Mitochondrial Encephalomyopathy, Lactic Acidosis, and Stroke-like Episodes (MELAS) Syndrome

Frequency, Clinical Features, Imaging, Histopathologic, and Molecular Genetic Findings in a Third-level Health Care Center in Mexico

Javier A. Galnares-Olalde, MD, Juan C. López-Hernández, MD,**
Edmar O. Benitez-Alonso, MD,† David J.D.-O. de Montellano, MD,†
Raúl N. May-Mas, MD, María E. Briseño-Godínez, MD,**
Esther Y. Pérez-Valdez, MD, Enrique Pérez-Jovel, MD,**
*Francisca Fernández-Valverde, MD,‡ Elizabeth León-Manríquez, MD,**
*and Edwin S. Vargas-Cañas, MD**

Introduction: Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) syndrome, is a multisystemic entity of mitochondrial inheritance. To date, there is no epidemiological information on MELAS syndrome in Mexico.

Case Series: A retrospective, cross-sectional design was employed to collect and analyze the data. The clinical records of patients with mitochondrial cytopathies in the period ranging from January 2018 to March 2020 were reviewed. Patients who met definitive Yatsuga diagnostic criteria for MELAS syndrome were included to describe frequency, clinical, imaging, histopathologic, and molecular studies. Of 56 patients diagnosed with mitochondrial cytopathy, 6 patients met definitive Yatsuga criterion for MELAS (10.7%). The median age at diagnosis was 34 years (30 to 34 y), 2 females and the median time from onset of symptoms at diagnosis 3.5 years (1 to 10 y). The median of the number of stroke-like episodes before the diagnosis was 3 (range, 2 to 3). The main findings in computed tomography were basal ganglia calcifications (33%), whereas in magnetic resonance imaging were a lactate peak in the spectroscopy sequence in 2 patients. Five patients (84%) had red-ragged fibers and phantom fibers in the Cox stain in the muscle biopsy. Four patients (67%) had presence of 3243A > G mutation in the mitochondrial *MT-TL1* gene. One patient died because of status epilepticus.

Conclusions: MELAS syndrome represents a common diagnostic challenge for clinicians, often delaying definitive diagnosis. It should be suspected in young patients with stroke of undetermined etiology associated with other systemic and neurological features.

Key Words: MELAS, mitochondrial, cytopathy, m.3243A > G, stroke-like episodes

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From the *Neuromuscular Disease Clinic; †Neurogenetics Unit; and ‡Neuromuscular Pathology Department, National Institute of Neurology Manuel Velasco Suárez, Mexico City, Mexico.

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Correspondence to: Edwin S. Vargas-Cañas, MD, Neuromuscular disease Clinic, National Institute of Neurology Manuel Velasco Suárez, Insurgentes Sur No 3877, Mexico City 14269, Mexico. E-mail: clinicaneuromuscular.innn@gmail.com.

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Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) syndrome is a multisystemic entity of mitochondrial inheritance.[1] As a group, the reported prevalence of mitochondrial disease is of 6.57 per 100,000 adults of working age. Regarding mitochondrial diseases, 50% of the adults harbor a point mutation related to primary Leber hereditary optic neuropathy, whereas m.3243A > G is responsible for 14% of cases (including oligosymptomatic patients and MELAS).[2,3] To date, there is no epidemiological information on MELAS syndrome in Mexico.

The clinical particularity of MELAS syndrome is the presentation of stroke-like episodes that manifest as hemiparesis, hemianopia, and/or cortical blindness. Other common features include focal or generalized seizures, migraine-like headaches, recurrent vomiting, short stature, hearing loss, and muscle weakness. Several tRNA mutations have been associated with MELAS syndrome. The most prevalent is m.3243A > G in the mitochondrial *MT-TL1* gene which is responsible for 80% of MELAS patients.[4,5]

MELAS syndrome is primarily a clinical diagnosis. Hirano and colleagues proposed in 1992 the first diagnostic criteria for MELAS syndrome, concluding that definite diagnosis requires the presence of encephalopathy, dementia or epileptic seizures, stroke-like episodes in young patients; with evidence of mitochondrial dysfunction demonstrated by an increase in serum lactate or the presence of red-ragged fibers in a muscle biopsy. Support criteria requires normal development, recurrent migraine-like headaches, and vomiting.

The most recent diagnostic criteria for MELAS syndrome were published by Yatsuga and colleagues in 2012. They divide the criteria into 2 categories: clinical symptoms (category A) and studies that define mitochondrial dysfunction (category B) (Table 1; Fig. 1). The definitive diagnosis of MELAS is made if 2 items of category A and 2 items of category B are met. In case only 1 item of category A and 2 of B are met, the diagnosis remains as possible MELAS syndrome.[6]

In Mexico, there are few case reports of MELAS syndrome reported. Nonetheless, the frequency is unknown. In this study we describe the frequency, clinical, imaging, histopathologic, and molecular characteristics of patients diagnosed with MELAS syndrome in a neuromuscular clinic in a third-level health care center in Mexico.

TABLE 1. Clinical, Laboratory, Imaging, Histopathologic, and Molecular Characteristics of MELAS Patients

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Age of initial symptom	24	23	32	24	16	25
Sex	Female	Female	Male	Male	Female	Female
Family history	Seizures (2 cousins), 1 of them had a stroke	Mother with juvenile diabetes mellitus	Sister with seizures (died from status epilepticus)	Uncle with stroke (23 y), aunt with seizures (both of mother side)	Uncle with seizures	Mother and brother with diabetes mellitus
Developmental delay	No	No	No	No	No	No
Stroke-like episodes	Yes	Yes	Yes	Yes	Yes	Yes
Migraine-like headaches	Yes	Yes	No	Yes	No	No
Encephalopathy	Yes	Yes	Yes	Yes	Yes	Yes
Hemiparesis	Yes	Yes	Yes	No	Yes	Yes
Recurrent vomiting	Yes	No	No	Yes	No	No
Seizures	Yes	Yes	Yes	Yes	Yes	Yes
Cortical blindness/ hemianopia	Yes	No	Yes	Yes	No	Yes
Hyperglycemia	Yes	No	No	No	No	Yes
Hipoacusis	Yes	No	No	No	No	No
Myopathy	No	No	No	No	No	Yes
Anxiety	No	Yes	Yes	Yes	No	Yes
Depression	No	Yes	No	No	Yes	Yes
Basal ganglia calcifications	Yes	No	No	Yes	No	No
CT hypointensities	Left and right fronto-parieto-temporo-occipital	Bilateral temporo-occipital	Left and right temporal	Left temporal	Left temporo-parieto-occipital	Left temporo-parieto-occipital
FLAIR hyperintensities (Fig. 1)	Left and right fronto-parieto-temporo-occipital	Bilateral temporo-occipital	Left and right temporal	No	Left temporo-parieto-occipital	Left temporo-parieto-occipital
Serum lactate (mg/dL)	4.5	5.4	4.8	7.5	4.2	4.9
CSF lactate	5.5 mg/dL	NR	NR	NR	NR	NR
Muscular biopsy	NR	Red-ragged fibers, pale COX fibers	Red-ragged fibers, pale COX fibers	Red-ragged fibers, pale COX fibers	Red-ragged fibers, pale COX fibers	Red-ragged fibers, pale COX fibers
Molecular findings	Positive for m.3243A > G	Positive for m.3243A > G	Positive for m.3243A > G	Positive for m.3243A > G	NR	NR
Time to diagnosis since the first symptom (y)	10	1	7	4	2	3
Definition by Yatsuga criterion	Definitive MELAS	Definitive MELAS	Definitive MELAS	Definitive MELAS	Definitive MELAS	Definitive MELAS

CSF indicates cerebrospinal fluid; CT, computed tomography; MELAS, mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes; NR, not registered.

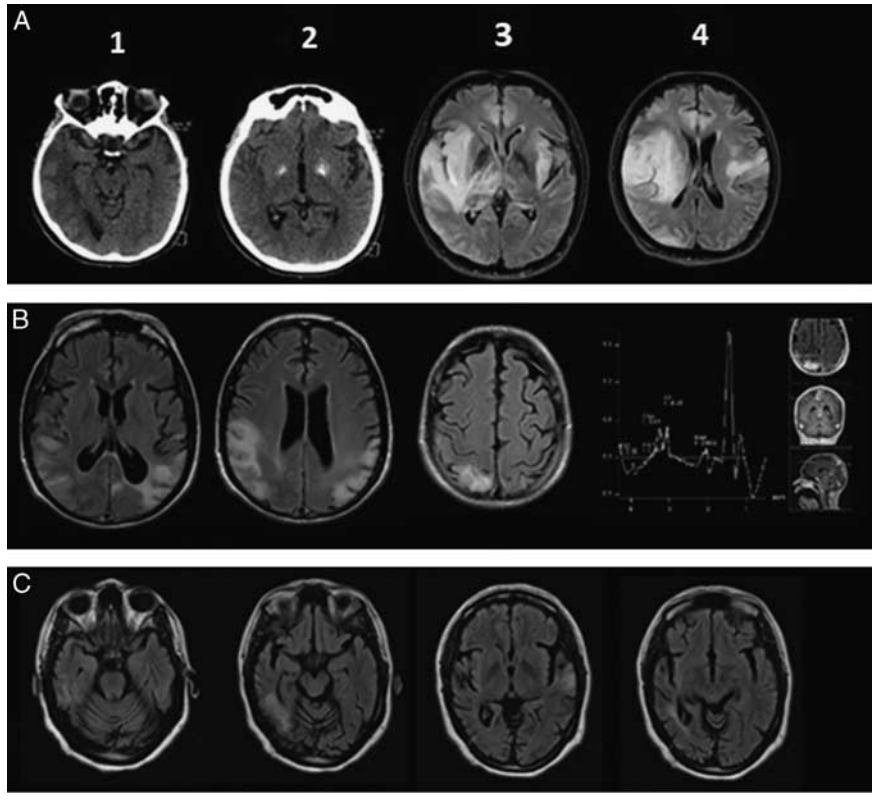

FIGURE 1. Imaging studies of 3 patients. In case (A) a simple computed tomography is observed in the first 2 images, showing a hypodense lesion in the right temporo-parietal cortico-subcortical region and calcification of the bilateral putamen; in images 3 and 4, magnetic resonance imaging (MRI) in the FLAIR sequence shows a cortico-subcortical hyperintense lesion with associated edema without respecting a vascular territory. In case (B) an MRI FLAIR sequence shows multiple bilateral parieto-occipital cortical-subcortical hyperintense lesions, not corresponding to a vascular territory, and in image 4 a lactate peak in the spectroscopy. In case (C) MRI FLAIR sequence shows hyperintense bilateral temporal and occipital cortico-subcortical lesions.

METHODS

A retrospective, cross-sectional design was employed to collect and analyze the data. All the clinical records of patients diagnosed with mitochondrial cytopathy in the National Institute of Neurology Neuromuscular Diseases Clinic in the period ranging from January 2018 to March 2020 were reviewed. Patients who met Yatsuga diagnostic criteria for definitive MELAS syndrome were included. Patients with alternative diagnosis or incomplete data were excluded.

We collected data from the patient's medical records including age of first symptoms, sex, family history, presence or absence of: stroke-like episodes, migraine-like headaches, encephalopathy, hemiparesis, recurrent vomiting, seizures, hyperglycemia, cortical blindness/hemianopia, neurosensorial hypoacusis, myopathy, neuropsychiatric symptoms; serum lactate, cerebrospinal fluid lactate, imaging features, findings on muscular biopsy and molecular analysis.

The biopsy was obtained from the deltoid muscle. The analysis was described based on the findings of hematoxylin and eosin stain, modified Gomori trichrome, and COX stain.

The mutation analysis was performed by the genetics department. A peripheral blood sample was obtained in a 3 mL tube with EDTA to obtain mtDNA from leukocytes using standard procedures. Direct bidirectional sequencing was performed in the *MT-TL1* gene of the mitochondrial genome of each of the peripheral blood samples, comparing the sequence with the reference sequence NC_012920.1.

RESULTS

From our database analysis, 56 patients were diagnosed with mitochondrial cytopathy. Nineteen patients (34%) accounted for progressive external ophthalmoplegia, 11 patients (19.6%) for Kearns-Sayre syndrome, 6 patients (10.7%) for MELAS syndrome, 4 patients (7.1%) for myoclonic epilepsy with red-ragged fibers, 7 patients (12.5%) for oligosymptomatic mutation carriers, and 9 (16.1%) for suspected mitochondrial cytopathy. These last 9 patients with suspected mitochondrial cytopathy were excluded because clinical, laboratory, and molecular findings did not fulfill criteria for MELAS diagnosis, even for a lesser degree of certainty.

Thus, our sample consisted of 6 patients that fulfilled Yatsuga diagnostic criteria. The age interval at the time of first symptom was between 16 and 32 years. Four of our patients were female (67%). Three of our patients' relatives had history of seizures (50%), 2 of stroke (33%), and 2 of diabetes mellitus (33%). None of them had history of development delay. The median of time from the initial symptom to diagnosis was 3.5 years (range, 1 to 10 y).

Table 2 describes the patients' clinical and paraclinical characteristics. All patients (100%) presented with classic MELAS syndrome symptoms: stroke-like episodes, encephalomyopathy, and lactic acidosis.

Three patients had history of migraine-like headaches (50%) and 2 of recurrent vomiting (33%). The principal focal signs associated with stroke-like events were hemiparesis

TABLE 2. Yatsuga Japanese Criteria for MELAS Syndrome

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**
Seizures	Mitochondrial abnormalities in muscle biopsy***
Hemiparesis/hemiplegia	Definitive gene mutation related to MELAS****
Cortical blindness/hemianopia	
Acute focal lesion observed by brain imaging*	

Definitive MELAS: 2 items of category A and 2 items of category B
Supportive MELAS: 1 item of category A and 2 items of category B
*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
****Mitochondrial gene mutations reported in the literature
CT indicates computed tomography; MELAS, mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes; MRI, magnetic resonance imaging.

(83%) and cortical blindness/hemianopia (66%). Other clinical features were hyperglycemia/diabetes (33%), neurosensorial hypoacusis (16%), and myopathy (16%).

Regarding imaging findings, 2 patients had basal ganglia calcifications (33%), whereas 5 patients (83%) presented FLAIR hyperintensities in bilateral fronto-parieto-temporo-occipital regions, and 4 (67%) with temporo-parietal lesions without typical arterial territories, compatible with stroke-like patterns. Two patients presented a lactate peak in magnetic resonance imaging spectroscopy.

All patients had elevated serum lactate (> 2 mg/dL) obtained in at least 2 different samples. Mean value of lactate serum was 5.2 mg/dL (range, 4.2 to 7.5 mg/dL).

Five patients had a deltoid muscle biopsy. All demonstrated red-ragged fibers and pale COX fibers (Fig. 2). Four patients had the pathogenic variant m.3243A > G in the mitochondrial *MT-TL1* gene.

DISCUSSION

Despite recent advances, identification of mitochondrial disorders remains a diagnostic challenge. This is not only due to ignorance of this condition in young adults, but also frequently due to the misinterpretation of diagnostic tests during the clinical approach.[7] This is a problem, because there is a significant delay in the diagnosis as showed in our patients. The reason for this is the late referral of patients to our center.

In most cases, MELAS patients are diagnosed initially as cryptogenic strokes or idiopathic epilepsy, like our patients. Atypical symptoms additional such as encephalopathy, seizures, and recurrent strokes were the most common reasons for referral to our center. However, there was a delay of 3.5 years since symptom onset to definite diagnosis. Although one of the differential diagnosis of stroke in young patients is MELAS syndrome, most hospitals in our country do not have neurology services and neuromuscular disease clinics to approach these patients. We consider that a prompt referral to a specialized center could shorten time to definitive diagnosis.

Stroke incidence in young patients (18 to 49 y) is 8.4 to 13 per 100,000 persons/y. Up to 40% of young patients with stroke have no identified etiology. Genetic and mitochondrial diseases such as MELAS are responsible for 0.8% of stroke causes.[8] An observational study in Mexican population reported that 11% of the patients with stroke under 45 years were labelled as cryptogenic with a mean age of 39.5 ± 5 years.[9] The mean age at diagnosis of MELAS in our population was 24 years (range, 16 to 32 y) and all of them had at least 1 stroke-like episode before the diagnosis was confirmed. For this reason, stroke in young patients without classic risk factors should raise suspicion for MELAS as differential diagnosis.

Features that raise suspicion for MELAS are: recurrent strokes-likes, specific neurological symptoms such as migraine-like headaches, seizures, unexplained or disproportionate encephalopathy; or family history of stroke in young relatives and epilepsy. Half of our patients had family history of seizures, stroke, or diabetes. None of them had a relative diagnosed or previously investigated for MELAS syndrome. Five patients of our series (83%) had a stroke-like episode as their initial symptom, while only 1 (17%) presented with a hyperglycemic crisis. The most frequent initial symptoms of MELAS syndrome reported in the literature are stroke-like episodes, seizures, migraine-like headaches, cortical blindness/hemianopia, or recurrent vomiting episodes.[10] In contrast, the principal symptoms that are sufficiently severe to bring patients to medical attention are: stroke-like episodes and seizures.[11]

Stroke-like episodes present as sudden focal neurological deficits (hemiparesis, aphasia, cortical blindness/hemianopia), associated with seizures (> 90%), migraine-like headaches (75% to 89%), encephalopathy/dementia (> 90%), or nausea/vomiting. In most cases, they have partial/complete recovery in first days after the event.[11]

Imaging is useful to differentiate infarct-like lesions from typical stroke lesions. Computed tomography may show multiple infarcts that involve multiple vascular territories with predilection for parieto-temporal or parieto-occipital regions. Another common finding is basal ganglia calcifications in approximately half of patients with MELAS syndrome.[12] In our series, 33% had basal ganglia calcifications in computed tomography. Nonetheless, in acute presentation findings may be indistinguishable from acute stroke.[13]

Magnetic resonance imaging is more effective in differentiating an acute stroke from MELAS. Stroke-like lesions from MELAS present increased signal on diffusion-weighted imaging with minimal change on adequate diffusion coefficient that suggests vasogenic rather than cytotoxic edema. Another differentiating feature in adequate diffusion coefficient is the gradual spread of the core of the edematous lesion, which has never been described for ischemic stroke. Slow progression of the edema can be also seen from the cortical gray matter to the adjacent white matter. The gray matter of the cortex is particularly sensitive to changes in energy balance with its large energy demand and the majority of the infarct-like lesions in MELAS preferentially involve the gray matter. MR spectroscopy may demonstrate elevated lactate in otherwise normal appearing brain parenchyma.[14]

The most prevalent mutation reported is m.3243A > G (80%) of the *MT-TL1* gene. Even though 80% of MELAS patients have the m.3243A > G mutation, it is not specific for MELAS syndrome. It may also found in patients with

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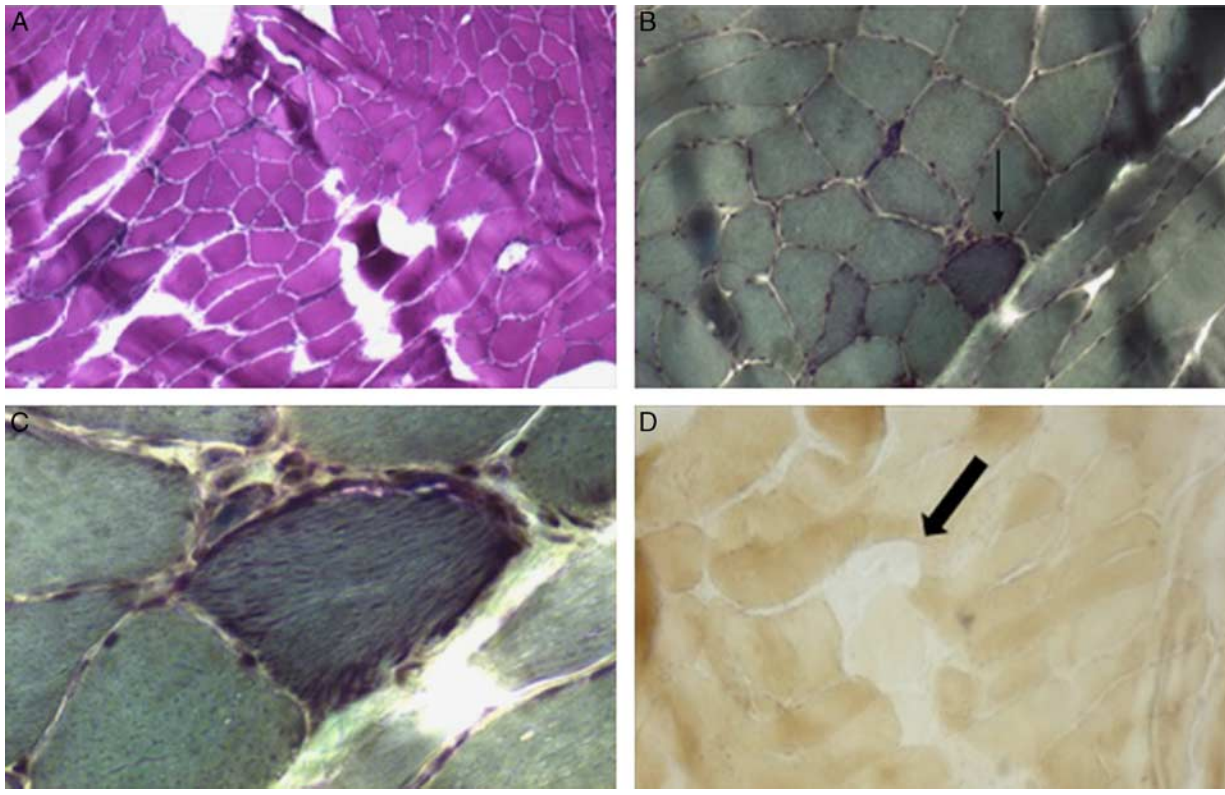

FIGURE 2. Biopsy of the left deltoid muscle of one of our patients (case 3). (A) Hematoxylin and eosin staining shows variability in the shape and size of muscle fibers. (B and C) Gomori modified trichrome stain with torn red fibers (arrow). (D) COX staining with the presence of pale fibers and phantom fibers (thick arrow).

cardiomyopathy, sensorineural hypoacusis, and diabetes with maternal inheritance. This is the reason why MELAS syndrome diagnosis must be built from the combination of symptoms, signs, laboratory and imaging findings, muscle biopsy analysis, and the presence of an identified MELAS-related mutation.[15,16] A Finland study reported an incidence of m.3243A > G mutation in 16.3 per 100,000 in adults.[17] In our country, the incidence is unknown.

The m.3243A > G in the mitochondrial *MT-TL1* gene consists of an adenine-guanine substitution. This affects the structure stability, methylation, and codon recognition by the transfer RNA Leu (UUR). Therefore, the functional level of production of mitochondrial proteins is decreased, causing dysfunction of the respiratory chain. The cascade of events results in decreased mitochondrial ATP production, oxidative stress, decreased nitric oxide, citrulline and arginine production, and nitrogenous reactants accumulation. As a final effect, vascular perfusion is altered.[18] Molecular analysis should not be the only diagnostic criteria for MELAS.

Treatment in these patients is diverse, however, so far none reverses the progression of the disease. L-Arginine has been shown to be useful in inducing nitric oxide synthesis, reversing stroke-like symptoms, or modestly reducing their frequency. Corticosteroids (prednisone, dexamethasone, and methylprednisolone) have also been shown to be useful in stabilizing the mitochondrial membrane and having modest improvement in neurological symptoms. Other drugs with potential benefit are cytochrome *c*, coenzyme Q10, idebenone, levocarnitine, riboflavin, succinate, and thiamine. However, the benefit is modest. No drug has been studied in clinical trials and its use is based on case series or expert recommendations.[19] There are current investigations to establish preventive measures for maternal transmission through mitochondrial replacement therapies, such as Maternal Spindle and Pronucleus Transfer.[20]

Treatment options in Mexico are limited. L-Arginine, idebenone, and cytochrome *c* are not commercially available in our country. Glucocorticoids and coenzyme Q10 are the main options for treating MELAS syndrome in our center. MELAS patients seem to profit from the use of glucocorticoids, but only case reports are available, and no randomized controlled trials have been carried out to investigate the effect in mitochondrial disorders.[21,22] Nonetheless, our patients have shown stabilization and improvement of neurological symptoms with administration of 1 g of methylprednisolone for 5 consecutive days. Coenzyme Q10 in clinical cases has shown that it may improve muscle strength, exercise tolerance, and cognitive function. We used a dose of 200 to 600 mg once a day, with mild clinical improvement.

The presence of m.3243A > G mutation confers a poor prognosis in MELAS syndrome. The mean age of death described in the literature was 34 years, the most frequent causes are epileptic status, intestinal pseudo-obstruction, and cardiomyopathy.[23] One patient of our series died secondary to stroke-like related complications and refractory epileptic status.

CONCLUSIONS

MELAS syndrome represents a diagnostic challenge for clinicians. Stroke-like episodes in young patients, usually

presenting with migraine-like headache, seizures, encephalopathy, and systemic features should raise suspicion for this entity. Prompt referral to specialized centers could shorten the time from symptom onset to diagnosis.

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