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Review

Neurological and non-neurological complications in adult-onset “Mitochondrial Myopathy, Encephalopathy, Lactic Acidosis and Stroke-like episodes” syndrome: a diagnostic challenge for internal medicine. A narrative review

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ABSTRACT

Mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episode (MELAS) syndrome is a rare genetic mitochondrial disease. Children are the most affected, but this syndrome can manifest at any age. The mA3243G is the most common mutation related to MELAS syndrome. Neurological complications are more frequently discussed in literature. However, it is imperative to address and discuss the non-neurological manifestations so that clinicians do not inadvertently overlook this disease. These are more common in adult patients and may appear before neurological symptoms.

We conducted a narrative review of articles published between 2012 and 2024, with particular focus on non-neurological disorders of MELAS syndrome.

We found 657 papers related to MELAS syndrome. Only 31 papers discussed non-neurological complications. We divided those into cardiovascular, endocrinological, digestive, renal, and nutritional symptoms. The most prevalent disorders include hypertrophic cardiomyopathy, Wolff-Parkinson-White syndrome, chronic renal disease, intestinal pseudo-obstruction syndrome and malnutrition.

The authors of this narrative review seek to shine light on non-neurological manifestations of MELAS syndrome. These are rarely described in the medical literature, despite their potentially significant clinical implications, especially in adult patients. Understanding the neurological and non-neurological complications associated with MELAS syndrome is essential for achieving a timely and definitive diagnosis.

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Complicaciones neurológicas y no neurológicas en el síndrome de «Miopatía mitocondrial, encefalopatía, acidosis láctica y episodios similares a ictus» de inicio en la edad adulta: un reto diagnóstico para la medicina interna. Revisión narrativa

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RESUMEN

El síndrome de “miopatía mitocondrial, encefalopatía, acidosis láctica y episodio similar a un ictus” (síndrome MELAS, del inglés: “Mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episode”) es una enfermedad poco frecuente, de causa genética, que afecta al funcionamiento de la cadena respiratoria mitocondrial. Los niños son los más afectados, pero este síndrome puede comenzar a cualquier edad. La mA3243G es la mutación puntual más frecuentemente relacionada al síndrome MELAS. Los trastornos neurológicos son los más característicos, especialmente los episodios similares al ictus. Sin embargo, los trastornos no neurológicos, comunes en pacientes adultos, pueden aparecer antes de los síntomas típicos.

Se realizó una revisión narrativa de los artículos publicados entre 2012 y 2024, centrándose en los trastornos no neurológicos del síndrome MELAS. Los trastornos neurológicos también fueron comentados en el artículo.

Se encontraron 657 publicaciones relacionadas con el síndrome MELAS. Solo 31 artículos se refirieron a complicaciones no neurológicas, las que dividimos en síntomas cardiovasculares, endocrinológicos, digestivos, renales y nutricionales. Los trastornos más comunes incluyen miocardiopatía hipertrófica, síndrome de Wolff-Parkinson-White, enfermedad renal crónica, síndrome de pseudo-obstrucción intestinal y desnutrición.

En conclusión, las complicaciones no neurológicas son frecuentes de observar en pacientes adultos que padecen el síndrome MELAS, pero son poco conocidas. Conjuguar estos trastornos con las complicaciones neurológicas de esta enfermedad, son claves para lograr un diagnóstico definitivo.

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1. INTRODUCTION

Mitochondria are cytoplasmic organelles whose main function in eukaryotic cells is to produce and deliver the energy necessary for different metabolic processes, synthesizing ATP in the respiratory chain through oxidative phosphorylation. Other functions of mitochondria include amino acid synthesis, fatty acid synthesis, and regulation of apoptosis [1].

Mitochondria have their own, circular, double-stranded DNA that synthesizes most of the proteins in the respiratory chain (37 genes encode 13 subunits of the respiratory chain plus transfer RNAs and ribosomes). However, proteins of subunit II, as well as other units involved in replication, are synthesized from nuclear DNA.

Mitochondrial diseases are rare genetic entities, most of which are maternally inherited. They are caused by

mutations that affect the synthesis of proteins that participate in different phases of the oxidative phosphorylation process. These mutations can affect both mitochondrial DNA and nuclear DNA genes that code for the protein synthesis of the respiratory chain.

Because mitochondria are widely distributed in the body, the symptoms of these diseases are multisystemic, mainly affecting the tissues that are most vulnerable to hypoxia or have a high metabolic rate, such as the brain and muscle.

“Mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episode” (MELAS) syndrome is the most common mitochondriopathy, with an estimated prevalence between 0.18 and 18.4/100,000 inhabitants in the general population [2]. Although MELAS syndrome primarily affects children, onset can occur at any age. The disorder is chronic, progressive, and has no specific treatment. Its severity depends fundamentally on the proportion of damaged mitochondria in the tissues (heteroplasmy).

MELAS syndrome exhibits varied clinical phenotypes. The pathological variant mA3243G, a point mutation of mitochondrial DNA MTL1 gene that encodes to synthesis of a transference RNA, is the most common genotype associated with MELAS syndrome, being found in 80% to 85% of patients. The main clinical manifestations of MELAS syndrome are neurological, with stroke-like episodes (SLE), migraines, cognitive deterioration, myopathy, sensorineural hearing loss and epileptic seizures being the most prominent. However, affected patients may also present with a variety of non-neurological disorders (lactic acidosis, cardiovascular disease, endocrinopathies, nephropathy, digestive diseases and nutritional disorders). Recently, Cox et al., in a retrospective study with 81 cases, found that patients with late-onset MELAS (over 40 years of age) have a higher prevalence of these non-neurological complications [3].

In 2012, criteria for the diagnosis of MELAS syndrome were published based on a cohort study with 96 Japanese patients [4]. These criteria involve a combination of clinical manifestations and laboratory findings (Table 1).

The main aim of this narrative review is to discuss in detail the non-neurological manifestations of MELAS syndrome in adulthood.

2. MATERIAL AND METHODS

Utilizing PUBMED and MEDLINE, both databases geared toward biological and health sciences, the authors reviewed literature published between 2012 and 2024. The only search criterion was “MELAS syndrome”. Articles written in English and referring to adult patients were included, while publications without full-text access were excluded. Following this, we separated the papers referring to non-neurological complications in MELAS syndrome that were included in this review.

3. RESULTS

Of the 657 articles identified, only 31 publications referred to non-neurological complications, most of them being case reports. Two articles were excluded due to lack of access to the full text. Non-neurological manifestations were further broken down based on organ system (cardiovascular, renal, digestive, endocrine, etc.). Fifteen papers related to neurological complications of MELAS syndrome were selected by the authors to be included in this narrative review.

3.1. NEUROLOGICAL COMPLICATIONS OF MELAS SYNDROME

The clinical presentation of MELAS syndrome may vary depending on the patient's age, the degree of tissues heteroplasmy, and the type of genetic mutation.

In a retrospective study of 35 patients, Alves et al. Identified two groups (classic MELAS and atypical MELAS) based on distinct significant clinical variables. The classic phenotype includes sensorineural deafness, SLE ≥ 30 mm, cortical blindness, SLE occurring after 10 years of age, and the mA3243G variant group. The atypical MELAS phenotype is characterized by developmental delay, clinical signs suggestive of Leigh syndrome, SLE occurring before 10 years of age, small cerebral lesions in SLE (predominantly located in both cerebellar or anterior regions of the brain), and others gene mutations that encode chain respiratory proteins [5].

A recent multicenter study in China analyzed the records of 1334 patients with confirmed mitochondrial disease, of which 608 patients suffer from MELAS syndrome. The most common neurological disorders in the latter patients were SLE, seizures, headache, and sensorineural hearing loss [6].

3.1.1. STROKE-LIKE EPISODES (SLE)

It is the most distinctive, although non-pathognomonic, disorder of MELAS syndrome, with an estimated prevalence

Table 1: Diagnostic criteria for MELAS syndrome

Category A	Category B
Headache with vomiting	Increased plasma or CSF lactate levels
Seizures	Abnormal mitochondria on muscle biopsy
Hemiplegia	Confirmation of a genetic mutation related to MELAS syndrome
Cortical blindness	
Acute focal lesions of the cerebral cortex	
Definitive MELAS syndrome: 2 items category A + 2 items category B	
Suspected MELAS syndrome: 1 item category A + 2 items category B	

between 31% and 90% of patients [7]. Its presentation is usually subacute, and the more commonly related symptoms are epileptic seizures, visual symptoms (especially cortical blindness) or a sensory-motor focal deficit. Brain MRI images show lesions that simulate an ischemic stroke, but do not have a distribution that corresponds to a defined vascular territory (Figure 1). The lesions predominate in the parietoccipital regions, can occur simultaneously in both hemispheres, are preferentially distributed in the cerebral cortex, and in some patients have an intermittent temporal pattern, disappearing without leaving sequelae [8].

in T2-FLAIR. The presence of hypointense cystic-like lesions inside the cerebral cortex suggests the diagnosis of MELAS syndrome ("black nail sign") [9]. In chronic phases of the disease, the lesions can leave sequelae as encephalomalacia, gliosis and cortical atrophy.

MR spectroscopy is very useful in helping to establish the diagnosis of MELAS syndrome. Typically, there is a decrease in the N-acetyl-aspartate peak and an increase in the lactate peak in acute lesions. In turn, in FDG-PET images the lesions usually show reduced metabolism.

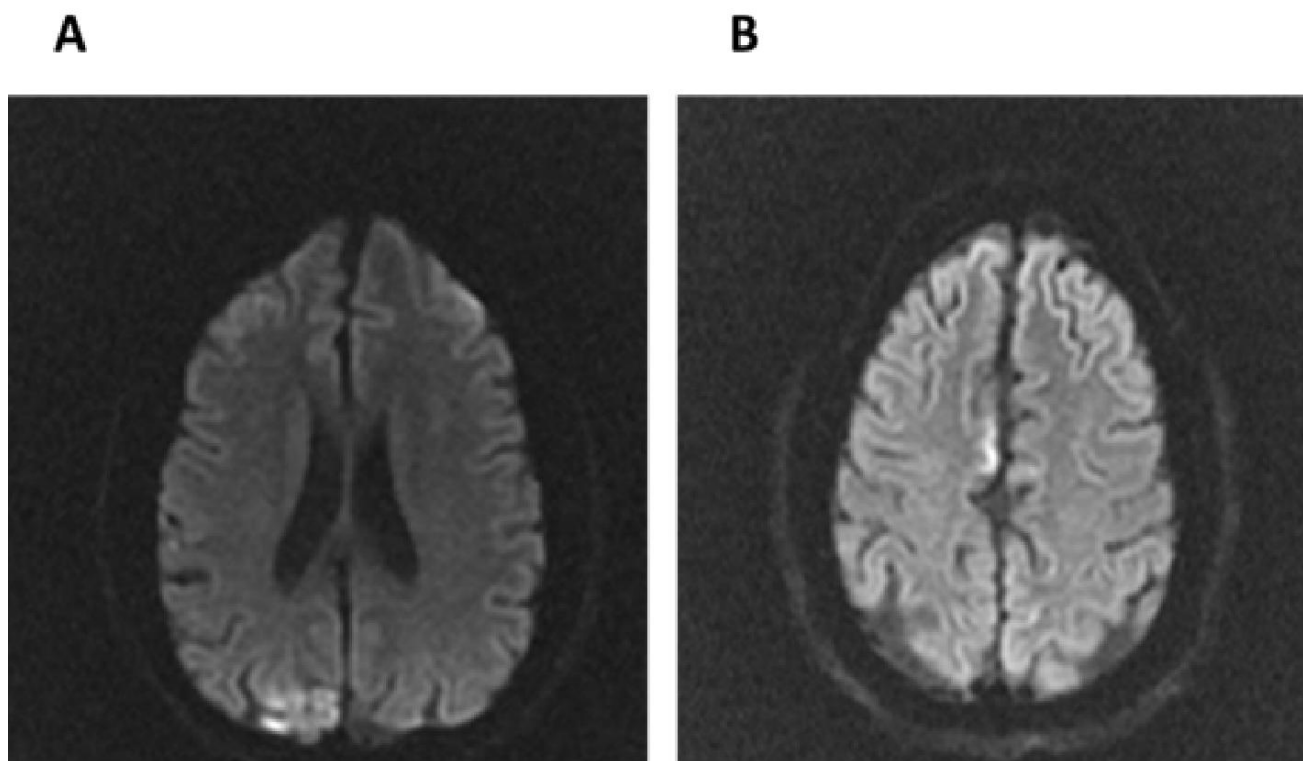


Figure 1: Brain MRI in adult patient diagnosticated with MELAS Syndrome. 24 years old woman with confirmed *mA3243G* mutation and classical MELAS syndrome. Diffusion weighted brain MRI images show two SLE. A: right temporoparietal cortical hyperintensity corresponding to first SLE; B: the same patient, hospitalized two weeks after by another SLE, image shows cortical hyperintensity in the medial right frontal region. The previous lesion is not visible.

SLE are caused by endothelial dysfunction secondary to failure of the mitochondrial respiratory chain and an increase in regional anaerobic metabolism. The cerebral cortex is very sensitive to hypoxia, which explains its vulnerability to damage generated by SLEs. Moreover, seizures can also contribute to triggering SLE by increasing neuronal energy demand.

In the acute phase, brain CT shows hypodense cortical lesions, while MRI T2 and FLAIR weighted images show hyperintensities, and T1 weighted images show cortical edema, and post-contrast linear enhancement. In subacute phases, lesions may show gyri cerebral cortex hyperintensities in T1 weighted images and hypointensities

3.1.2. COGNITIVE IMPAIRMENT

There are few publications focused on the specific study of neuropsychological disorders in patients with MELAS, most of them correspond to clinical cases. The prevalence of cognitive impairment in people with a confirmed diagnosis varies between 40% and 90%, is generally progressive and worsens with each SLE [10]. The most severe forms of MELAS syndrome that begin in childhood occur with a delay or severe intellectual disabilities. Patients who have a late onset may have a normal cognitive level until the onset of the disease.

Mental functions can be globally altered with varying degrees of severity, including dementia. As SLE have a preferential distribution in posterior regions of the brain, it is common for patients to show alterations in tests assessing attention, visuospatial functions, and executive functions [11].

3.1.3. SEIZURES

About 71-90% of patients with confirmed diagnosis of mitochondrial diseases have seizures during the course of the disease, with an estimated prevalence of epilepsy between 10-23% (versus ± 2 -10/1.000 inhab. in the general population). Studies in Europe have shown that in patients suffering from epilepsy-related mitochondrial disease, the m.3243A>G mutation is the most found genotype. In a cohort in the United Kingdom, 34.9% of patients with this mutation developed epilepsy [12, 13].

Focal onset seizures are the most common, which can manifest in the context of an acute episode of SLE or as consequences to previous episodes. Myoclonic seizures are

can also occur at any time during the disease. Cases of status epilepticus are also described, especially in relation to SLE. The electroencephalogram is generally altered with nonspecific findings, highlighting a slowing of the base rhythms and different types of epileptiform activity patterns [14].

The treatment of epilepsy in patients diagnosed with MELAS syndrome is not very different from that used in other etiologies, except that valproic acid should be avoided because it worsens mitochondrial function. Levetiracetam is a good alternative due to its clinical safety profile and its efficacy in the management of different types of seizures, especially myoclonus.

3.1.4. MYOPATHY

It presents with different phenotypes. It is common to observe marked atrophy and generalized muscle weakness. The ocular muscles can also be affected, generating progressive external ophthalmoplegia. Muscle biopsy may be useful for the diagnosis of MELAS syndrome, specially

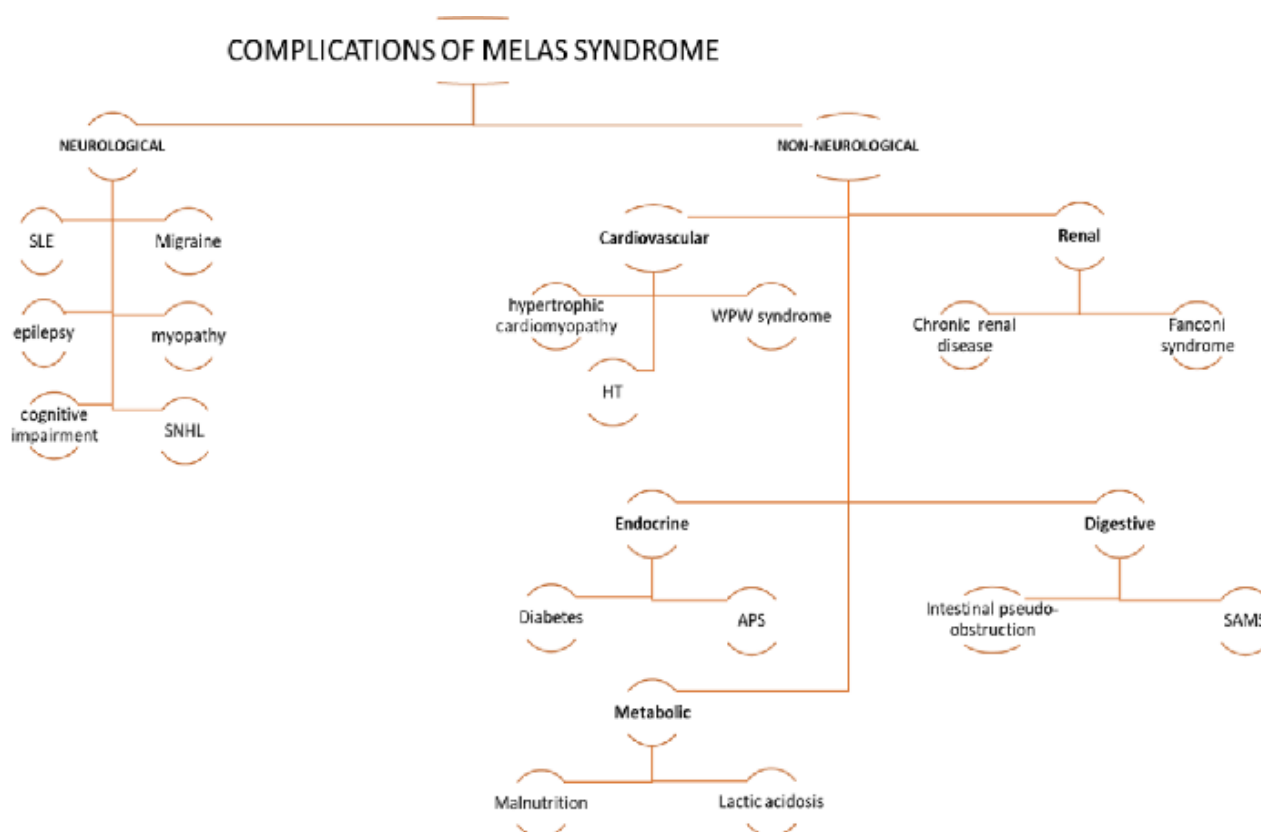


Figure 2: Diagram showing the main medical complications in MELAS syndrome.

SLE: stroke-like episodes; SNHL: sensory-neural hearing loss; WPW: Wolff-Parkinson-White syndrome; HT: chronic arterial hypertension; APS: autoimmune polyglandular syndrome; SAMS: superior arterial mesenteric syndrome.

frequently described in different forms of mitochondrial diseases, including MELAS syndrome. Generalized seizures

if it shows ragged red fibers by abnormal mitochondrial deposits in the sarcolemma. Alterations in COX

(cytochrome C oxidase) and SDH (succinate dehydrogenase) stains reveal abnormalities of oxidative phosphorylation.

3.1.5. MIGRAINE

It is another very common symptom in patients suffering from MELAS syndrome, with a higher prevalence than in the general population (40% to 50%). Migraine tends to present with visual or somesthetic auras and has a lower response to usual treatment [15].

3.1.6. OTHER NEUROLOGICAL DISORDERS IN MELAS SYNDROME

Sensorineural hearing loss is a common disorder, often unnoticed by patients until an audiometric study is performed. Some patients with MELAS may present with the diabetes mellitus-deafness phenotype, described as another clinical pattern of mitochondrial diseases. Involuntary movements such as chorea, tremor, or parkinsonism are rare in patients with MELAS syndrome.

3.2. NON-NEUROLOGICAL COMPLICATIONS OF MELAS SYNDROME

For a better understanding, we divided non-neurological complications into cardiovascular, renal, digestive, endocrine and metabolic (Figure 2).

3.2.1. CARDIOVASCULAR COMPLICATIONS RELATED TO MELAS SYNDROME

Hypertrophic cardiomyopathy is the most described disorder. Its prevalence is not well defined. Niedermayer et al. found that 8 out of 9 patients with MELAS syndrome, carriers of the classic mutation, had signs of hypertrophic cardiomyopathy. In addition, three patients had a shortening of the PR interval and one had an A-V conduction block [16]. Bambrilla et al., after a 16-year follow-up of 21 patients with MELAS syndrome, found eight patients with cardiac involvement, six of them (75%) were diagnosed with hypertrophic cardiomyopathy, while one patient presented with dilated cardiomyopathy and another with persistent pulmonary artery hypertension [17]. Lioncino et al. suggest that hypertrophic cardiomyopathy is the most frequent cardiological disorder in MELAS syndrome, affecting about 40% of patients [18]. Hypertrophic cardiomyopathy is also described in patients with MELAS syndrome who carry mutations other than mA3243G, or in patients with this mutation but with atypical phenotypes [19-23].

The second most common cardiological condition in MELAS syndrome is Wolff-Parkinson-White syndrome [24]. Other studies show that patients with MELAS syndrome have higher prevalence of chronic hypertension compared to the general population, ranging from 41.5% to 58.9% of patients [25, 26]. Dilated cardiomyopathy is also described in a small number of patients with MELAS syndrome [27].

3.2.2. KIDNEY DISEASE RELATED TO MELAS SYNDROME

Chronic renal disease is probably the second most common non-neurological condition in MELAS syndrome. Clinically, the disease mimics Fanconi syndrome due to proximal tubular involvement, which presents with proteinuria, glycosuria and hyperphosphaturia. Kidney biopsy typically shows focal or segmental glomerulosclerosis [28] and renal perfusion abnormalities [29-31]. Chronic kidney disease occurs in patients with different phenotypes or genotypes [32, 33].

Patients with MELAS syndrome may also have acute renal failure. Fukutake et al. describe the case of a patient who died due to acute renal disease related to rhabdomyolysis, whose necropsy showed tubular necrosis with interstitial edema [34].

3.2.3. DIGESTIVE COMPLICATIONS RELATED TO MELAS SYNDROME

A high proportion of patients report gastrointestinal symptoms such as dysphagia, constipation, or diarrhea [35, 36]. The most described disorder is intestinal pseudo-obstruction syndrome, with an estimated prevalence of 40% of patients. It generally presents as an acute and severe complication in advanced stages of the disease, having a high lethality [37, 38].

Other rare disorders include recurrent superior mesenteric artery syndrome, which is characterized by postprandial vomiting, abdominal pain, and radiological images that show great dilation of the upper portion of the digestive tract [39]. Cases of sigmoid volvulus, intestinal perforation [40], and intestinal pneumatosis secondary to necrosis of the mucosa and lamina propria of the intestine have also been described, with the presence of antimitochondrial antibodies in the affected tissue [41].

3.2.4. ENDOCRINOLOGICAL COMPLICATIONS RELATED TO MELAS SYNDROME

The most observed disorder is diabetes mellitus, with an estimated prevalence of 31.9% [42]. It usually begins at an early age, and patients quickly require insulin. The

"maternal diabetes-deafness" phenotype is observed in many patients carrying the A3243G mutation, usually several years before the onset of neurological manifestations [43]. Metformin is contraindicated in patients suffering from MELAS syndrome, as it increases the risk of SLE. Autoimmune polyglandular syndrome has been described in very few cases of patients suffering from MELAS syndrome [44].

3.2.5. METABOLIC COMPLICATIONS RELATED TO MELAS SYNDROME

Although we did not find recent publications on this topic, it is well known that patients diagnosed with MELAS syndrome generally have a short stature and a decreased body mass index, usually related to generalized muscle atrophy.

Lactic acidosis is an important marker for the diagnosis of the disease. However, it is not present in all patients.

4. CONCLUSIONS

MELAS syndrome is a genetic mitochondrialopathy that, in adult-onset patients, presents a wide spectrum of neurological and non-neurological disorders, being a challenge for the practicing internist. A high clinical suspicion is required to establish a definitive etiological diagnosis. The goal of this narrative review is further shed light on the lesser-known manifestations of MELAS syndrome, so that clinicians around the world can make a timely diagnosis and provide prompt treatment.

5. CONFLICT OF INTERESTS

The authors have no conflict of interest to declare. The authors declared that this study has received no financial support.

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