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When should MERRF (myoclonus epilepsy associated with ragged-red fibers) be the diagnosis?

Quando o diagnóstico deveria ser MERRF (epilepsia mioclônica associada com fibras vermelhas rasgadas)?

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ABSTRACT

Myoclonic epilepsy associated with ragged red fibers (MERRF) is a rare mitochondrial disorder. Diagnostic criteria for MERRF include typical manifestations of the disease: myoclonus, generalized epilepsy, cerebellar ataxia and ragged red fibers (RRF) on muscle biopsy. Clinical features of MERRF 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 $tRNA^{Lys}$ gene of the DNAmt, mainly A8344G, are responsible for almost 90% of MERRF cases. Morphological changes seen upon muscle biopsy in MERRF include a substantive proportion of RRF, muscle fibers showing a deficient activity of cytochrome *c* oxidase (COX) and the presence of vessels with a strong reaction for succinate dehydrogenase and COX deficiency. In this review, we discuss mainly clinical and laboratory manifestations, brain images, electrophysiological patterns, histology and molecular findings as well as some differential diagnoses and treatments.

Keywords: MERRF, mitochondrial, epilepsy, myoclonus, myopathy.

RESUMO

Epilepsia mioclônica associada com fibras vermelhas rasgadas (MERRF) é uma rara doença mitocondrial. O critério diagnóstico para MERRF inclui as manifestações típicas da doença: mioclonia, epilepsia generalizada, ataxia cerebelar e fibras vermelhas rasgadas (RRF) na biópsia de músculo. Na fase inicial da doença, as manifestações clínicas podem não ser uniformes, e correlação entre as manifestações clínicas e fisiopatologia não estão completamente elucidadas. Estima-se que as mutações de ponto no gene $tRNA^{Lys}$ do DNAmt, principalmente a A8344G, sejam responsáveis por quase 90% dos casos de MERRF. As alterações morfológicas na biópsia muscular incluem uma grande proporção de RRF, fibras musculares com deficiência de atividade da citocromo *c* oxidase (COX) e presença de vasos com forte reação para succinato desidrogenase e deficiência da COX. Nesta revisão, são discutidas as principais manifestações clínicas e laboratoriais, imagens cerebrais, padrões eletrofisiológicos, histológicos e alterações moleculares, bem como, alguns dos diagnósticos diferenciais e tratamentos.

Palavras-chave: MERRF, mitocondria, epilepsia, mioclonia, miopatia.

In 1973, a group of patients with a unique mitochondrial disease, whose common clinical features included mitochondrial myopathy associated with familial myoclonic epilepsy, were first described[1]. In the following decade, additional cases with similar presentations were included in the literature, and on this basis, Fukuhara et al. gave the best characterization of the disease, which they referred to as MERRF (Myoclonus Epilepsy associated with Ragged-Red Fibers)[2]. The disease was so named because the patients all had myoclonus epilepsy and mitochondrial dysfunction was found upon muscle biopsy[2].

The MERRF diagnostic criteria described in 1980 by Fukuhara et al included as typical manifestations of the disease the following: myoclonus, generalized epilepsy, cerebellar ataxia and ragged-red fibers (RRF) on muscle biopsy[2].

Cases previously reported in the international literature which fit a possible diagnosis of MERRF were reviewed, reinforcing the presence of the myoclonus, epilepsy, ataxia and RRF as diagnostic criteria required for the disease[3,4]. Although the main manifestation of this group of patients with mitochondrial disease is the presence of myoclonus

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and epilepsy, other multisystemic alterations can be found as follows: deafness, exercise intolerance, dementia, peripheral neuropathy, short stature, abnormal cardiac conduction, cardiomyopathies, opthalmoparesis, pigmentary retinopathy, and lipoma, among others[3,4].

In Brazil, the first report of MERRF was made by Arruda et al in 1990 who described a family in which three siblings had myoclonic epilepsy associated with dementia, cerebellar ataxia, muscle weakness and sensory neuropathy[5]. The siblings all showed an elevation of lactic acid, electroencephalogram (EEG) with photoparoxysmal response, muscular COX activity deficiency, muscle biopsy with ragged-red fibers (RRF) and abnormal mitochondria as viewed by electron microscopy. Since this first description in Brazil, few MERRF patients have been described in the country to date[5,6].

Two other important medical landmarks are ascribed to MERRF. MERRF was the first human disease in which a maternal inheritance pattern was clearly demonstrated, suggesting a defect in mtDNA. MERRF was also the first disease in which a molecular defect was associated with a particular form of epilepsy[7,8,9].

WHAT IS THE PATHOGENESIS?

MERRF is a mitochondrial disease caused by pathogenic mutations usually in DNAmt. The pathogenesis of the disease depends upon the relative proportions of mutant and wild-type DNAmt and the threshold of vulnerability to mitochondrial dysfunction of each tissue. Correlations between clinical manifestations and physiopathology in MERRF patients are not fully elucidated, and two main hypotheses have been considered to explain its pathogenesis (Figure 1):

(1) neuronal hyperexcitability, which suggests the presence of an "intracellular ion disturbance" (sodium, potassium and calcium) triggering an abnormal threshold in the action potential of the neuronal membrane that could lead to changes in the pattern of the neuronal excitability and synaptic transmission in some areas of the brain tissue[10,11].

(2) neuronal loss, which suggests that a "mitochondrial cytopathy" triggers an energy failure in some areas of the brain causing neuronal death[10,11].

However, neither of these hypotheses alone could explain comprehensively all of major disease manifestations in MERRF patients, and similar presentations can occur in other mitochondrial diseases. The formation of ATP in mitochondria is essential for both the excitability and self preservation of the neuron[10,11]. Thus, the mechanisms that trigger the main manifestations are correlated with a combination of neuronal loss and hyperexcitability dysfunction, perhaps

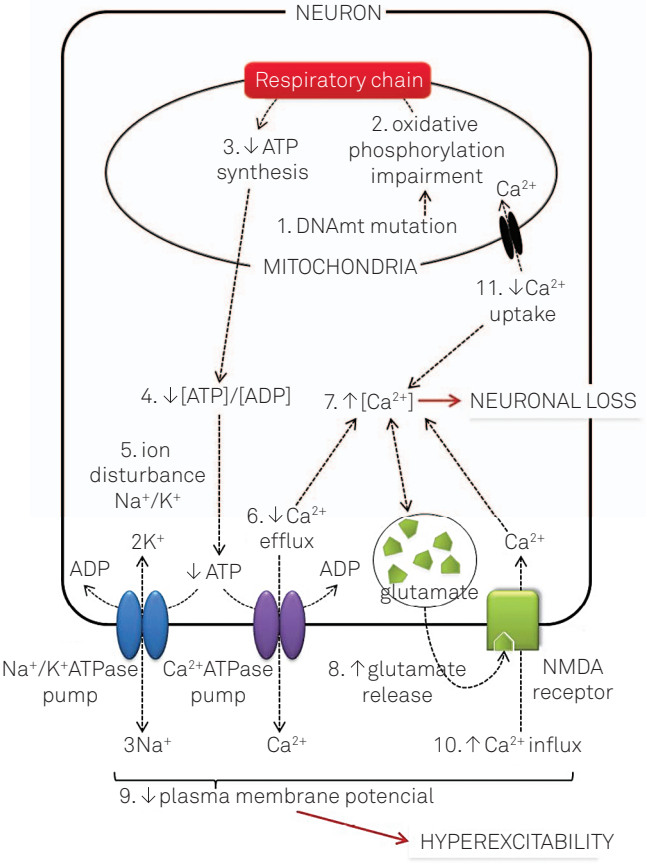

Figure 1. The mechanism of "intracellular eletrolytic disturbance" (sodium, potassium and calcium) proposed to cause neuronal loss and hyperexcitability dysfunction in MERRF patients (adapted with permission from JAMES et al.)[11].

both, initiated by the failure of oxidative phosphorylation in specific areas of the brain tissue, and they may be responsible for the pathogenesis of the major clinical manifestations of MERRF patients (Figure 2)[10,11].

WHAT ARE THE GENETIC ABNORMALITIES?

In 1990, Shoffner et al and Yoneda et al, described a point mutation, affecting the mtDNA gene encoding the RNA transporter of lysine ($tRNA^{Lys}$) at position 8344 by exchange of the nucleotide A for G (A8344G), in the muscle of patients with MERRF[8,9]. This mitochondrial $tRNA^{Lys}$ gene, also known as *MT-TK* or *TRNK*, is located between nucleotides 8295 and 8364 on the mtDNA, and it is responsible for decoding the codons AAR (R = A or G)[12]. After this initial description, other studies have shown that the A8344G mutation is responsible for most cases of MERRF[13].

In the years following the discovery of the A8344G mutation, three additional point mutations have also been found in patients with MERRF in the $tRNA^{Lys}$ gene of mtDNA as follows: T8356C, G8361A and G8363A[14,15,16]. The T8356C

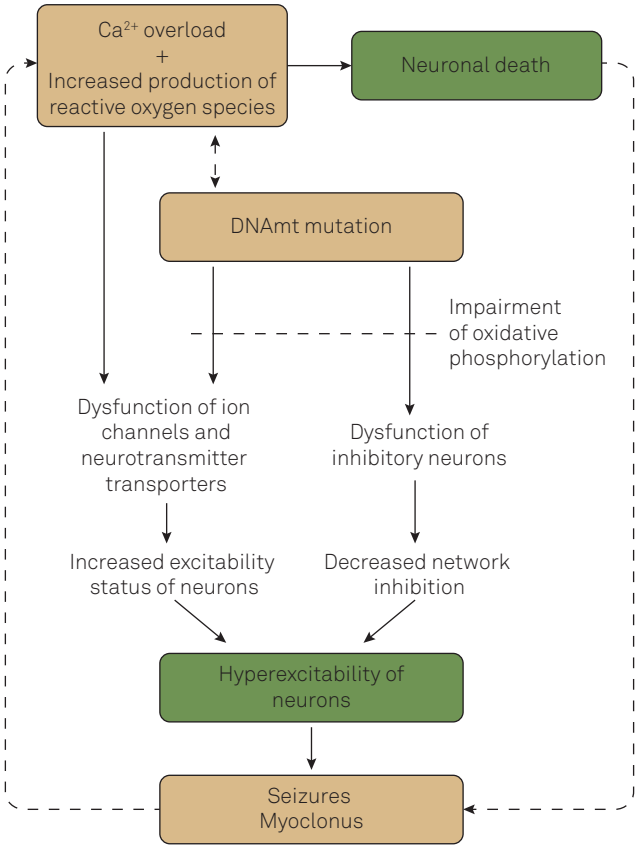

Figure 2. A combination of mechanisms that may be responsible for triggering the major manifestations of MERRF (adapted with permission from Folbergrová and Kunz)[10].

point mutation was found in patients with MERRF who also had stroke-like episodes, suggesting an overlap between MERRF and mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS)[16,17]. The A8361G point mutation was described in patients associated with MERRF manifesting with deafness and dementia[14]. The G8363A point mutation appears to be related to the presence of cardiomyopathy and deafness in patients with MERRF, and, in some cases, it overlap with Leigh syndrome[15,18,19,20].

Over the years, the few point mutations in mtDNA that have been found in patients with MERRF have usually been in the $tRNA^{Lys}$ gene of mtDNA or have overlapped with other mitochondrial diseases (Table 1). Thus, it is estimated that the A8344G mutation remains responsible for over 80% of MERRF patients: mutations T8356C, G8361A and G8363A account for approximately 10%[13,21,22,23]. The remaining mutations account for less than 5% of cases, but up to 10% of MERRF patients have still no identifiable mutations in mtDNA[13,21,22,23].

The A8344G mutation appears to be specific to patients with MERRF, because this mutation has rarely been described in other mitochondrial diseases, even without the presence of myoclonus or epilepsy[24,25]. Additionally, MERRF patients who present with other mutations in mtDNA have usually been reported to present with another mitochondrial disease, such as MELAS, Leigh syndrome, Kearns-Sayre syndrome, NARP, neuropathy, deafness or

Table 1. Published mutations in mitochondrial (DNAmt) and nuclear (DNAn) DNA associated with MERRF.

Mutation	Gene	Reference
DNAmt point mutation		
nt-611 (G>A)	*tRNA-Phe*	Mancuso et al. (2004)
nt-3243 (A>G)	*tRNA-Leu(UUR)*	Crimmins et al. (1993)[1]
nt-3255 (G>A)	*tRNA-Leu(UUR)*	Nishigaki et al. (2003)[5]
nt-3291 (T>C)	*tRNA-Leu(UUR)*	Emmanuele et al. (2011)[5]
nt-4284 (G>A)	*tRNA-Ile*	Hahn et al. (2011)
nt-5521 (G>A)	*tRNA-Trp*	Herrero-Martín et al. (2010)[1]
nt-7512 (T>C)	*tRNA-Ser(UCN)*	Nakamura et al. (1995)[1]
nt-8344 (A>G)	*tRNA-Lys*	Shoffner et al. (1990) Yoneda et al. (1990)
nt-8356 (T>C)	*tRNA-Lys*	Silvestri et al. (1992)[1]
nt-8361 (G>A)	*tRNA-Lys*	Rossmanith et al. (2003)[4]
nt-8363 (G>A)	*tRNA-Lys*	Santorelli et al. (1996)[2]
nt-12147 (G>A)	*tRNA-His*	Melone et al. (2004)[1]
nt-12300 (G>A)	*tRNA-Leu(CUN)*	Martín-Jiménez et al, (2012)[7]
nt-13042 (A>T)	*ND5*	Naini et al. (2005)[1]
nt-15967 (G>A)	*tRNA-Pro*	Blakely et al. (2009)[6]
DNAmt rearrangement		
multiple deletion	-	Blumenthal et al. (1998)[3]
DNAn missense mutation		
multiple deletion	*POLG*	Van Goethem et al. (2003)[3]

MERRF associated with: [1]: MELAS; [2]: Leigh syndrome; [3]: sensitive neuropathy; [4]: deafness and dementia, cardiomyopathy and deafness; [5]: Kearns-Sayre syndrome; [6]: deafness and retinopathy; [7]: NARP; nt: nucleotide. MERRF: myoclonus epilepsy associated with ragged-red fibers. MELAS: mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes.

pigmentary retinopathy (Table 1). Although the mitochondrial diseases caused by point mutations of mtDNA have heterogeneous phenotypes, the phenotype of patients with the A8344G point mutation usually results in MERRF.

In rare cases, the presence of rearrangement type deletion in mtDNA or the presence of recessive missense mutations in polymerase gamma (POLG) gene in nuclear DNA has been associated with MERRF (Table 1).

The proportion of mutant mtDNA appears to be similar in the majority of the different tissues affected in MERRF patients[18,20,26]. This observation allows the mtDNA used for the molecular study of patients with MERRF to be extracted from peripheral blood leukocytes, achieving results similar to those of patients with mtDNA extracted from muscle and making it easier to identify MERRF patients.

WHAT ARE THE CLINICAL FEATURES?

Clinical symptoms are highly variable among patients with mitochondrial diseases[4,22]. 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[22,24,27,28].

A clinical follow-up scheme was recently reported by Mancuso et al for patients with the A8344G mutation (Table 2)[28]. We believe that this scheme could be used with MERRF patients, even though larger prospective studies are needed to obtain a complete picture of the natural history of this disease and clinical symptoms may occur with a different frequency in patients with MERRF, depending upon the type of mtDNA point mutation[4,28,29]. Similar manifestations occur in patients with the T8356C mutation, who have some overlap of symptoms such as stroke-like with MELAS, as well as in patients with the G8363A mutation who have cardiomyopathy[4,28,29].

Although the onset of clinical manifestation often occurs in childhood and early adulthood, a late onset in adults is not uncommon in patients with MERRF[4,30]. Moreover, the age of onset may be different among affected members of the same family[22]. Psychomotor development in children is usually normal in almost all patients with MERRF[4]. Affected parents of MERRF patients can be found and family history may be positive in up to 50% of cases when muscle biopsy or genetic studies are performed in asymptomatic or mildly symptomatic family members[4,22,24,31,32].

However, as the presence of myoclonus and epilepsy are diagnostic criteria for MERRF, it is expected that all patients have both clinical manifestations[4,22]. The myoclonus may occur alone or in association with generalized seizures[4,30].

The presence of clonic or myoclonic seizures, with electroencephalographic correlation, is greater in the chronic than in the initial phase of the disease[33]. Generalized seizures are frequently observed in different forms of myoclonic epilepsy, mainly associated with mutations in the $tRNA^{Lys}$ and $tRNA^{Ser}$ genes of mtDNA. Partial seizures are most commonly found in mitochondrial encephalopathies, such as MELAS associated with mutations in the $tRNA^{Leu}$ gene[8,9,33,34].

In MERRF, myoclonus are clinically indistinguishable from those presented by patients with other myoclonic diseases (irregular rhythm, which may increase with movement or stimuli), but their pathogenesis has not been fully elucidated, most likely because, like most of the diseases that cause myoclonus, there are multiple affected structures in the CNS. Regarding the type of myoclonus and its origin in the central nervous system, there is substantial evidence indicating the occurrence of more cortical myoclonus than subcortical type, although both may occur in patients with MERRF[34].

Cerebellar ataxia is one of the most common clinical manifestations of MERRF and is supportive of the diagnostic criteria of MERRF, occurring in up to 83% of cases[6,35]. The presence of manifestation cerebellar ataxia is an important

Table 2. Follow-up scheme for A8344G patients suggested by Mancuso et al. in 2013.

	Time interval between assessments
Clinical assessments	
Neurologic examination	6 months
Cardiologic evaluation with echocardiography and ECG	12 months (or 3-6 mo after the development of heart disease)
Ophthalmologic evaluation with fundoscopy	18 months (or less in symptomatic patients)
Respiratory function tests	24 months (or 3-6 mo after the development of respiratory involvement)
Swallowing evaluation	24 months (or 6 mo after the development of swallowing impairment)
Audiologic assessment	24-36 months (or less in symptomatic patients)
Psychiatric evaluation	24-36 months (or less in patients with clinically apparent psychiatric involvement)
Neuropsychological tests	36-48 months (or less in patients with clinically apparent cognitive impairment)
Laboratorial assessments	
CK and lactate	6 months
Thyroid hormones, glucose, liver and kidney function, complete blood count	24-36 months (or less in some instances, e.g., treatment with new antiepileptic drugs)

indicator in patients with MERRF, although it may not be present in the early phase of the disease[27,34]. However, clinical and radiological findings in patients with MERRF vary and may suggest spinocerebellar degeneration, especially in early phase of the disease[36]. Similarly, atrophy of the superior cerebellar peduncle and cerebellum, in addition to changes in the brain and basal ganglia, suggest MERRF, especially in patients with a dissociation between clinical manifestation with severe cerebellar symptoms and radiological manifestation with mild abnormalities[36].

WHAT ARE THE IMAGING FEATURES?

MERRF preferentially involves the inferior olivary nucleus, cerebellar dentate nucleus, red nucleus and pons of the brainstem, as well as the gray matter[22,34,37]. Conventional imaging studies of the brain, such as computed tomography or magnetic resonance imaging, have confirmed that the gray matter is altered early on in patients with MERRF, while changes in the white matter can be seen more often in the later stages of the disease and are never an isolated finding[37,38]. Cerebral, cerebellar and brainstem atrophy occurs as a result of progressive neuronal loss[4,36,39]. Thus, one expects to find in patients with MERRF frequent cortical atrophy, predominantly in the brain and cerebellum, and discrete changes in the inferior olivary nucleus, cerebellar dentate nucleus, red nucleus and pons of the brainstem.

WHAT ARE THE LABORATORY AND BIOCHEMICAL FEATURES?

The lactic acid level in the blood and cerebrospinal fluid (CSF) is elevated at rest in patients with MERFF and can increase moderately after physical activity[4,27]. These high lactic acid serum levels can also be found in the asymptomatic family members of patients with MERRF[24]. The level of ventricle lactic acid, measured by spectroscopy, is usually increased in most patients with MERRF and in their families, but these levels are lower overall than those found in patients with MELAS[4]. Other tests may be used in initial investigation, such as dosages of creatine kinase (CK), but their results are not specific for MERRF, mainly helping to differentiate the diagnosis from other diseases. Thus, although nonspecific to demonstrate mitochondrial myopathy, serum CK may be slightly increased in some patients and may demonstrate muscle involvement in these patients[40,41]. The CSF protein level is also high in 1.6-8% of patients, but it generally does not exceed 100mg/dl[4,31]. A laboratory scheme suggested by Mancuso et al could also help in the follow-up of the patients with the A8344G mutation (Table 2)[28].

Biochemical studies have shown that several complexes of respiratory chains can be disabled either in isolation or in combination. Complexes I and IV seem to be more involved in the respiratory chain in patients with MERRF, and they are usually associated with changes in other respiratory chain complexes, whereas complex II seems to be the least affected[8,23,27,34,42,43,44]. The number of muscle fibers with deficient activity of COX observed upon muscle biopsy suggests that respiratory chain complex IV could be one of the complexes that are most affected in MERRF patients[45,46,47,48,49,50,51,52,53,54,55,56,57]. This reasoning can also be supported by the fact that patients with MERRF who have the A8344G point mutation also exhibit a high frequency of muscle fibers (RRF and no-RRF) with deficient COX activity upon muscle biopsy[26,45,48]. In contrast to patients with MELAS, patients with point mutations of A3243G show a high incidence of RRF fibers with a normal COX histochemical reaction[26,45,48]. The biochemical analysis of respiratory chain complexes may be normal in some cases[27,34].

WHAT ARE THE ELECTROPHYSIOLOGICAL FEATURES?

The EEG of patients with MERRF usually exhibits variation in the degree of slowing of background activity and generalized epileptiform activity, which may worsen with intermittent photic stimulation[27,33,49,50,51]. Epilepsy can be observed in other mitochondrial disorders, and, hence, patients with other mitochondrial diseases may exhibit changes in EEG similar to those of patients with MERRF[33]. However, patients with MERRF show fewer focal EEG signs than patients with MELAS or Leigh syndrome[33,51]. Moreover, EEG reveals abnormalities in patients with MERRF that closely resemble those found in other progressive myoclonic epilepsies[49,50,51]. Additionally, photoparoxysmal response to EEG can be observed both in patients with MERRF and in patients with other mitochondrial myopathies such as MELAS or Leigh syndrome or other overlapping syndromes[33,50]. Intermittent photic stimulation is occasionally described to trigger seizures in patients with MERRF[51].

Needle electromyography and nerve conduction studies are consistent with the myopathic process in patients with MERRF, but neuropathy can coexist in some patients. The presence of alterations in the needle electromyography shows that changes in muscle fibers occur in approximately 50% of patients with MERRF[27]. However, these changes in needle EMG can vary depending upon when the test is performed and the severity of the disease, presenting with a myopathic, neurogenic or mixed (myopathic and neurogenic) pattern[27]. Because neuropathy may occur in patients with MERRF, nerve conduction studies also have utility for the evaluation of these patients, showing

the presence of motor and sensory axonal neuropathy in most cases[4,50,51].

WHAT ARE THE HISTOLOGICAL FEATURES?

The muscle biopsy is an important diagnostic tool for MERRF because RRF are found in over 92% of patients with this disease (Figure 3)[4,22,27]. Initially, the muscle biopsy may show only muscle fibers with subsarcolemmal accumulation of mitochondria without forming typical RRF, but virtually all patients with MERRF present RRF during the evolution of the disease[40,45,52]. RRF frequency is usually greater in the histochemical reaction for succinate dehydrogenase (SDH) than in staining by modified Trichrome Gomori (TGM), as is the case in other mitochondrial diseases[40,45,52]. The absence of RRF is rarely be observed in muscle biopsies from patients with MERRF[18,22,34,46]. The degree of heteroplasmy (proportion of normal and mutant mtDNA in each tissue) is also an important factor influencing the variability of muscle biopsy findings[18,27]. A quantitative analysis shows that 80 to 90% of muscle fibers have a higher amount of mtDNA (normal and mutant), and the proportion of mutant mtDNA is extremely high in RRF when compared with fibers that do not form RRF[18,27,53].

The morphological changes observed in muscle biopsies that can help distinguish MERRF from other mitochondrial diseases are as follows: (1) a large proportion of muscle fibers (RRF and no-RRF) that have deficient activity of cytochrome *c* oxidase (COX), and (2) the presence of COX deficient vessels with a strong reaction for SDH[45,46,47].

COX activity in muscle fibers is decreased or absent in most patients with MERRF (Figure 3)[4,27,45,54,55]. As mentioned previously, the presence of COX- fibers in patients with MERRF is greater than that found in other mitochondrial diseases, such as MELAS, demonstrating that different mutations of mtDNA may influence the histological findings in different mitochondrial disorders[40,45,46,47,48,52].

The presence of vessels in the muscle biopsy, usually arterioles, with a strong reaction to SDH (SDH+) can be found more often in patients with MELAS or MERRF than in PEO patients[40,52,56,57]. Histological studies of MERRF patients, regardless of the type of point mutation, have shown that the incidence of vessels with a strong reaction to SDH (SDH+) is below 8%[4]. However, these vessels can be found in up to 50% of arterioles intramuscularly in patients with the A8344G mutation, showing that the incidence of this change may also be related to the type of mutation in the mtDNA of the patient[27,57]. The SDH+ vessels found in patients with MERRF are also deficient in COX, unlike in MELAS, suggesting that, in these patients, the COX deficiency has greater relevance to the pathophysiology of the disease[43,57].

WHAT ARE THE MAIN DIFFERENTIAL DIAGNOSES?

MERRF should be considered in the differential diagnosis of all progressive myoclonic epilepsies, including Lafora disease, neurolipofuscinose and Unverricht-Lundborg disease[49,50,51].

In other diseases with epilepsy, myoclonus and ataxia, the affected structures of the CNS have similar locations, but different types of lesion. Thus, in a review of some of the cases previously diagnosed as Friedreich's ataxia, atrophy dentate palido-red-luisiana or Ramsay-Hunt syndrome, a diagnosis of MERRF has been found[22,34,51]. Additionally, patients with cerebellar ataxia, myoclonus and lipomas, initially described by Ekbom in 1975, have

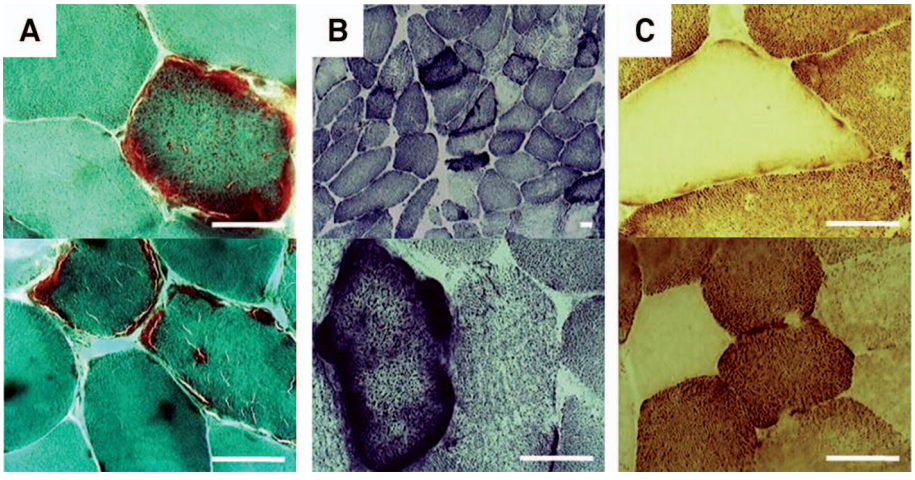

Figure 3. Classic muscle biopsy features of MERRF: (A) ragged-red fibers (RRF) stained with modified Gomori-trichrome; (B) RRF stained with succinate dehydrogenase (SDH); and (C) deficient muscle fiber activity using a cytochrome *c* oxidase (COX) stain. Bar=50 μm.

the same mtDNA mutation as found in patients with MERRF, suggesting that these patients have MERRF[34,58,59].

These findings strengthen the hypothesis that neuronal loss plays an important role in the pathophysiology of these diseases. In addition, this clinical, and sometimes pathological, similarity also suggests these alternative diseases as candidates in the differential diagnosis of patients with MERRF.

WHAT IS THE TREATMENT?

As with other mitochondrial diseases, there is no specific treatment for MERRF[4,49]. 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 of the extant therapeutic strategies have been adopted based upon the results of isolated case reports or limited clinical studies that have included a heterogeneous population of patients with MERRF or other mitochondrial disorders. The therapeutic compounds that have been used in treatment are mainly meant to improve respiratory chain function or to reduce the levels of reactive oxygen species arising from disrupted mitochondrial metabolism. Some of the most frequently prescribed agents include ubidecarenone (coenzyme Q10, CoQ), B complex vitamins and levocarnitine (L-carnitine). The concomitant administration of these different drugs can be useful in some MERRF patients. Medications with potential to increase mitochondrial toxicity should be recognized and avoided.

In addition, MERRF management includes additional therapy for complications, for example, cardiac disease, diabetes mellitus, deafness, myoclonus or epilepsy. The main symptomatic treatments include drugs used to control myoclonus and epilepsy[4,49]. The myoclonus is often refractory to conventional treatment, but clonazepam and zonisamide can be used in these patients[4]. Treatment of epilepsy in mitochondrial disorders is generally not at variance from treatment of epilepsy due to other causes. The management of epilepsy in MERRF includes antiepileptic drugs, as phenobarbital, phenytoin, carbamazepine, gabapentin, lamotrigine, benzodiazepines and zonisamide[6]. We are not aware of any controlled studies comparing the efficacy of different antiepileptic drugs in MERRF. Valproate is the first-line antiepileptic drug for generalized seizures and myoclonic epileptiform abnormalities[49]. Valproic acid is considered to be one of the drugs of first choice in progressive myoclonic epilepsy, but in the treatment of patients with MERRF, its use is usually empirical[6,49]. In addition, valproic acid causes inhibition of carnitine uptake and should be used with caution when treating patients with MERRF, and whenever possible, it should be combined with L-carnitine to prevent the worsening of the mitochondrial dysfunction[4,49].

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