A Young Child with Recurrent Episodes of Headaches and Vision Loss: Diagnostic Clues?

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MELAS is a mitochondrial cytopathy, with maternal inheritance and variable phenotype expression and severity depending on the degree of heteroplasmy. It presents with waxing and waning symptoms, in form of recurrent migrainous headache, transient loss of sight, hemianopsia, transient ischemic attack, or stroke-like episodes, focal seizures and even periods of altered sensorium. Here we present an 8-year-old boy presented with recurrent episodes of migrainous headache associated with vomiting sometimes and recurrent episodes of loss of vision for the past one year. As many of these episodes were precipitated by some febrile illness, so the child was suspected to have neurotuberculosis outside, because of Mantoux positivity. His mother also had similar episodes of recurrent headache and ultimately succumbed to cerebrovascular accident. Mitochondrial genome sequencing revealed heteroplasmic missense variation in the MT-TL1 gene (chrM:3243A>G).

**KEYWORDS:** Lactate peak, mitochondrial disorder, recurrent stroke, vision loss

An 8-year-old boy presented with recurrent episodes of migrainous headache associated with vomiting sometimes and recurrent episodes of loss of vision for the past one year. The episodes of vision loss used to last for a few minutes at most, but once it lasted for three days at a stretch. As many of these episodes were precipitated by some febrile illness, so the child was suspected to have neurotuberculosis outside, because of Mantoux positivity. Although the cerebrospinal fluid (CSF) examination was normal, the child was started on antitubercular therapy empirically without any benefit from an outside hospital. On further questioning, it was revealed that the mother of the child also had similar episodes of recurrent headache and ultimately succumbed to cerebrovascular accident. The exact nature of maternal illness leading to the final terminal event could not be delineated properly. Given probable maternal inheritance with suggestive symptoms, mitochondrial cytopathy was suspected. The general physical, fundoscopic, and neurological examination was normal. Arterial lactate of the child was high (10.6 mmol/L). Magnetic resonance imaging (MRI) of the brain revealed bilateral (left>right) parieto-occipital grey and white matter T1 hypointense and T2/FLAIR hyperintense signal changes with overlying gyral atrophy and lactate peak at 1.3 ppm in involved areas [Figure 1]. CSF lactate was also high (7.4 mmol/L). A possibility of myoclonic epilepsy with ragged red fibers (MERRF), Leigh's syndrome, posterior reversible encephalopathy syndrome, viral encephalitis with sequelae, moyamoya disease, and cerebral vasculitis was considered. A heteroplasmic missense variation in the MT-TL1 gene (chrM:3243A>G) was detected in mitochondrial genome sequencing. The observed MT-TL1 (A3243G) variation was found to be previously reported in patients affected with mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes syndrome (MELAS). The child showed resolution of episodes of headache and vision loss, after being started on antioxidant...
MELAS is a mitochondrial cytopathy, with maternal inheritance and variable phenotype expression and severity depending on the degree of heteroplasmy. At least 80% of cases are due to the aforementioned mitochondrial transfer RNA A3243G point mutation in the MT-TL1 gene. Typically, MELAS presents in children and young adults before 40 years with waxing and waning symptoms, in form of recurrent migrainous headache, transient loss of sight, hemianopsia, transient ischemic attack, or stroke-like episodes, focal seizures and even periods of altered sensorium. These episodes are usually precipitated by periods of metabolic stress like febrile illness, thereby mimicking symptoms of acute/subacute meningencephalitis. Over the course, the affected persons may develop sensorineural hearing loss, gait ataxia, hypertrophic cardiomyopathy, and neuropsychiatric problems.

Ischemic vascular theory, the most plausible pathophysiological mechanism, attributes the stroke-like symptoms to widespread cerebral ischemia and hypoperfusion caused by disruption of microvascular circulation and decreased production of nitric oxide by vascular endothelium, due to accumulation of dysfunctional mitochondria. Although the nonischemic neurovascular theory attributes the symptoms to cerebral blood flow changes caused by altered ion homeostasis and change in vascular permeability, another generalized cytopathic theory proposes the role of defective oxidative phosphorylation and intracellular energy production.

During the acute phase, the MRI brain shows stroke-like cortical lesions with a predilection for parietal and occipital lobes. These lesions classically span multiple cerebral vascular territories and may disappear and reappear elsewhere over time. Diffusion restriction along with the lactate peak in MR spectroscopy images are other key diagnostic features. Ultimately, these multifocal cortical and subcortical lesions lead to generalized cerebral and cerebellar atrophy, with ventricular prominence and encephalomalacia in previously affected areas.

The most accepted clinical practice is to initiate a combination of antioxidant and cofactor therapies including Coenzyme Q10 and L-carnitine, which might help in replenishing constituents of oxidative metabolism pathways. Limited evidence also favors the use of L-arginine, citrulline, and creatine.
monohydrate in MELAS patients. Clinicians need to be aware of the variable presentation of MELAS mimicking migraine, meningoencephalitis, psychosis and even retinal artery occlusion, as timely initiating the above-mentioned treatments may alleviate these life-threatening symptoms. Inquiring a history of similar symptoms in mother and siblings often helps in clinching the correct diagnosis.

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Conflicts of interest
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REFERENCES
1. El-Hattab AW, Adesina AM, Jones J, Scaglia F. MELAS syndrome: clinical manifestations, pathogenesis, and treatment options. Mol Genet Metab 2015;116:4-12.
2. Koga SJ, Hodges M, Markin C, Gorman P. MELAS syndrome. West J Med 1995;163:379-81.
3. Henry C, Patel N, Shaffer W, Murphy L, Park J, Spieler B. Mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes-MELAS syndrome. Ochsner J 2017;17:296-301.
4. Aurangzeb S, Vale T, Tofaris G, Poulton J, Turner MR. Mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS) in the older adult. Pract Neurol 2014;14:432-6.
5. Scaglia F, Northrop JL. The mitochondrial myopathy, encephalopathy, lactic acidosis with stroke-like episodes (MELAS) syndrome: a review of treatment options. CNS Drugs 2006;20:443-64.