrated reduced activity in complexes I, III and IV of the mitochondrial respiratory chain (figure 2).

DIFFERENTIAL DIAGNOSIS

The clinical symptoms and the chest X-ray suggested severe heart failure with New York Heart Association classification IV.^{2,3} The patient was diagnosed with MELAS syndrome, based on the diagnostic criteria for MELAS,⁴ two items of category A (clinical findings of stroke-like episodes; headache with vomiting and seizure) and two items of category B (evidence of mitochondrial dysfunction, high lactate levels in plasma and cerebral spinal fluid or deficiency of mitochondrial-related enzyme activities and mitochondrial abnormalities in muscle biopsy).

OUTCOME AND FOLLOW-UP

During the period of intensive medical care, the patient had severe progressive heart failure and died on the 26th day after hospital admission.

DISCUSSION

We report the case of a 40-year-old man with MELAS syndrome. Although many mutations have been reported to be associated with MELAS syndrome, in the present case, genetic testing revealed a homoplasmic point mutation (m.1616A>G) in mitochondrial tRNA-Val. The presence of this newly observed tRNA-Val mutation (m.1616A>G) may induce multiple respiratory chain enzyme deficiencies and contribute to MELAS syndrome symptoms that are associated with mtDNA mutations. The pathognomonic symptom in our patient was severe heart failure.

MELAS syndrome includes mitochondrial disorders that typically involve many organs and systems, including encephalopathy, myopathy, deafness, small stature, diabetes mellitus and exercise intolerance.⁵ There are some previous reports of patients who presented with severe heart failure and were subsequently diagnosed with MELAS syndrome.^{6,7} These cases indicate that there may be a phenotype of MELAS syndrome that includes multiple organ failure, particularly cardiomyopathy and severe heart failure. Consequently, the pathognomonic symptoms of MELAS syndrome caused by this newly observed mtDNA mutation might be conditions such as cardiomyopathy and severe heart failure, delayed mental development, epilepsy, bilateral cataracts and deafness.

Current genetic data indicate a complex aetiology of complex I, III and IV deficiencies associated with progressive severe heart failure. Although cardiomyopathy that is associated with mitochondrial syndrome is not common, cardiomyopathy due to the mutation of mitochondrial DNA should be considered as possible causes of heart failure.⁸ Patients with respiratory chain disease should be carefully and repeatedly assessed during the process of diagnosing and managing cardiac involvement.⁹

We herein described a case of a Japanese man with MELAS syndrome, with associated cardiomyopathy, severe heart failure and a mitochondrial tRNA mutation (m.1616A>G) of the (tRNA-Val) gene. We suggest that MELAS syndrome caused by this newly observed mtDNA mutation should be considered as a differential diagnosis in patients with rapid progression of cardiomyopathy and other disturbances such as delayed mental development, epilepsy, bilateral cataracts and deafness.

Learning points

- We report the case of a 40-year-old man with mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes (MELAS) syndrome.
- Although many mutations have been reported to be associated with MELAS syndrome, in the present case, genetic testing revealed a homoplasmic point mutation (m.1616A>G) in mitochondrial transfer RNA (tRNA)-Val.
- The presence of this newly observed tRNA-Val mutation (m.1616A>G) may induce multiple respiratory chain enzyme deficiencies, and contribute to MELAS syndrome symptoms that are associated with mitochondrial DNA mutations.
- The pathognomonic symptom in our patient was severe heart failure.

Contributors YT: acquisition of data and analysis. YT: corresponding author. KS: study supervision.

Competing interests None declared.

Patient consent Obtained from guardian.

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