Case Report

# MELAS: A Case Report

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## Abstract

**Introduction: Mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes (MELAS) is a rare, neurodegenerative and fatal disease caused by mutations in the mitochondrial DNA. Multiple systems of the body, including the oral cavity, can be affected by this disease. An electronic search of Medline spanning the years 1985 to 2003 was carried out using the key words "MELAS, Dentistry." It yielded no literature on the dental aspects of MELAS. Clinical Picture: This report documents the case of a 6-year-old Chinese boy diagnosed with MELAS and highlights problems encountered in the multidisciplinary management of MELAS patients, including its dental management. Treatment and Outcome: Dental management was successfully performed under general anaesthesia with close medical supervision by paediatrician and anaesthetist. Conclusions: There is no known treatment of the underlying disease and the clinical course is usually unpredictable. Preventive dental care is important in this group of patients as concurrent medical conditions can complicate dental care.**

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**Key words: General anaesthesia, MELAS, Mitochondrial DNA mutations, Oral cavity, Preventive dentistry**

## Case Report

A 6-year-old Chinese boy presented at the Oral and Maxillofacial Surgery clinic with gingival bleeding due to poor oral hygiene, odontogenic pain due to multiple dental caries, phenytoin-induced gingival hyperplasia and severely worn-down and eroded dentition. He is under regular follow-up by the Paediatrics Department of the National University Hospital and was diagnosed to have mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes (MELAS). The patient presented with developmental delay, hypotonia of all 4 limbs, gross motor delay, epilepsy, elevated serum lactate levels and poor head control. His developmental milestones corresponded to that of an 8- to 9-month-old child.

Past medical history revealed maternal gestational diabetes and 2 episodes of threatened abortion during the first trimester. Emergency caesarean had to be performed due to fetal distress. His birth weight of 3.6 kg was good, but he had muscular weakness and has been "floppy and passive" since birth. He was able to feed well till the age of 8 months. Subsequently, however, he would vomit after every feed and had been placed on nasogastric feeding for the last 2 years.

The diagnosis of MELAS was made following muscle biopsy, magnetic resonance imaging (MRI) of the brain and DNA analysis studies. The muscle biopsy showed polygonal-shaped skeletal muscle with occasional internal nuclei. Many of these showed accumulation of basophilic granules in the sub-sarcolemmal region and sarcoplasm. These granules were stained red with Gomori Trichrome (characteristic ragged-red fibres of MELAS). These were also stained with NADH (oxidative enzymes) and fat. Electron microscopy showed many large aggregates of mitochondria. These varied considerably in size and showed abnormal cristae formation (mitochondrial myopathy).

Mitochondrial DNA analysis (mtDNA) was positive for the MELAS A3243G. Point mutation was noted to be at a level of 75% to 85% heteroplasmy. A pH probe study (EsopHogram Reflux Analysis using Digitrapper pH400, Medtronic, Denmark) was performed to exclude

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gastrointestinal reflux. A moderate reflux of 8% was noted. In this study, acid reflux was defined as a drop in pH below 4.0. The study duration was 19 hours and 46 minutes, during which time the patient experienced 119 acid refluxes, of which 2 were prolonged (more than 5 minutes each).

The clinical course of the child's development was complicated by numerous episodes of aspiration pneumonia secondary to gastroesophageal reflux. He also developed epileptic seizures, which were treated with phenytoin. He had frequent admissions to the hospital for episodes of vomiting and poor feeding which were associated with lactic acidosis induced by the stress of infection.

Examination under anaesthesia was performed due to poor patient compliance. Propofol and alfentanil were used for anaesthesia. Inhalational agents and muscular paralytic agents were avoided. Full-mouth scaling, multiple extractions and dental restorations with glass ionomer cement were performed. The patient was haemodynamically stable throughout the operation and was extubated immediately. He was then transferred to the paediatric intensive care unit for monitoring, with specific instructions given by the anaesthetist to watch out for development of malignant hyperthermia. There was 1 episode of post-operative vomiting but on the whole, he was otherwise quite comfortable, his vital signs were stable and he was subsequently discharged.

**Discussion**

MELAS patients may present either as sporadic cases or as members of maternal pedigrees. It is one of the classic mitochondrial encephalopathies and has variable clinical presentation and multisystem involvement, including the central nervous system, skeletal muscle, eye, cardiac muscle and gastrointestinal system. It has high morbidity and mortality rates and can affect people at different times of life, but the majority of patients show symptoms before the age of 20.[1,2] In the adult population in the United States, the frequency of MELAS was reported at about 16.3 per 100,000.

MELAS is considered to be a rare, neurodegenerative disorder caused by mutations in the genetic material (DNA) located in a specialised cell subunit called the mitochondria. The majority of DNA in cells are located in the chromosomes within the cell nucleus. Another important cell structure that carries DNA is the mitochondria. DNA within the mitochondria is used to manufacture proteins that help in the mitochondria's energy-producing function.

About 80% of MELAS syndrome are caused by the A-to-G substitution of $tRNA^{leu}$ at bp (base pair) 3243 of the mitochondrial DNA (i.e. A323G mutation). Mitochondrial DNA is responsible for encoding portions of respiratory chain enzymes, and the mutation causes a defect in the translation of the respiratory chain enzymes, which in turn reduces the capacity of oxidative phosphorylation. Hence, cells with higher metabolic activity are severely and adversely affected because of the reduction in aerobic respiration.[3]

Patients with MELAS develop brain dysfunction, ventricular dilatation, cortical atrophy, basal ganglia calcification and infarcts (encephalopathy). These infarcts have been hypothesised to be non-vascular and caused by transient oxidative phosphorylation dysfunction within the brain parenchyma and are exhibited on computerised tomography scan or MRI. Positron emission tomography studies may reveal a reduced cerebral metabolic rate for oxygen. Single photon emission computed tomography studies can ascertain strokes in individuals with MELAS. These infarcts lead to seizures, headaches, mental deterioration, and psychiatric abnormalities, such as dementia and schizophrenia. Axonal and demyelinating mixed sensorimotor polyneuropathy has been described in MELAS and white matter changes have been reported.

Muscle disease (myopathy) with a build-up of lactic acid in the blood (lactic acidosis) may be very debilitating. Hypertrophic cardiomyopathy and conduction abnormalities, such as arteriovenous blocks or Wolff-Parkinson-White syndrome, may develop.

The features of MELAS are variable and include weakness, easy fatigability, exercise intolerance, developmental delay, learning disabilities, attention deficit disorders, failure to thrive, focal or generalised seizures (tonic-clonic or myoclonic), visual abnormalities, hemiplegia, migraine or migraine-like headaches, ophthalmoplegia, blindness due to optic atrophy, pigmentary retinopathy (poor night vision), sensorineural hearing loss, diabetes mellitus, palpitations, shortness of breath, gastrointestinal manifestations, peripheral neuropathy, oliguria associated with nephritic syndrome and renal failure due to focal segmental glomerulosclerosis.[4-7]

Muscle biopsies in MELAS patients show characteristic ragged-red (Gomori trichrome stain) due to proliferation of abnormal mitochondria. Brain biopsies show stroke-like changes.

Enhanced sensitivity to neuromuscular blockade or intravenous anaesthetic agents and susceptibility to malignant hyperthermia have been reported, all of which complicate the management of MELAS patients under general anaesthesia. Lactic acidosis in MELAS is usually worsened by stress. Increase of metabolism should be avoided by adequate surgical anaesthesia. Prolonged nervous system depression and decreased ventilatory response to hypoxaemia and hypercarbia are noted. Dantrolene is used in cases where patients develop malignant hyperthermia.[8-13]

## Conclusion

Multidisciplinary management of patients with MELAS is required and would involve a geneticist, neurologist, cardiologist, nephrologist, ophthalmologist and endocrinologist. The dental surgeon also plays an important role as the patient may be unable to care for his dentition and may present with dental caries, periodontal disease, tooth wear due to erosion from recurrent bouts of vomiting resulting in tooth sensitivity, pulpal pathology and loss in occlusal vertical dimension. A thorough search of the literature failed to reveal any reports of oral manifestations and their management in MELAS cases. To the best of our knowledge, this is the first report in the English literature of oral manifestations and dental management of a patient with MELAS syndrome.

There is no known treatment of the underlying disease, which is progressive and fatal. Patients are managed according to what area is affected at a particular time. Metabolic therapies have been used to increase the production of ATP. Coenzyme Q10 (CoQ10), ascorbate, riboflavin, and vitamins K-1 and K-3 have proven quite successful. Both the patient and family members should receive genetic counselling, and the family should be educated about further deterioration and possible complications. The clinical course is usually unpredictable, with fluctuation and gradual deterioration, leading to coma or death, usually from respiratory failure. From the dental point of view, early institution of preventive dental care is essential. This would include regular visits to the dentist, oral hygiene instructions, prophylaxis, dietary advice and fluoride treatment.

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