

TWO SIBLINGS WITH DIFFERENT PRESENTATION OF MELAS

QIN JIAN LOW¹, SITI BAIZURA BINTI ABDUL KADZIR², SENG WEE CHEO³

Abstract

Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) is a rare disease. It is a maternally inherited multisystem disorder caused by mutations of the mitochondrial DNA. MELAS usually occur during childhood period after a normal early development. Commonly, the patients will have a relapsing and remitting course of illness with stroke like episodes and seizures. It will subsequently lead to progressive neurological dysfunction and memory problems. We would like to present two siblings who presented to us with different age of onset and presentation of their illness.

Keywords : MELAS, Stroke.

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Introduction

Mitochondrial diseases present with a wide range of clinical presentation. The nervous system is commonly involved. Mitochondria are responsible for oxidative phosphorylation which produces energy in the form of adenosine triphosphate (ATP)¹. Tissues with high energy requirements are preferentially affected². Typically, patient may present with focal or generalized seizures, recurrent migraine, vomiting and muscle weakness.

Case Presentation

Case 1

A 19-year-old diploma student with no comorbid presented with new onset worsening headache for two weeks' duration. It is associated with one-week history altered behavior and two episodes of vomiting. There was no fever, aura or limb weakness. He is the eldest among three siblings. His younger brother passed away at the age of eight years old. On physical examination, he has a short stature with slow memory recall but no hearing impairment. Contrast enhanced computed tomography of the brain showed recent left occipital and temporal infarcts with old right occipital and temporal infarcts. Magnetic resonance imaging of the brain showed recent infarct at his right parietotemporooccipital region. After 2 weeks of his initial

presentation, he developed generalized tonic clonic seizures and was started on anti-epileptic agents (Levetiracetam). His genetic study and muscle biopsy confirmed the diagnosis of MELAS. After 6 months of treatment, he presented with severe headache and blurring of vision. Repeated CT brain showed multifocal infarction of varying ages. MRI Brain showed T2W1/FLAIR hypertintensity and T1W1 hypointensity involving the grey white matter at the right parietotemporooccipital region, which does not show significant enhancement in post contrast study. There was associated diffusion restriction at these regions on ADC/DWI sequences in keeping with area of infarct. In view of the new stroke episodes, he was given adequate hydration with intravenous arginine 10 g/m² within 6 hours from stroke onset. Medications on discharged included levetiracetam 500 mg twice a day, Riboflavin 100 mg twice a day, coenzyme Q10 200 mg twice a day, oral arginine 1.5g four times a day.

Case 2

An 8-year-old boy was admitted for persistent vomiting for one week duration. There was no diarrhea or fever. He was treated as acute gastroenteritis. His symptoms did not improve with hydration and anti-emetic therapy. He was further worked up for sub acute intestinal obstruction, intussusception which were all negative. During the admission, the child reported

1. Department of Internal Medicine, Hospital Sultanah Nora Ismail, Jalan Korma, Taman Soga, 83000, Batu Pahat, Johor, Malaysia.
2. Department of Radiology, Hospital Sultanah Nora Ismail, Jalan Korma, Taman Soga, 83000, Batu Pahat, Johor, Malaysia.
3. Department of Internal Medicine, Hospital Lahad Datu, Peti Bersurat 60065, 91110, Lahad Datu, Sabah, Malaysia.

Address of Correspondence: Dr. Qin Jian Low, Department of Internal Medicine, Hospital Sultanah Nora Ismail, Jalan Korma, Taman Soga, 83000, Batu Pahat, Johor, Malaysia.

worsening headache and vomiting. He was lethargic but not dehydrated. There was reduced muscle tone with bilateral upper and lower limbs power MRC grade 4. A plain brain computed tomography (CT) showed left cerebrum ill defined, non enhancing hypodensities involving the grey and white matters associated with sulci effacement at the left occipitotemporoparietal regions and the left external capsule. There is post contrast gyriform enhancements in this region. This findings may represent infarction. Further workup for mitochondrial disorder was pursued.

MRI Brain shows multifocal acute infarction with the largest area at the left parieto-temporo-occipital region and smaller infarcted areas as mentioned above. No definite enhancement in post contrast study. The findings of non-territorial multifocal infarcts may be due to MELAS.

The child deteriorated requiring mechanical ventilation and inotropic support. He passed away before the definitive result of MELAS came back. His genetic test came back positive for MELAS.

Table-I

Investigations for both patients in case 1 and case 2.

Tests	Case 1	Case 2	Normal Range
CSF Opening pressure	19 cmH ₂ O	12 cmH ₂ O	
CSF Appearance	Clear, colorless.	Clear, colorless.	
CSF Protein	0.3 g/L	0.328	0.15-0.45 g/L
CSF Glucose Ratio	$\frac{3.5 \text{ mmol/L}}{7 \text{ mmol/L}}$ =	$\frac{4.5 \text{ mmol/L}}{7 \text{ mmol/L}}$ =	CSF glucose 3.33-4.44 mmol/L
CSF Cell Count	< 5 cells/mm ³ 0% neutrophils, 0% lymphocytes.	< 5 cells/mm ³ 0% neutrophils, 0% lymphocytes.	
CSF Latex agglutination for bacterial antigen	Negative	Negative	
CSF Gram Stain	Negative	Negative	
CSF Indian ink, TB PCR, AFB	Negative	Negative	
CSF Viral Study	Negative	Negative	
CSF IEM & Amino Acids	Negative	Negative	
CSF Lactate	17.53 mmol/L	15.53 mmol/L	
Plasma Lactate	5.53 mmol/L	15.53 mmol/L	0.5-2 mmol/L
Thyroid function test	Normal	Normal	
Blood culture	Negative	Negative	
Erythrocyte sedimentation rate	11 mm/hour	15 mm/hour	
C reactive protein	< 5 mg/L	< 5 mg/L	
Deltoid muscle biopsy	Ragged red fibers seen consistent with mitochondrial myopathy.	Not done	
MELAS Mutation analysis report	m.3243A>G mutation of tRNA is detected at approximately 50% of heteroplasmy in blood derived DNA sample.	m.3243A>G mutation of tRNA is detected at approximately 50% of heteroplasmy in blood derived DNA sample.	
CSF IEM and Amino acids	Not done	Negative	
CSF Amino acids (Ion exchange HPLC)	Not done	Normal CSF to plasma glycine ratio. Mild elevation of alanine suggest lactic acidosis. Non significant changes of one or more acylcarnitines/amino acids.	

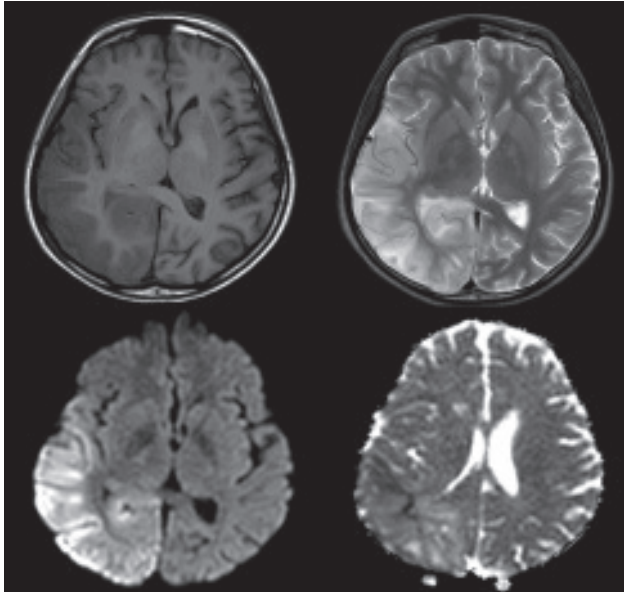


Figure 1 (Case 1): Abnormal T1WI hypointense T2WI hyperintense signal at right temporoparietooccipital region associated with effacement of the overlying sulci (a & b). Some areas shows restricted diffusion on DWI/ADC (c & d).

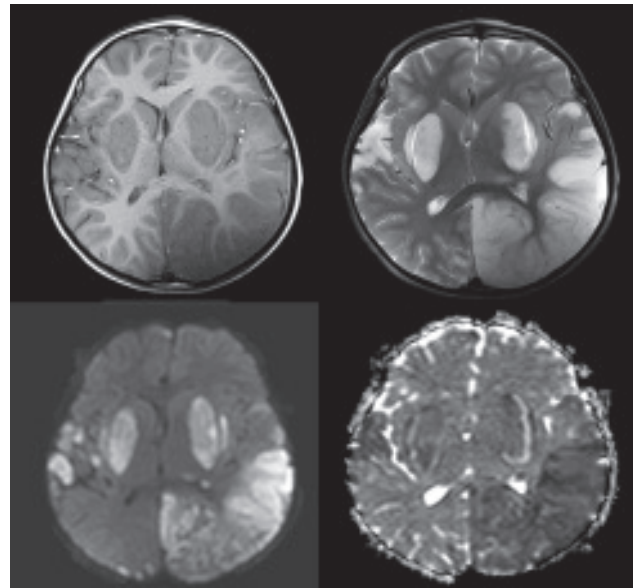


Figure 2 (Case 2) : Multiple patchy and territorial abnormal signal of the grey matter, subcortical white matter and bilateral basal ganglia associated with effacement of the overlying sulci and swollen of the cortex (a & b). It demonstrates restricted diffusion on DWI/ADC (c & d).

Discussion

MELAS stands for mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke like episodes. It was first reported and described by Pavlakis et al in year 1984³. MELAS can present with a wide range of different clinical phenotypes. It commonly causes a metabolic stroke⁴. The brain lesions as seen in case 2 does not follow any vascular territories. It can lead to hemiparesis, hemianopia or cortical blindness⁵. The stroke-like episodes are believed to be a result of both mitochondrial cytopathy and angiopathy⁶. Mitochondrial cytopathy is due to defective mitochondrial energy production in brain tissue⁶. Mitochondrial angiopathy is due to abnormal mitochondria in endothelial and smooth muscle cells which causes impairment of vasodilatation⁷. MELAS have a heteroplasmic A-to-G point mutation in the dihydrouridine loop of the transfer RNA (tRNA) gene at base pair (bp) 3243 (i.e. 3243 A G Mutation)⁸. There are a multitude of transfer RNA mutations that are responsible of MELAS. 80 percent of such cases are related to the m.3243A>G mutation while 10 percent is due to m.3271T>C transfer RNA mutation⁹. The heteroplasmy in MELAS varies from patient to patient, reflecting segregation in the ovum¹⁰.

Management of mitochondrial diseases is mainly supportive depending on the degree of impairment

and extent of neurologic involvement¹¹. A multidisciplinary care involving the pulmonologist, neurologist, genetic expert, ophthalmologist, cardiologist and audiology services are often required. Often, the family will require genetic counselling to understand the medical, psychological and familial implications of the disease¹². Patients in reproductive age should be offered genetic counselling to help with planning in having children¹³.

There is no proven and effective treatment for MELAS. The pharmacologic strategies are based on respiratory chain cofactors, antioxidants and agents that correct secondary biochemical deficits¹⁴. Succinate, riboflavin, thiamine and coenzyme Q10 are cofactors in the electron transport chain enzymes¹⁵. Hence, supplementation is believed to improve the activity of these enzymes when they are inadequate¹⁶. Coenzyme Q10 is both an antioxidant and an integral part of the mitochondrial respiratory chain. Both L-arginine and citruline are precursors to nitric oxide which leads to vasodilatation. Arginine supplementation is given as an infusion during an acute phase of stroke-like episodes and as an oral daily therapy¹⁶.

Conclusion

Mitochondrial diseases can manifest with a wide range of clinical phenotypes which presents a significant diagnostic dilemma and challenge to the clinician. The mainstay for patients with mitochondrial disease remains supportive.

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