

# Diagnostic Considerations On Melas Syndrome

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## Abstract

MELAS syndrome is a mitochondrial disease which precise clinical features and complementary test useful to diagnosis are still controversial. It may mimic Herpes Simplex Encephalitis. Elevated lactic acid levels in blood, neuroimaging, EEG, muscle biopsy, and molecular genetics are helpful in the diagnosis but the absence of findings does not reject a MELAS syndrome such as it happens in the case reported.

## INTRODUCTION

MELAS syndrome (mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke like episodes) is a mitochondrial disease described by Pavlakis in 1984 and related to a mitochondrial DNA mutation. We regard that MELAS syndrome is still insufficiently known and are frequently misdiagnosed. The lack of standardized criteria poses difficulties in evaluating diagnostic methodologies. Some considerations in the matter are expounded in this article and previously we present a quite representative case.

## CASE REPORT

A 38-year-old right-handed man presented with fever, headache, confusion, partial seizures with secondary generalisation and a right parieto-temporal syndrome consisting on left hemiparesis with hypoesthesia, left homonymous hemianopia, prosopagnosia, topographical disorientation and sensorineural deafness of acute onset. Antiviral treatment with acyclovir was initially set. Hearing difficulty and familiar history of deafness and diabetes mellitus show up among his antecedents.

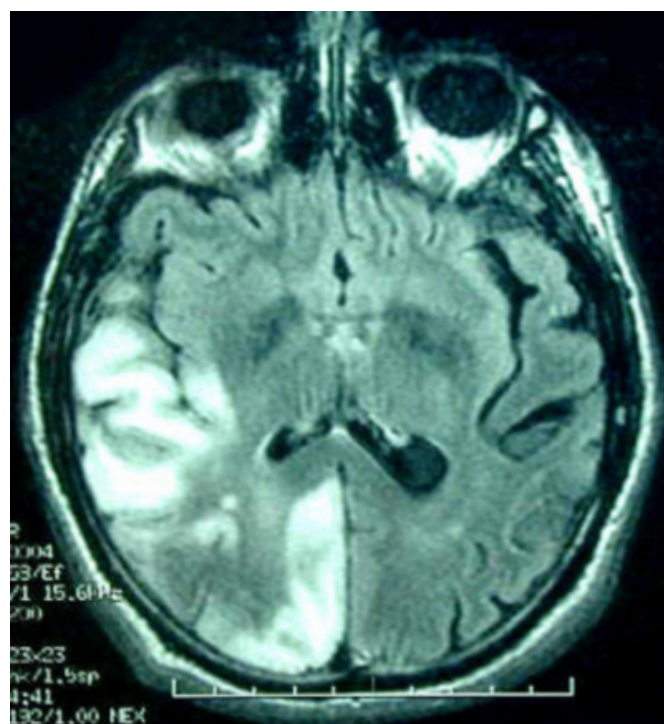
Computed tomography revealed a low-density area, which did not correlate with the vascular supply, in the parietal lobe. Cerebrospinal fluid was normal. Brain Magnetic Resonance showed cortical and subcortical hyperintensities located unilaterally in the right parietal and temporo-occipital lobes and diffuse atrophy of the cerebellar cortex (Figures 1 and 2.). On an ictal record, high amplitude, rhythmic sharp waves were observed at right parieto-temporo-occipital region with a high amplitude slow waves background. Lactic acid in blood was not elevated. Muscle biopsy and neuropathological study with cytochrome-c

oxidase (COX) and trichrome stain was normal.

Mitochondrial DNA analysis detected an A3243G mutation. His mother, two sisters and a brother were also genetically studied and the mutation was detected in all of them but the proportion of A3243G mtDNA in blood was very variable (5-87%) being the mother initially informed as negative even.

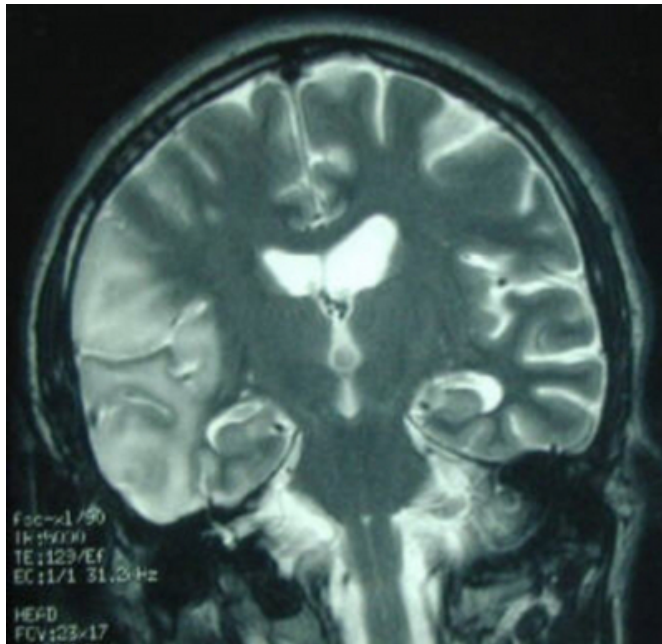
## Figure 1

Figure 1



**Figure 2**

Figure 2



### COMMENTS

The stroke-like episodes in MELAS may reflect neuronal hyperexcitability, which increases energy demand and creates energy imbalance between energy requirement and adequate availability of adenosine triphosphate due to oxidative phosphorylation defect particularly in the susceptible neuronal population, causing cortical necrosis. The episodic nature of stroke-like episodes is unexplained <sup>1</sup>

Seizures, stroke like episodes, extrapyramidal movements, autonomic dysfunction headache, fever and confusion are potential symptoms of acute or subacute onset. The onset with the stroke like episodes is often before the age 40. Deafness, sterility and diabetes mellitus are common familial and personal antecedents. Due to headache, confusion, and other symptoms in common, MELAS syndrome and Herpes Simplex Encephalitis (HSE) may occasionally have a similar clinical presentation so differential diagnosis between HSE and MELAS syndrome must be established <sup>2</sup>

Plasma or CSF lactic acid levels are typically high, but normal levels does not rule out a mitochondrial disorder <sup>3</sup>

A common EEG feature of all the mitochondrial encephalomyopathic syndromes is background slowing. Photoparoxysmal EEG responses and periodic lateralized epileptiform discharges could be seen <sup>4</sup>

Both Brain Magnetic Resonance Imaging and Brain Computed tomography frequently shows a low-density area in the cerebral cortex, which did not correlate with the vascular supply. Brain Magnetic Resonance Imaging fluid attenuated inversion recovery images show multifocal cortical and subcortical hyperintensities located bilaterally in the frontobasal and the temporo-occipital lobes and usually reveal progressive spread of the cortical lesion to the surrounding cortex for a few weeks after the onset of symptoms. Diffusion weighted images show normal to increased apparent diffusion coefficient values in the acute left temporo-occipital lesion and increased values in the older stroke-like lesions. These diffusion-weighted findings support the metabolic rather than the ischemic pathophysiological hypothesis for stroke-like episodes occurring in MELAS. Normal or increased apparent diffusion coefficient values within 48 hours of a neurological deficit of abrupt onset should raise the possibility of MELAS, especially if conventional MR images show infarct-like lesions <sup>5</sup> By Brain Magnetic Resonance Spectroscopy exciting new work suggests that carefully supervised physical conditioning in conjunction with sodium dichloroacetate administration can markedly enhance both biochemical measures of aerobic metabolism and functional performance of patients with mitochondrial myopathies <sup>6</sup> The regional cerebral blood flow is altered specifically in patients with MELAS, suggesting that brain perfusion SPECT will be useful in diagnosing and assessing such patients. The decreased cerebral perfusion reserve in patients with MELAS may represent an important feature of the pathogenesis of the stroke-like episodes. There are no SPECT findings in patients with other types of mitochondrial encephalomyopathy<sup>7</sup>. Using PET to investigate cerebral metabolism by 2-[18F] fluorodeoxy-d-glucose uptake it show that cerebral glucose uptake is impaired in all patients, both with and without Central Nervous System symptoms, particularly in the occipital and temporal lobes <sup>8</sup>.

Muscle biopsy usually shows many ragged red fibers (RRFs) mostly positive for COX activity. A direct correlation exists between A3243G levels and impairment of COX function at the single-muscle fiber level. Moreover, the evidence of a clinical myopathy in a patient with higher amounts of COX-negative RRFs bolsters the concept that a differential distribution of mutant mtDNAs at the cellular level may have effects on the clinical involvement of individual tissues<sup>9</sup> However, the occurrence of a similar morphological and biochemical muscle phenotype also in progressive

external ophthalmoplegia (PEO) patients suggests that other genetic factors involved in the interaction between mitochondrial and nuclear DNA, rather than the stochastic distribution of mtDNA genomes during embryogenesis, are primarily implicated in determining the various clinical expressions of the A3243G of mtDNA. Nevertheless, absence of pathological findings in muscle biopsy does not rule out a MELAS syndrome because encephalopathy not ever associates myopathy<sup>10</sup>.

The characteristics of mitochondrial genetics are maternal inheritance, polyplasmia, heteroplasma, mitotic segregation and threshold effect that largely explain the characteristic phenotype behaviour specific to these changes<sup>11</sup>. In MELAS, diabetes accelerates the accumulation of the somatic 3243 A to G mutation in mitochondrial DNA, which can accelerate the ageing process<sup>12</sup>. Several mutations in mitochondrial DNA (mtDNA) were described and it could be one of the factors that modulate the different clinical features and prognosis in each family<sup>13</sup>. The common MELAS mutation, due to the A3243G transition of mitochondrial DNA (mtDNA) leucine (UUR) gene, affects approximately 80% of cases and is associated with respiratory chain complex deficiency. The A3243G mutation creates an ApaI restriction endonuclease site and can be detected by polymerase chain reaction (PCR) amplification of a region of mtDNA containing nt 3243, followed by ApaI digestion and electrophoretic analysis of the resulting fragments<sup>14</sup>. The reasons for the phenotypic heterogeneity of the 3243 mutation have not been clarified, although it may be closely related with mtDNA heteroplasmy and their differing proportions in different tissues. It has been reported that the 3243 mutation also occurs in individuals with non-MELAS phenotypes. In subjects in whom both muscle and blood are studied, the percentage of mutations are significantly lower in blood and in aged carriers it could be even positive in muscle but in blood<sup>15</sup>, therefore if patient mothers' blood were negative it could suggest the mechanism of de novo mutation for the pathogenesis of patient's syndrome or else a very low percentage of mutations in the mother.

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