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Minireview

MELAS syndrome: Clinical manifestations, pathogenesis, and treatment options

Ayman W. El-Hattab [a], Adekunle M. Adesina [b], Jeremy Jones [c], Fernando Scaglia [d,*]

[a] Division of Clinical Genetics and Metabolic Disorders, Department of Pediatrics, Tawam Hospital, Al-Ain, United Arab Emirates
[b] Department of Pathology and Immunology, Baylor College of Medicine, Houston, TX, USA.
[c] Singleton Department of Radiology, Texas Children's Hospital, Houston, TX, USA
[d] Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, TX, USA

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ABSTRACT

Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) syndrome is one of the most frequent maternally inherited mitochondrial disorders. MELAS syndrome is a multi-organ disease with broad manifestations including stroke-like episodes, dementia, epilepsy, lactic acidemia, myopathy, recurrent headaches, hearing impairment, diabetes, and short stature. The most common mutation associated with MELAS syndrome is the m.3243A>G mutation in the *MT-TL1* gene encoding the mitochondrial $tRNA^{Leu(UUR)}$. The m.3243A>G mutation results in impaired mitochondrial translation and protein synthesis including the mitochondrial electron transport chain complex subunits leading to impaired mitochondrial energy production. The inability of dysfunctional mitochondria to generate sufficient energy to meet the needs of various organs results in the multi-organ dysfunction observed in MELAS syndrome. Energy deficiency can also stimulate mitochondrial proliferation in the smooth muscle and endothelial cells of small blood vessels leading to angiopathy and impaired blood perfusion in the microvasculature of several organs. These events will contribute to the complications observed in MELAS syndrome particularly the stroke-like episodes. In addition, nitric oxide deficiency occurs in MELAS syndrome and can contribute to its complications. There is no specific consensus approach for treating MELAS syndrome. Management is largely symptomatic and should involve a multidisciplinary team. Unblinded studies showed that L-arginine therapy improves stroke-like episode symptoms and decreases the frequency and severity of these episodes. Additionally, carnitine and coenzyme Q_{10} are commonly used in MELAS syndrome without proven efficacy.

Contents

* Corresponding author at: Department of Molecular and Human Genetics, Baylor College of Medicine, One Baylor Plaza, MS BCM225, Houston, TX 77030, USA.
E-mail address: fscaglia@bcm.edu (F. Scaglia).

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1. Introduction

Mitochondria are double membrane organelles found in all nucleated human cells and perform a variety of essential functions, including the generation of most cellular energy in the form of adenosine triphosphate (ATP). The inner mitochondrial membrane harbors the electron transport chain (ETC) complexes that transfer electrons, translocate protons, and produce ATP. Mitochondria contain extra-chromosomal DNA (mitochondrial DNA, mtDNA). However, only a very small proportion of mitochondrial proteins are encoded by that DNA; whereas the majority of mitochondrial proteins are encoded by nuclear DNA (nDNA). Mutations in mtDNA or mitochondria-related nDNA genes can result in mitochondrial dysfunction leading to mitochondrial diseases. Dysfunctional mitochondria are unable to generate sufficient ATP to meet the energy needs of various organs, particularly those with high energy demand, including the nervous system, skeletal and cardiac muscles, kidneys, liver, and endocrine systems. Some patients with mitochondrial diseases display a cluster of clinical features that fall into a discrete clinical syndrome. However, there is often considerable clinical variability, and many affected individuals do not fit into one particular syndrome [1].

Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) syndrome is one of the most frequent maternally inherited mitochondrial disorders which was first delineated in 1984 [2]. The molecular basis of MELAS syndrome was initially discovered in 1990 when adenine to guanine transition at position 3243 of mtDNA (m.3243A>G) in the *MT-TL1* gene encoding $tRNA^{Leu(UUR)}$ was found to be associated with this syndrome [3,4]. In 1992, clinical diagnostic criteria for MELAS syndrome were published indicating that the clinical diagnosis of this syndrome is based on the following three invariant criteria: 1) stroke-like episodes before age 40 years, 2) encephalopathy characterized by seizures and/or dementia, and 3) mitochondrial myopathy evident by lactic acidosis and/or ragged-red fibers (RRFs). The diagnosis is considered confirmed if there are also at least two of the following criteria: 1) normal early psychomotor development, 2) recurrent headaches, and 3) recurrent vomiting episodes [5]. More recently, the MELAS study group committee in Japan published other diagnostic criteria by which the diagnosis is considered definitive with at least two category A criteria (headaches with vomiting, seizures, hemiplegia, cortical blindness, and acute focal lesions in neuroimaging) and two category B criteria (high plasma or cerebrospinal fluid (CSF) lactate, mitochondrial abnormalities in muscle biopsy, and a MELAS-related gene mutation) [6]. The prevalence of MELAS syndrome has been estimated to be 0.2:100,000 in Japan [6]. Other mtDNA mutations were subsequently found to cause MELAS syndrome; however, the m.3243A>G remained the commonest universally. The m.3243A>G, which was subsequently found to be associated with other phenotypes that collectively constitute a wide spectrum ranging from MELAS syndrome at the severe end to asymptomatic carrier status, was found to be relatively common with a prevalence of 16–18:100,000 in Finland [7,8]. In this review, we summarize the clinical manifestations of MELAS syndrome along with its pathogenic mechanisms and management options.

2. Clinical manifestations

MELAS syndrome is a multi-organ disease with broad manifestations including stroke-like episodes, dementia, epilepsy, lactic acidemia, myopathy, recurrent headaches, hearing impairment, diabetes, and short stature. Childhood is the typical age of onset with 65–76% of affected individuals presenting at or before the age of 20 years. Only 5–8% of individuals present before the age of 2 years and 1–6% after the age of 40 years [6,9–11].

Individuals with MELAS syndrome frequently present with more than one initial clinical manifestation. Table 1 summarizes the initial manifestations in affected individuals [6,9,10]. Table 2 summarizes the clinical manifestations of MELAS syndrome organized according to their prevalence [6,9–11]. Below the manifestations of MELAS syndrome are presented according to the organ or system involved.

2.1. Neurological manifestations

Stroke-like episodes are one of the cardinal features of MELAS syndrome that occur in 84–99% of affected individuals [6,9,10]. These episodes present clinically with partially reversible aphasia, cortical vision loss, motor weakness, headaches, altered mental status, and seizures with the eventual progressive accumulation of neurological deficits. The affected areas in neuroimaging do not correspond to classic vascular distribution (hence called "stroke-like"), are asymmetric, involve predominantly the temporal, parietal, and occipital lobes, and can be restricted to cortical areas or involve subcortical white matter [5,11] (Fig. 1). Brain magnetic resonance (MR) angiography is usually normal; whereas MR spectroscopy shows decreased N-acetylaspartate signals and accumulation of lactate [11]. The high ventricular lactate measured using MR spectroscopy was found to correlate with the degree of the neurological impairment in individuals with MELAS syndrome [12].

Dementia occurs in 40–90% of affected individuals [6,9,10]. Both the underlying neurological dysfunction and the accumulating cortical injuries due to stroke-like episodes contribute to the observed dementia which affects intelligence, language, perception, attention, and memory function [11]. Additionally, executive function deficits have been observed despite the relative sparing of the frontal lobe in neuroimaging suggesting an additional diffuse neurodegenerative process besides the damage caused by the stroke-like episodes [11].

Epilepsy is another common neurological manifestation occurring in 71–96% of individuals with MELAS syndrome [6,9,10]. Epilepsy in

Table 1
Initial manifestations of MELAS syndrome.

Frequency	Manifestations
>25%	Seizure
	Recurrent headaches
	Stroke-like episode
	Cortical vision loss
	Muscle weakness
	Recurrent vomiting
	Short stature
10–24%	Altered consciousness
	Impaired mentation
	Hearing impairment
	Diabetes
<10%	Developmental delay
	Fever