

When should MELAS (*Mitochondrial myopathy, Encephalopathy, Lactic Acidosis, and Stroke-like episodes*) be the diagnosis?

Quando o diagnóstico deveria ser MELAS (Miopatia mitocondrial, encefalopatia, acidose láctica, e episódios semelhantes a acidente vascular cerebral)?

Paulo José Lorenzoni, Lineu Cesar Werneck, Cláudia Suemi Kamoi Kay, Carlos Eduardo Soares Silvano, Rosana Herminia Scola

ABSTRACT

Mitochondrial myopathy, Encephalopathy, Lactic Acidosis, and Stroke-like episodes (MELAS) is a rare mitochondrial disorder. Diagnostic criteria for MELAS include typical manifestations of the disease: stroke-like episodes, encephalopathy, evidence of mitochondrial dysfunction (laboratorial or histological) and known mitochondrial DNA gene mutations. Clinical features of MELAS are not necessarily uniform in the early stages of the disease, and correlations between clinical manifestations and physiopathology have not been fully elucidated. It is estimated that point mutations in the tRNA^{Leu(UUR)} gene of the DNAm, mainly A3243G, are responsible for more of 80% of MELAS cases. Morphological changes seen upon muscle biopsy in MELAS include a substantive proportion of ragged red fibers (RRF) and the presence of vessels with a strong reaction for succinate dehydrogenase. In this review, we discuss mainly diagnostic criterion, clinical and laboratory manifestations, brain images, histology and molecular findings as well as some differential diagnoses and current treatments.

Keywords: MELAS, mitochondria, myopathy, stroke, encephalopathy, genetics.

RESUMO

Miopatia mitocondrial, encefalopatia, acidose láctica, e episódios semelhantes a acidente vascular cerebral (MELAS) é uma rara doença mitocondrial. Os critérios diagnósticos para MELAS incluem as manifestações típicas da doença: episódios semelhantes a acidente vascular cerebral, encefalopatia, evidência de disfunção mitocondrial (laboratorial ou histológica) e mutação conhecida em genes do DNA mitocondrial. Na fase inicial da doença, as manifestações clínicas podem não ser uniformes, e sua correlação com a fisiopatologia não está completamente elucidada. Estima-se que as mutações de ponto no gene tRNA^{Leu(UUR)} do DNAm, principalmente a A3243G, sejam responsáveis por cerca de 80% dos casos de MELAS. As alterações morfológicas na biópsia muscular incluem uma grande proporção de fibras vermelhas rasgadas (RRF) e presença de vasos com forte reação para succinato desidrogenase. Nesta revisão, são discutidos os principais critérios diagnósticos, manifestações clínicas e laboratoriais, imagens cerebrais, padrões eletrofisiológicos, histológicos e alterações moleculares, bem como alguns dos diagnósticos diferenciais e tratamentos atuais.

Palavras-chave: MELAS, mitocôndria, miopatia, acidente vascular cerebral, encefalopatia, genética.

The first description of cases with clinical features suggested MELAS was in 1975^{1,2}. The patients common point was the presence of mitochondrial myopathy associated with brain changes, such as mental retardation, seizures, myoclonus, ophthalmoplegia, retinitis pigmentosa, blindness, calcification in basal ganglia and sudden hemiplegia suggestive of stroke^{1,2}. In the following years other cases with similar findings were added to the literature, and in 1984, Pavlakis et al., better characterize the patients who had normal early development, short stature, seizures, alternating hemiparesis, hemianopsia and cortical blindness, through

the framework that called MELAS (*Mitochondrial myopathy, Encephalopathy, Lactic Acidosis, and Stroke-like episodes*)³.

In Brazil, the first report of MELAS was made by Werneck et al. in 1987 who describe a boy who had recurrent episodes of seizures, headache and vomiting associated with focal neurological signs⁴. The brain computed tomography showed lesions similar to ischemic stroke and calcification of the basal ganglia, ragged-red fiber (RRF) in muscle biopsy, elevation of lactic acid and determination of enzyme activity consistent with the respiratory chain complex IV deficiency also were found⁴.

Universidade Federal do Paraná, Hospital de Clínicas, Departamento de Clínica Médica, Serviço de Neurologia e Doenças Neuromusculares, Curitiba PR, Brazil.

Correspondence: Rosana Herminia Scola; Serviço de Doenças Neuromusculares, Hospital de Clínicas - UFPR; Rua General Carneiro, 181 / 3º andar; 80060-900 Curitiba PR, Brasil; E-mail: rosana.scola@hc.ufpr.br

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WHAT IS THE DIAGNOSTIC CRITERION?

The cases previously published with a diagnosis suggestive of MELAS have been reviewed by Hirano et al. in 1992 with the purpose of obtaining diagnostic criteria for this group of patients⁵. After this literature review, the diagnostic criteria for MELAS must include the following events: (1) signs of encephalopathy, often with dementia and seizures, (2) episodes similar to stroke (stroke-like episodes) in young age, and (3) biochemical evidence of mitochondrial dysfunction such as lactic acidosis or RRF in muscle biopsy (Table 1)⁵. The diagnosis may also be supported if at least two of the following was present: normal development, recurrent headache and vomiting (Table 1)⁵.

Recently, the MELAS Study Group in Japan included obligatory presentation of stroke-like episodes associated to evidence of mitochondrial dysfunction and known mitochondrial gene mutations as diagnostic criterion. In Japan, the disease is also defined using the Japanese diagnostic criteria for MELAS (Table 2)⁶. Different of the Hirano et al. diagnostic criteria, Japanese's diagnostic criteria did not consider signs of encephalopathy and includes mitochondrial gene mutations^{5,6}.

WHAT IS THE PATHOGENESIS?

On clinical evaluation, stroke-like episodes of patients with MELAS are indistinguishable from those reported by patients with acute ischemic stroke, but the pathogenesis of these lesions in patients with MELAS is different and not fully elucidated. The two main hypotheses being considered are: (1) ischemic, with suggestion of a "mitochondrial

angiopathy" caused by mitochondrial dysfunction in smooth muscle cells of the small cerebral vessels leading to vascular occlusion with neuronal loss^{7,8,9,10}; and (2) metabolic, due to a "mitochondrial cytopathy", that trigger energy failure of brain tissue causing neuronal damage^{11,12,13}.

Currently, the mechanisms that trigger these episodes are correlated to a combination of these two hypotheses, in which both (neuronal and vascular dysfunction) are responsible for the pathogenesis of stroke-like episodes¹⁴. Iizuko and Sakai in 2005 proposed a possible mechanism for the formation of stroke-like episodes, based on the main pathological findings related to these episodes (Figure 1): headache, seizures, focal hyperemia, vasogenic edema, lesion progression after the stroke-like episode and neuronal loss¹⁴.

WHAT ARE THE GENETIC ABNORMALITIES?

In 1990, Goto et al. and Kobayashi et al., described a point mutation of mtDNA affecting the gene encoding the leucine tRNA (UUR) (tRNA^{Leu(UUR)}) by the exchange at position 3243 of the nucleotide A by G (A3243G) in muscle of MELAS patients^{15,16}. The tRNA^{Leu(UUR)}, also known as *MT-TLI*, is located between nucleotides 3230 and 3304 and is responsible for decoding of UUR codons (R = A or G)¹⁷. The A3243G mutation affects the stability of the structure, methylation, aminoacylation and codon recognition of the tRNA^{Leu(UUR)}, more sharply than other mutations in this gene^{14,17,18}. This could reduce the functional level of tRNA^{Leu(UUR)} that participates in the process of mitochondrial protein synthesis¹⁴. After this first description other studies have shown that the A3243G mutation was responsible for most cases of MELAS^{19,20,21}.

In the years following the discovery of mutation A3243G, a second point mutation by substitution of T for C nucleotide at position 3271 (T3271C) in the tRNA^{Leu(UUR)} of the mtDNA was also found in patients with MELAS²². Over the years, other point mutations in mtDNA were found in patients with MELAS, revealing their genetic heterogeneity. However, the A3243G mutation still is responsible for remained about 80% of patients with MELAS and T3271C by approximately 7.5%, but up to 10% of patients with MELAS the mutations of mtDNA

Table 1. Hirano's diagnostic criteria for MELAS (Hirano et al., 1992)⁵.

Absolute criteria*	Supportive criteria**
Encephalopathy (dementia and/or seizures)	Normal development
Stroke-like episodes in young age	Recurrent headache
Evidence of mitochondrial dysfunction (lactic acidosis or ragged-red fibers in muscle biopsy)	Recurrent vomiting

*definitive diagnosis requires all absolute criteria; **diagnosis may also be more secure if at least two of three supportive criteria were present.

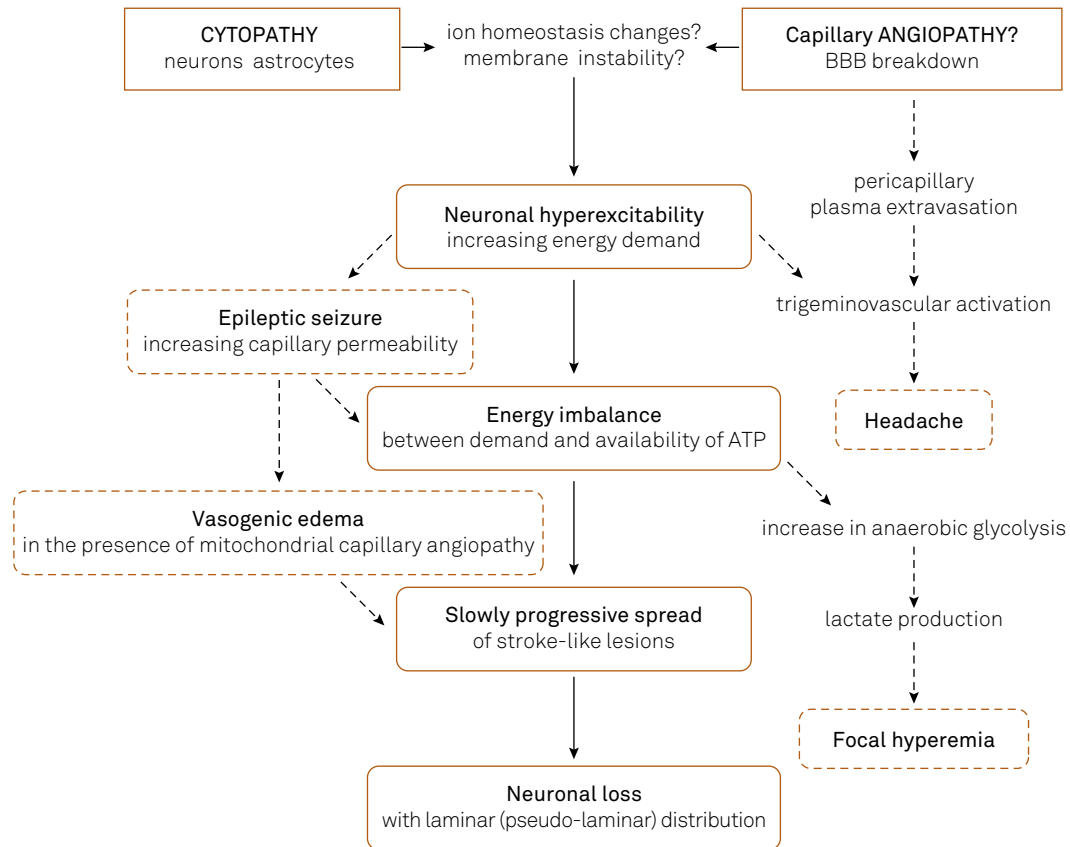
Table 2. Japanese's diagnostic criteria for MELAS (Yatsuga et al., 2012)⁶.

Category A. Clinical findings of stroke-like episodes	Category B. Evidence of mitochondrial dysfunction
Headache with vomiting	High lactate levels in plasma and/or cerebral spinal fluid or deficiency of mitochondrial-related enzymes activities** Mitochondrial abnormalities in muscle biopsy*** Definitive gene mutation related to MELAS****
Seizures	
Hemiplegia	
Cortical blindness or hemianopsia	
Acute focal lesion observed via brain imaging*	

Definitive MELAS: two items of category A and two items of category B (four items or more)

Supportive MELAS: one item of category A and two items of category B (at least three items)

*focal brain abnormalities in CT and/or MRI; **2 mmol/L (or 18 mg/dl) or more lactate in plasma at rest or in cerebral spinal fluid and/or deficiency of electron transport chain enzyme, pyruvate-related, TCA cycle-related enzymes or lipid metabolism-related enzymes in somatic cells (desirable for muscle cells); ***ragged-red fiber in modified Gomori trichrome stain, cytochrome c oxidase deficient fibers or abnormal mitochondria in electron microscopy; ****definitive mitochondrial gene mutations reported in the literature.



BBB: blood-brain barrier.

Figure 1. Iizuka and Sakai's proposed mechanism of stroke-like episodes (with permission from *Curr Neurovasc Res* 2005;2:29-45)¹⁴.

remain unknown (Table 3)^{7,16}. The mutations in DNAm genes coding to mitochondrial complex I, as *ND5* gene, have been appointed as the second more frequent (Table 3)²³. The presence of mutation by rearrangement of the deletion type, large or small, has rarely been described in mtDNA associated to MELAS phenotype. The presence of nuclear DNA gene mutations has been also rarely associated to MELAS.

Although most MELAS patients have the A3243G point mutation, this mutation is not specific for this group of patients, also found in patients with progressive external ophthalmoplegia (PEO), cardiomyopathy, sensorineural deafness and diabetes mellitus with maternal inheritance²⁴. Moreover, the clinical and laboratory evaluation of other family members have found relatives with incomplete features for MELAS, usually with maternal inheritance pattern. However, genetic studies have showed that maternal relatives clinically asymptomatic but with the A3243G mutation, might have mitochondrial dysfunction with RRF in muscle biopsy^{5,19}. In addition, patients with MELAS concomitant with other mitochondrial diseases such as myoclonic epilepsy associated with ragged red fibers (MERRF), Leigh syndrome and Leber's hereditary optic neuropathy have been reported with associated mutation of the mtDNA. These data contribute to state that mitochondrial diseases caused by mtDNA point mutations have heterogeneous phenotype⁷.

The proportion of mutant mtDNA usually is different in tissues of MELAS patients associated to mutations of tRNA^{Leu(UUR)}^{5,7,19,20}. For these reasons the use of clinically affected tissues, such as muscle, to perform the extraction of mtDNA for the molecular study could be recommended due to better results^{5,7,19,20,25}. If clinically unaffected tissues were used, such as peripheral blood leukocytes, the pathogenic mutation may be undetectable^{5,7,19,20,25}.

The methods used to detect each mutation may vary among laboratories (often PCR, PCR/RFLP or direct sequencing), but usually is recommended first screening to targeted mutations to then perform the full sequence analysis.

WHAT ARE THE CLINICAL FEATURES?

Clinical symptoms are highly variable among patients with mitochondrial diseases. Some of these clinical findings may be absent in the early stage of the disease, while in advanced disease patients usually have more uniform clinical manifestations.

Although the onset of clinical manifestation often occurs in childhood and early adulthood, a late onset in adults is not uncommon in patients with MELAS. Moreover, the age of stroke-like episodes may be different among affected members of the same family²⁶. Children psychomotor development is usually normal in almost all patients with MELAS.

Table 3. Summary of mutations in mitochondrial DNA in the two most frequent genes associated with MELAS.

Gene	Mutation	Proportion of affected individual
MT-TL1 [tRNA ^{Leu(UUR)}]	3243 A > G	~80%
	3271 T > C	~7.5%
	3252 A > G	< 5%
	3256 C > T	< 10%
	3260 A > G	
	3291 T > C	
	3302 A > G	
	MT-ND5	13513 G > A
	12770 A > G	< 5%
	13042 A > T	
	13045 A > C	
	13046 T > C	
	13084 A > T	
	13514 G > A	
	13528 A > G	

Stroke-like episodes are diagnostic criteria for MELAS and is expected that all patients have this clinical manifestation^{5,6}. The stroke-like episode may occur alone or in association with signs of the encephalopathy, such as seizures^{5,6}. The clinical outcome of stroke-like episodes is more benign, with improvement of symptoms in a few months, but the symptoms related encephalopathy, such as dementia and seizures, may progressively worsen^{6,12,14,27}.

The presence of progressive dementia has also been found associated with changes in cerebral perfusion even in the absence of stroke-like episode, but with marked cortical atrophy in the chronic phase of the disease characterized neuronal loss, similar to what occurs in vascular dementia^{27,28}. Partial seizures are commonly reported in MELAS associated with mutations in the tRNA^{Leu(UUR)} gene, similar other mitochondrial diseases as MERRF or PEO, but generalized seizures also occurs in MELAS^{29,30}.

Headaches occur in the majority of affected individuals and are often severe during the acute phase of the stroke-like^{25,29,31}.

Other multisystemic dysfunctions could be found in MELAS patients: psychiatric manifestations, cerebellar ataxia, myoclonus, neuropathy, ocular motility abnormalities, exercise intolerance, pigmentary retinopathy, optic atrophy, deafness, short stature, diabetes mellitus, alteration of cardiac conduction, cardiomyopathy, gastrointestinal changes, among others^{5,6,20,27,25,29}. Cardiac involvement can occur in up to 50% of patients with MELAS^{32,33}. However, these disorders are not the main clinical manifestation of the disease.

MELAS patients should be followed at regular intervals to monitor disease progression and the appearance of new symptoms. Annual ophthalmologic, audiologic, cardiologic (electrocardiogram and echocardiogram), and endocrinologic (fasting blood sugar and TSH) assessments also are recommended²⁵.

Children of woman with mtDNA mutation can inherit the mutation³⁴. The risk to other family members depends on the genetic status of the mother^{25,34}. However, it is appropriate to evaluate other family members because the phenotype

manifestation results from a combination of factors, due to the different inherit percentages of mutant mtDNA, and therefore, can have a wide range of clinical symptoms from asymptomatic to full manifestation.

WHAT ARE THE IMAGING FEATURES?

Brain conventional radiological studies, such as CT or MRI, in patients with MELAS reveal changes in gray matter more than in white matter, predominate in the occipital, parietal and temporal lobes, which simulate ischemic stroke (Figure 2)^{14,35,36}. Most injuries occur in the cortical region of the cerebral hemispheres and more rarely in the cerebellum or basal ganglia^{32,36}. These brain lesions can be unilateral or bilateral (Figure 2). However, these areas do not occur in a specific vascular territory and angiographic studies show that the vessels in the affected regions have blood flow and sometimes are dilated^{5,32,36}. Brain MRI revealed that the lesion in the acute phase begins in the temporal region on focal form, but in 2 to 3 weeks may progress to the parietal and occipital regions, in one third of patients³⁷. This shows that even after the stroke episode the disease process continues to progress³⁷. The changing pattern of lactic acid concentration between these regions during the clinical outcome of stroke-like episodes, was also observed in patients with MELAS³⁸. These findings may mean that the vulnerability of neurons to mitochondrial dysfunction may be higher in these regions. The exact mechanism of the disease predilection for certain locations in the central nervous system has not been elucidated, but the possibility of heteroplasmy in brain tissue was ruled-out by genetic studies when comparing tissue from different brain areas^{11,14,39}. Studies using spectroscopy show increased lactic acid in acute lesions while the use of magnetic resonance diffusion can reveal increased coefficient of diffusion^{35,40,41}. Both methods being more sensitive than conventional in the acute phase of the injury^{35,40,41}. The MRI images are compatible with subcortical laminar necrosis in the subacute phase of episodes^{36,37}.

The presence of multiple focal areas of cortical necrosis associated with diffuse cortical atrophy in both cerebral hemispheres and cerebellum, are the most frequent pathological findings in the brain of patients with MELAS, while the brainstem is rarely affected^{32,36,42}. The presence of cortical atrophy and calcifications in the basal ganglia are also found in the progression of some patients^{36,42}.

WHAT ARE THE LABORATORIAL AND BIOCHEMICAL FEATURES?

The concentration of cerebrospinal fluid (CSF) protein may be elevated but rarely surpasses 100 mg/dL^{25,29}. The lactic acid level in blood and CSF is elevated during, or shortly after, the

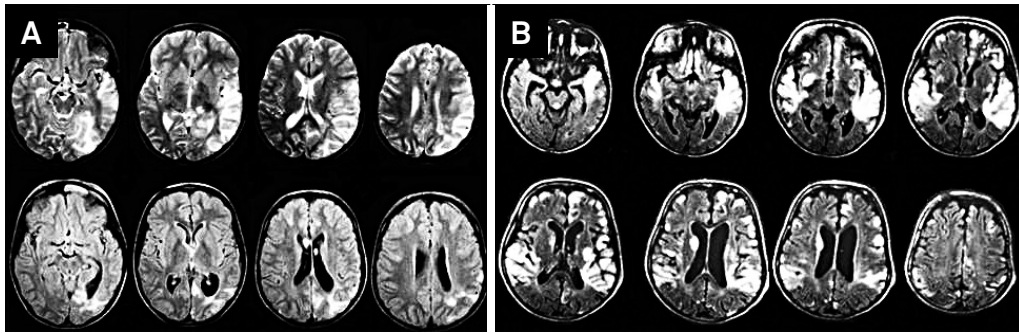


Figure 2. Imaging features in brain MRI showing unilateral (A) or bilateral (B) lesions in MELAS patients (with permission from *Arq Neuropsiquiatr* 2009;67:668-676)²⁹.

stroke-like episodes in virtually all patients with MELAS^{20,25}. The level of ventricular lactic acid measured by spectroscopy, is usually increased in most patients with MELAS and their families, and this increase is associated with the severity of neurological symptoms⁴³. Other tests may be used in MELAS investigation, such as serum levels of creatine kinase (CK), but their findings are not specific for MELAS, even though helps especially in the differential diagnosis with other diseases²⁹. Serum CK may be slightly increased in some patients, usually during or after stroke-like episodes, helping to demonstrate the muscular involvement in these patients, although non-specific to demonstrate mitochondrial myopathy^{20,29}.

Biochemical studies have showed that several complex of mitochondrial respiratory chain may be deficient, isolated or in combination, but the complex I appears to be more involved, typically associated with changes to other respiratory chain complexes, while the complex II seems least affected^{15,19,20,32,44}. This can also be observed in MELAS cases with A3243G mutation who present RRF with normal cytochrome c oxidase (COX) staining in muscle biopsy⁷. In contrast to patients with PEO with A3243G mutation, who show a high incidence of RRF with deficiency of COX activity⁷. The relationship between the defects of complex I of the respiratory chain and MELAS phenotype is also suggested by the identification of mutations of the *ND* genes of mtDNA, coding subunits of complex I, in patients with MELAS. Complex II seems less involved in patients with MELAS, possibly by being encoded by nDNA^{5,19}. The biochemical analysis of respiratory chain complexes may be normal in some cases.

WHAT ARE THE HISTOLOGICAL FEATURES?

Initially the muscle biopsy may show only muscle fibers with subsarcolemmal accumulation of mitochondria without typical RRF, but all patients with MELAS have RRF in the course of the disease, and its frequency is usually higher in the histochemical reaction for succinic dehydrogenase (SDH) staining than by modified Gomori Trichrome (TGM), similar to what occurs in other mitochondrial diseases (Figure 3)^{7,20,29}. The degree of heteroplasmy (proportion of normal and mutant

mtDNA in each tissue) is also an important factor influencing the variability of the muscle biopsy findings^{45,46}.

However, the two morphological abnormalities in muscle biopsy that can help distinguish MELAS from other mitochondrial diseases are: a large proportion of RRF with normal activity of COX and the presence of vessels with strong reaction for SDH (Figure 3)^{29,32,47,48}. The quantitative analysis showed that 80-90% of the muscle fibers have greater amount of mtDNA (normal and mutant), and the ratio of mtDNA mutant RRF is extremely high in comparison with the other fibers which do not form RRF^{45,46}. However, as mentioned earlier, the presence of COX negative fibers in patients with MELAS is lower than that found in other mitochondrial diseases, as MERRF or PEO^{7,20,30}. Some authors report that the COX activity in the muscle fibers is variable, and the presence of COX negative areas is segmentally along the same fiber muscle in patients with MELAS, similar to what occurs in other mitochondrial disorders, suggesting that the alteration of complex IV is not the main change in this group of patients^{7,48,49,50}. Thus, it may occur in a single muscle fiber portions well demarcated with COX positive and COX negative^{49,50,51}. These muscle fibers might have the ratio of mtDNA normal and mutant in those regions influence the functional impairment of complex IV, even in patients with mutations without involvement of genes encoding the COX subunits, for example, with A3243G mutation^{50,51,52}.

The presence of vessels in the muscle biopsy, usually arterioles, with strong reaction to SDH (SDH+) is a common finding in patients with MELAS or MERRF, but rarely found in patients with PEO^{7,20,29,30,53}. These vessels may also occur in other tissues such as brain and gastrointestinal tract^{7,20,53}. Electron microscopy has been observed that these vessels have mitochondria in number and size similar to what occurs in the central nervous system^{11,53}. Similarly to what occurs in RRF, the study of these vessels with strong reaction to SDH shows that the ratio of mtDNA mutant is extremely high in these vessels when compared to vessels with normal reaction to SDH^{45,46}. This type of vascular involvement in patients with MELAS has no meaning pathogenic fully known, however, some researchers still believe that this change in the blood vessels indicates that MELAS is a systemic angiopathy^{32,45,46}.

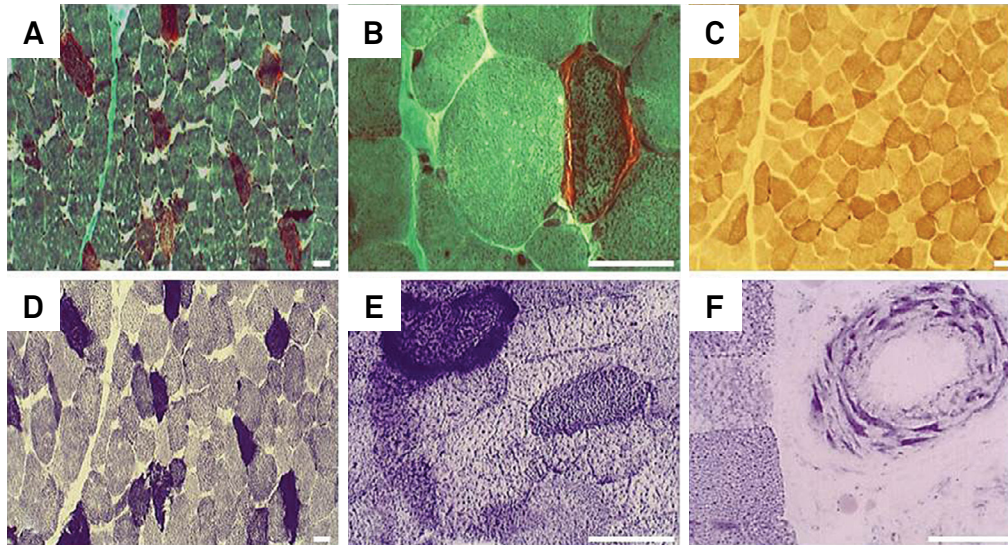


Figure 3. Classic features in the muscle biopsy of MELAS: ragged-red fibers (RRF) on modified Gomori trichrome stain (A, B); muscle fibers with normal activity of the cytochrome c oxidase (COX) (C); RRF on succinic dehydrogenase (SDH) stain (D, E); and SDH strongly reactive blood vessel (F). Bar = 50 μ m.

For some authors, even in the absence of RRF in muscle biopsy of patients with suspected, MELAS can be supported by the histological diagnosis when is found a strong reaction of these vessels in SDH^{7,20}.

Thus, the muscle biopsy of MELAS patients, especially those with the A3243G mutation, usually has vessels with strong reaction for SDH and RRF with normal COX activity^{29,45,46,50}.

WHAT ARE THE MAIN DIFFERENTIAL DIAGNOSES?

Many differential diagnoses have been published, but three categories should be especially considerate in investigation of MELAS patients:

First, MELAS should be considered in the differential diagnosis of all acute stroke in young people along with heart disease, carotid or vertebral diseases, sickle cell disease, vasculopathies, lipoprotein dyscrasias, venous thrombosis, Moyamoya disease, complicated migraine (as familial hemiplegic migraine), Fabry disease, homocystinuria caused by cystathionine beta-synthase deficiency, and other²⁵. Previous studies not support screening for mtDNA mutations to diagnose oligosymptomatic forms of MELAS in cryptogenic strokes in the absence of other features of the disease³¹. Besides appropriate specific tests, a maternal history of other problems suggesting mitochondrial dysfunction (short stature, migraine, hearing loss, diabetes mellitus, cardiac involvement), clinical manifestation (improvement of the stroke symptoms but worsening, or start, seizures and/or encephalopathy) and brain imaging (stroke not corresponding to a vascular distribution or change in stroke pattern after acute ictus) can help orient the clinician toward the correct diagnosis and guide mitochondrial histological and/or genetic testing.

Second, stroke-like episodes can also be rarely associated with a variety of other mitochondrial disorders including PEO, Kearns-Sayre syndrome, MERRF, Leigh syndrome, optic neuropathy, maternally inherited diabetes mellitus with or without deafness, cardiomyopathy, deafness, and other. In addition, some patients also present MELAS with mutations in the nuclear DNA genes, as *POLG*, and typical phenotype can suffer changes. The family history, clinical features and laboratorial data can help orient the clinician toward the correct diagnosis.

Third, the inborn errors of metabolism which causes progressive encephalopathies, especially when onset is in childhood and early adulthood, as X-linked adrenoleukodystrophy, metachromatic leukodystrophy, Krabbe disease, GM1 gangliosidosis, GM2 gangliosidosis, Fabry disease, Niemann Pick type C, amino acidopathies, organic acid disorders, among other diseases⁵⁴. Because of the multiplicity of conditions, many different diagnostic tests are used for screening. An abnormal result is often followed by a subsequent “definitive test” to confirm the suspected diagnosis.

WHAT IS THE TREATMENT?

Similar to occurs in other mitochondrial diseases, there is no specific treatment for MELAS. Therapeutic compounds may ameliorate symptoms in individual cases; however, the available therapeutic interventions are not able to affect the essential progression of this disease.

Many therapeutic strategies have been adopted based in the result of isolated case reports or limited clinical studies that have included a heterogeneous population of patients with MELAS or other mitochondrial disorders. The therapeutic compounds were used in the treatment of MELAS to

improve respiratory chain or to reduce the levels of reactive oxygen species arising from disrupted mitochondrial metabolism. Some of the most frequently prescribed agents include ubiquinone (coenzyme Q10, CoQ), idebenone, edaravone, levoarginine (L-arginine), complex B vitamins, vitamin C, vitamin E, and levocarnitine (L-carnitine) in various combinations and doses^{25,55,56,57,58}. The concomitant administration of these different medications can be useful and has been benefit to some MELAS patients.

There is no standardized treatment of stroke-like episodes but there is increasing evidence that these patients benefit from the administration of L-arginine and consequent antiepileptic treatment if the stroke-like episodes are associated with epileptic activity^{25,55}. Although the underlying mechanisms are not completely understood, in acute phase of the stroke-like episodes in MELAS, seems that L-arginine therapy improve microcirculation and endothelial dysfunction, and improve almost all symptoms associated with stroke-like, with the exception of migraine headaches and visual fields^{55,56,57,59}. According to these studies L-arginine is applied in a dosage until 0.5 g/kg body weight intravenously during the acute phase, followed by oral administration thereafter^{55,56,57}. Occasionally, L-arginine is also given together with other drugs⁵⁵. Symptomatic drug treatment of stroke-like episode include antiepileptic treatment if it was accompanied by seizures, analgesic treatment if it was accompanied by headache, or anti-psychotic or sedative therapy if it was dominated by confusion, agitation, anxiety, hyperactivity, or psychosis⁵⁷. Physical therapy should be implemented in individuals after stroke-like²⁵.

MELAS management also includes additional therapy for its complications, such as, cardiac disease (standard pharmacologic therapy), diabetes mellitus (dietary modification, oral hypoglycemic agents and/or insulin therapy), deafness (hearing devices and cochlear implantation) or epilepsy (traditional antiepileptic treatment)^{25,58,60}. Because febrile illnesses may trigger acute exacerbations, MELAS patients should receive standard childhood vaccinations, flu vaccine, and pneumococcal vaccine^{25,55}. In addition, toxins or drugs that had potential to cause mitochondrial dysfunction or lesion, such as aminoglycoside antibiotics, linezolid, aspirin, Zidovudine, cigarettes or alcohol consumption, should be recognized and avoided^{55,58}. Valproic acid for seizure treatment (high risk by carnitine uptake inhibition) and dichloroacetate for acute stroke-like episodes (high risk for peripheral neuropathy) are not recommended^{58,60}. Exercise (endurance and resistance training) is helpful in MELAS as well other mitochondrial diseases⁵⁸.

It is appropriate to offer genetic counseling (including discussion of potential risks to children and reproductive options) to young women in fertile age who are affected or at risk⁵⁸. Prenatal testing and preimplantation genetic diagnosis may be an option for some families in which the disease-causing mutations have been identified but their interpretation is complex yet^{25,34,58}. The transfer of nuclear DNA from fertilized oocytes or zygotes harboring a mtDNA mutation to an enucleated recipient cells could theoretically prevent transmission of mtDNA diseases and this promising therapy is under investigation^{34,58}. In the pregnancy, MELAS women should be monitored, mainly for diabetes mellitus and respiratory failure, which may require specific therapeutic interventions²⁵.

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