Case Report

MELAS syndrome: a case report

Haque MR[a], Abdullah AM[b], Azad AI[b], Kundu NC[3]

ABSTRACT

*Mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS) is a group of maternally inherited disorders caused by mutations or deletions in mitochondrial genes characterized by metabolic stroke, seizures, cognitive decline, lactic acidosis, ragged-red fibers, headache, vomiting and in 80% of cases it occurs due to the mtDNA variant m.3243A>G. Here, we present case history of a 17-year-old boy who was diagnosed with MELAS syndrome, whose brain magnetic resonance spectroscopy showed decreased N-acetylaspartate and choline peak and markedly increased lipid and lactate peak. Genetic study revealed positive mutation variant in subunit-5 of the respiratory chain (*MT-ND5*) which is reported in MELAS.*

Key words: *MELAS, mtDNA, convulsion, stroke-like episodes, blindness, MT-ND5 mutation, lactic acidosis.*

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INTRODUCTION

Mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS) is a rare, progressive mitochondrial disorder caused by maternally inherited mutations in mitochondrial DNA (mtDNA) characterized by diverse clinical manifestations that develop gradually, including strokes, headaches, seizures, cognitive decline, hearing loss, visual impairment, muscle weakness etc. MELAS is diagnosed according to the Japanese[1] or Hirano criteria.[2] The TL1m.3243A>G mutation in their mtDNA occurs in 80% of MELAS patients, with an incidence of <"8 to 236/1,00,000 population.[3,4] Even if genetic testing comes out to be inconclusive, current guidelines do not encourage invasive testing, such as skeletal muscle biopsy.[5] Rarely, random mutations without a family history may cause MELAS. Although the exact cause of the stroke-like episodes in MELAS is still unknown, recent research has suggested that endothelial cell mitochondrial failure may be the cause of small vessel angiopathy.[6] This disorder is among the most difficult to diagnose because it is uncommon and has a complicated clinical appearance. It is particularly challenging to distinguish between MELAS and an ischemic stroke.[7] Despite their widespread prevalence, they are still frequently under diagnosed particularly in low- and middle-income nations. This case is a classic example of the progression of the disease, with clinical relapses and fluctuant lesions similar to ischemia on neuroimaging.

CASE REPORT

A 17-year-old boy presented with repeated attacks of convulsion. Convulsion first started from 2019 which involved all limbs simultaneously with tongue biting and urinary incontinence but without any premonitory symptoms, eye rolling or head turning towards any side. There was no history of headache or fever during or preceding the illness. There was no family history of seizure attack, no parental consanguinity. Mother and grandmother from the mother's side were clinically unaffected (Figure 1).

Author information

a. Md. Rezwanul Haque, Specialist, Neurology, Bangladesh Specialized Hospital PLC, 21 Shyamoli, Mirpur Road, Dhaka-1207, Bangladesh.

b. Asif Mohammad Abdullah, Ahad-Ul-Islam Ahad, Senior Medical Officer, Neurology, Bangladesh Specialized Hospital PLC, 21 Shyamoli, Mirpur Road, Dhaka-1207, Bangladesh.

c. Narayan Chandra Kundu, Professor and Head, Department of Neurology, Shaheed Suhrawardy Medical College & Hospital, Dhaka, Bangladesh and Consultant, Neurology, Bangladesh Specialized Hospital PLC, 21 Shyamoli, Mirpur Road, Dhaka-1207, Bangladesh.

Address of correspondence: Md. Rezwanul Haque, Specialist, Neurology, Bangladesh Specialized Hospital PLC, 21 Shyamoli, Mirpur Road, Dhaka-1207, Bangladesh. Email: rezwan0103@gmail.com

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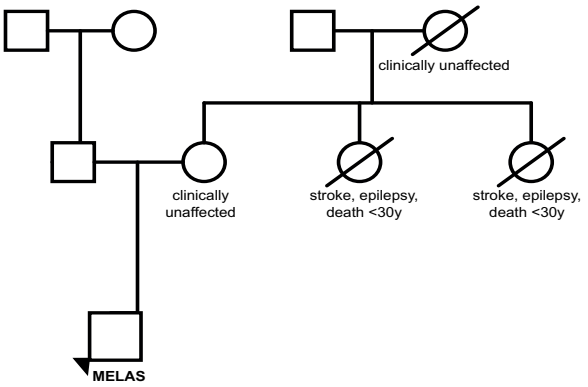


Figure 1. Family tree of the index

Routine biochemistry, magnetic resonance imaging (MRI) of brain with epilepsy protocol and electroencephalography (EEG) were non-informative. He was prescribed sodium valproate 300 mg twice daily. With anti-seizure medication patient was free of convulsion for almost 1 year. After 1 year, he again developed convulsion of similar nature and was treated conservatively. As his seizure frequency was increasing despite taking regular dose of sodium valproate, dose was increased from 300 mg twice daily to 500 mg twice daily. Thereafter, he had convulsions 3-5 episodes per year until few months back. Each of this convulsions was preceded by feeling of uneasiness, was of short duration (1-2 min), started with head turning, right-sided facial grimacing and eye deviation with gradual involvement of all limbs, tongue biting, salivation followed by confusion. Serum valproic acid level was done which was in the therapeutic range.

In 2022, he developed right sided weakness and was initially diagnosed as a case of ischemic stroke. Evaluation of early age onset of stroke revealed protein C and protein S deficiency for which anti-coagulant was started. His serum lactate level was persistently high in several subsequent measurements which did not come down to reference (2.1 mmol/L) value (17.4 mmol/L in 2022, 11.2 mmol/L in 2023, 8.7 mmmol/L in 2024). Despite taking anti-epileptic and anti-coagulant, patient developed bilateral (right>left) painless diminished vision, headache and vomiting in 2024. There was no history of fever or any recent vaccination. Again his serum lactate level was higher in value (4.1 mmol/L). MRI of brain (DWI sequence) showed fairly large recent hypointense shadow in left occipital lobe and small recent hypodense shadow in right occipital and frontal lobe in 4D view (Figure 2). Magnetic resonance spectroscopy of brain showed decreased N-acetylaspartate and choline and markedly increased lipid and lactate peaks in area of hypodense shadow (Figure 3).

Visual disturbance gradually improved to near normal within one month. So, after adequate counselling, we went for genetic testing which showed positive mutation variant in subunit-5 of the respiratory chain (*MT-ND5*) which is reported in MELAS (Figure 4).

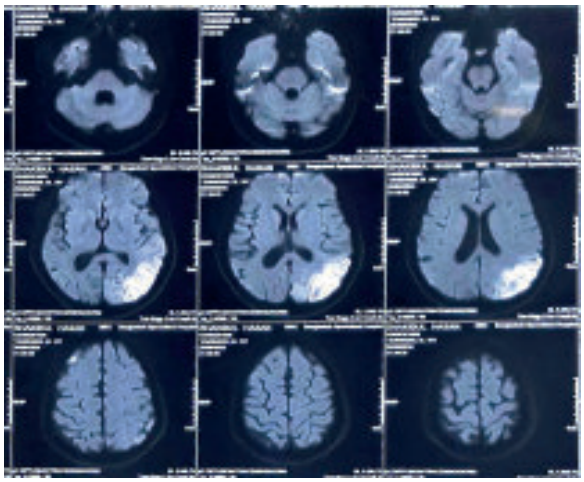


Figure 2. Magnetic resonance imaging of brain (DWI sequence) showing hypointense shadow in left occipital lobe

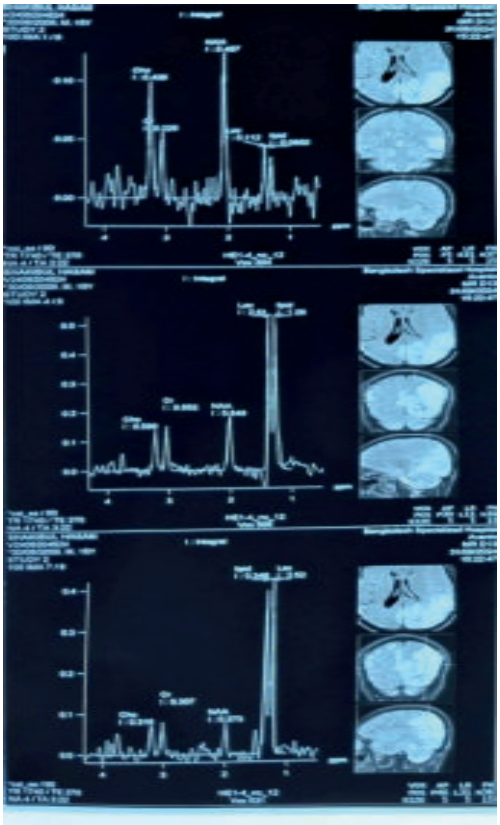
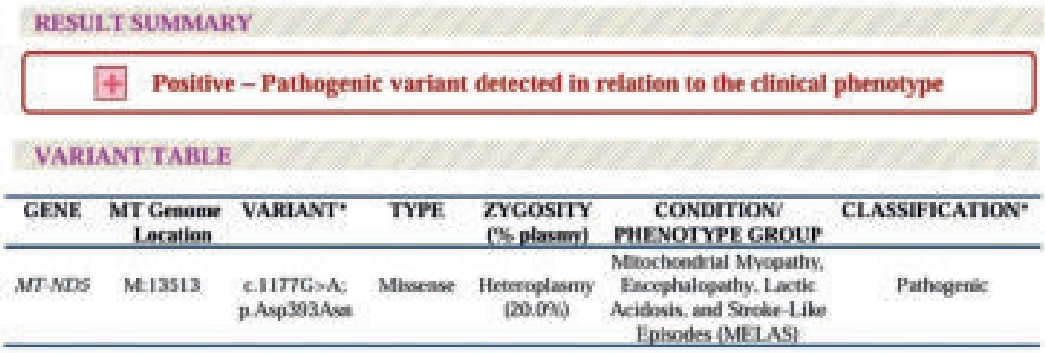


Figure 3. Magnetic resonance spectroscopy of brain showing markedly increased lipid and lactate peaks in area of hypodense shadow with decreased N-acetylaspartate and choline peak



RESULT SUMMARY

Positive – Pathogenic variant detected in relation to the clinical phenotype

VARIANT TABLE

GENE	MT Genome Location	VARIANT*	TYPE	ZYGOSITY (% plasmy)	CONDITION/ PHENOTYPE GROUP	CLASSIFICATION*
MT-ND5	M:13513	c.1177G>A; p.Asp393Asn	Missense	Heteroplasmy (20.0%)	Mitochondrial Myopathy, Encephalopathy, Lactic Acidosis, and Stroke-Like Episodes (MELAS)	Pathogenic

Figure 4. Genetic study (Next generation sequencing test- whole mitochondrial genome sequencing) showing positive mutation variant in subunit-5 of the respiratory chain (*MT-ND5*)

So, MELAS was diagnosed and sodium valproate was substituted by levetiracetam. Coenzyme Q10, L-arginine, rivoflavin, thiamine, L-carnitine and lipoic acid were prescribed. There was no episode of convulsion after the start of above mentioned medications till date.

DISCUSSION

MELAS is one of the most common maternally inherited mitochondrial disorders. This condition is mainly related to a mutation involving an adenine-to-guanine transition at position 3243 of mtDNA (m.3243A>G) within the MTTL1 gene, which encodes tRNALeu (UUR).[8-10] The MELAS study group committee has established diagnostic criteria that incorporate clinical, laboratory and genetic testing parameters.[11]

Category A: Clinical Findings of episodes similar to stroke, headache with vomiting, seizures, hemiplegia, cortical blindness and acute focal lesion observed by brain imaging.

Category B: Evidence of mitochondrial dysfunction, such as high lactate levels in plasma and cerebral spinal fluid or deficiency of mitochondrial-related enzyme activities, mitochondrial abnormalities in muscle biopsy, definitive gene mutation related to MELAS.

Definitive diagnosis of MELAS: Two items of Category A and two items from Category B (four items or more).

Suspicion of the diagnosis of MELAS: One item from Category A with two items from Category B (at least three items).

According to above mentioned category, our patient was diagnosed as a definitive case of MELAS, presented with headache, vomiting, seizures, hemiplegia, cortical blindness, high plasma lactate levels, high lactate peak in cortical lesions and definitive MD NT5 gene mutation.

This mutation disrupts mitochondrial protein synthesis, leading to reduced energy production and multi-organ dysfunction. Energy deficiency can stimulate mitochondrial proliferation, which in blood vessels causes angiopathy, impairs blood flow and leading to complications such as stroke-like episodes. Furthermore, deficiency of nitric oxide (NO), resulting from decreased precursors such as arginine and citrulline, oxidative stress, and mitochondrial dysfunction exacerbates these issues by altering vascular function.[12]

In a study by Cox BC et al.[13] a total of 81 patients were analysed, including those with MELAS and those with positive genetic markers but not meeting the full clinical criteria. Patients were divided into MELAS, non-MELAS symptomatic and asymptomatic groups based on their symptoms and genetic findings. MELAS was also classified as 'standard-onset' if the initial stroke-like episode occurred before age 40 and as 'late-onset' otherwise. It revealed that MELAS patients had a significantly lower body mass index. Symptomatic non-MELAS patients often presented sensory neural hearing loss as an initial symptom, while MELAS patients had higher rates of seizures and a shorter survival time. Standard-onset MELAS was associated with greater neurological involvement at onset. Furthermore, patients with late-onset MELAS had higher rates of diabetes and nephropathy and were affected in more organ systems. In this patient, seizures followed by stroke like episodes and vision loss.

Conclusion

MELAS is a rare, inherited and progressive disease that affects multiple organ systems. Awareness of this condition is essential when evaluating stroke-like episodes in young patients. The timely diagnosis, genetic counseling, comprehensive evaluations and regular follow-up are crucial to improving the quality of life of the affected patients.

Authors' contribution: MRH managed the case, did literature review and drafted the manuscript. AMA and AIA helped in literature review and drafting manuscript. NCK supervised managing the case and revised the manuscript. All authors read the final manuscript and approved it.

Consent: Informed written consent was taken from patient for publication of these case report and any accompanying images.

Conflicts of interest: Nothing to declare.

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