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Review

Management of epilepsy in MERRF syndrome

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ABSTRACT

Myoclonic epilepsy with ragged-red fibers (MERRF) syndrome is a rare syndromic mitochondrial disorder (MID) with a broad phenotypic but narrow genotypic heterogeneity. One of the predominant phenotypic features in addition to myopathy is epilepsy. The most frequent seizure type in MERRF is generalised myoclonic seizure but also focal myoclonic, focal atonic, generalised tonic-clonic, generalised atonic, generalised myoclonic-atonic, typical absences, or tonic-clonic seizures of unknown onset have been reported. There are no guidelines available for the management of epilepsy in MERRF syndrome but several expert opinions and general recommendations for the treatment of mitochondrial epilepsy have been published. According to these recommendations the antiepileptic drugs (AEDs) of choice are levetiracetam, topiramate, zonisamide, piracetam, and benzodiazepines. Perampanel has not been applied in MERRF patients but is promising in non-mitochondrial myoclonic epilepsy. Mitochondrion-toxic agents, including mitochondrion-toxic AEDs, such as valproate, carbamazepine, phenytoin, and barbiturates, should be avoided as well as AEDs potentially enhancing the frequency of myoclonus, such as phenytoin, carbamazepine, lamotrigine, vigabatrin, tiagabine, gabapentin, pregabalin, and oxcarbazepine.

1. Introduction

Myoclonic epilepsy with ragged-red fibers (MERRF) syndrome is a rare syndromic mitochondrial disorder (MID) with a broad range of clinical manifestations (Table 1) and a less heterogeneous genotype [1]. MERRF is most frequently due to mutations in the tRNA(Lys) gene (m.8344A>G, m.8356T>C, m.8363G>A) [2] but rarely also due to mutations in the MT-TL1/tRNA(Leu) (m.3291T>C) [3,4], tRNA(Ile) (m.4279A>G) [5], MT-TF/tRNA(Phe) [6], or MT-TP/tRNA(Pro) [7] genes respectively. Clinically, MERRF does not only manifest with epilepsy and myopathy but also with abnormalities of the eyes, ears, endocrine organs, heart, gastrointestinal tract, and the skin (Table 1). However, epilepsy is the most prevalent manifestation of MERRF and requires particular attention since it is a dominant feature of the phenotype and difficult to treat. This review aims at summarising and discussing current and previous findings concerning the management of epilepsy in MERRF patients.

2. Methods

Data for this review were identified by searches of MEDLINE, Current Contents, EMBASE, Web of Science, Web of Knowledge, LILACS, SCOPUS, and Google Scholar for references of relevant articles. Search terms used for these databases were “MERRF”, “myoclonic epilepsy with ragged-red fibers”, or “m.8344A>G”, combined with “epilepsy”, “seizures”, “antiepileptic drugs”, and “antiepileptic treatment”. Results of the search were screened for potentially relevant studies by application of inclusion and exclusion criteria for the full texts of the relevant studies. Included were randomized controlled trials (RCTs), observational studies with controls, case series, and case reports. Reviews, editorials, and letters were not included. Only original articles about humans, and published between 1966 and 2016 were included. Reference lists of retrieved studies were checked for reports of additional studies.

3. Results

3.1. Literature search

By searching the literature according to the criteria mentioned above, the number of hits achieved was 504. By filtering these results through exclusion of articles on non-human subjects, of

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Table 1
Clinical manifestations of MERRF syndrome.

Organ/tissue	Manifestation	Reference
Brain	Myocloni	[33,34]
	Epilepsy	[34]
	Migraine, migraine-like	[33]
	Cognitive impairment, dementia	[33]
	Optic atrophy	[33]
	Tremor	[33]
	Cerebellar ataxia	[34,35]
	Depression	[36]
	Parkinson syndrome	[37,38]
	Dystonia	[14]
	Dyskinesia	[14]
	Bulbar involvement	[2]
	Stroke-like episodes	[28,39]
	Leucencephalopathy	[40]
	Bilateral thalamic lesions	[41]
	Psychiatric disease	[42]
	Leigh syndrome	[8,43]
	Elevated CSF protein	[44]
Skeletal muscle	Myopathy	[34]
	Respiratory involvement	[34,45]
	Exercise intolerance	[33]
	Elevated creatine-kinase	[46]
	Myalgia	[33]
	Ptosis	[45]
	Ophthalmoplegia	[47]
Eyes	Visual impairment	[48]
	Pigmentary retinopathy	[46]
	Cataract	[14]
Ears	Hypoacusis	[33]
Endocrine organs	Diabetes	[33]
	Short stature	[46]
	Hypothyroidism	[14]
Heart	Arrhythmias	[34,44,49]
	Cardiomyopathy	[1]
Gastrointestinal	Chronic pancreatitis	[50]
	GI dysfunction (paralytic ileus)	[51]
	Diarrhea	[2]
	Vomiting	[14]
	Dysphagia	[14]
Peripheral nerves	Polyneuropathy	[34]
Bone marrow	Anemia	[52]
Skin	Multiple lipomatosis	[33]
	Psoriasis	[2]
Other	Lactic acidosis	[34,46]
	Arterial hypertension	[43,53]
	Fibrous bone dysplasia	[48]
	Hyperlipidemia	[2]
	Clubfeet	[54]

GI: gastrointestinal.

Table 2
Seizure types reported in MERRF.

Seizure type	Reference
Focal motor	
Tonic	nr
Atonic	[2]
Myoclonic	[2]
Clonic	[13]
Epileptic spasms	nr
Hypermotor	nr
Focal non-motor	
Sensory	nr
Cognitive	nr
Emotional	nr
Autonomous	nr
Generalised motor	
Tonic-clonic	[9]
Tonic	nr
Atonic	[2]
Myoclonic	[1]
Myoclonic-atonic	[2]
Clonic	nr
Clonic-tonic-clonic	nr
Epileptic spasms	nr
Generalised absences	
Typic	[10]
Atypic	nr
Myoclonic	[10]
Lid myoclonic	nr
Unknown onset motor	
Tonic-clonic	[11]
Tonic	nr
Atonic	nr
Epileptic spasms	nr
Unknown onset non-motor	nr
Non-classified seizures	nr

Nr: not reported.

letters, and of editorials, and exclusion of articles in a language inaccessible to translation, the number was reduced to 104 hits. After studying the abstracts, 93 were selected for detailed studying but only 64 were accessible as full papers and thus included in the list of References

3.2. Types of seizures reported in MERRF syndrome

Myoclonic epilepsy in MERRF is part of the group of progressive myoclonic epilepsies, which additionally include Unverricht-Lundborg disease, Lafora disease, various types of neuronal ceroid lipofuscinoses, and sialidoses type 1 and 2. The most frequent seizure type in MERRF is generalised myoclonic seizure (Table 2) [1]. Other types of seizures reported in MERRF include focal myoclonic, focal atonic, focal clonic, generalised tonic-clonic, generalised atonic, generalised myoclonic-atonic, typical absences [8], myoclonic absences, or tonic-clonic of unknown onset seizures (Table 2) [2,9,10,11,12,13]. Some patients may develop status epilepticus [9]. Myoclonus in MERRF may be constant or intermittent, photosensitive, or intensified by action (writing, eating) [12]. Myoclonic jerks in MERRF may correlate with electroencephalographic spike or polyspike activity, and there may be suppression of epileptic activity upon eye opening [12]. Myoclonus in MERRF may not only be the clinical manifestation of epileptic activity but also due to cerebellar dysfunction [14].

3.3. AEDs for epilepsy in MERRF syndrome

There are no specific recommendations available about the treatment of epilepsy in MERRF syndrome. However, general recommendations for the treatment of mitochondrial epilepsy have been repeatedly reported [15,16,17,18,19] and several expert opinions have been published (Table 3).

3.3.1. Classical antiepileptic drugs

Tonic-clonic seizures may be easy to treat but treatment of myoclonus may be challenging [12]. Some authors recommend clonazepam or zonisamide for myoclonus in MERRF syndrome [20]. However, these antiepileptic drugs (AEDs) have been only rarely applied in clinical practice. By means of a PubMed search clonazepam was mentioned only 3 times in association with MERRF syndrome and zonisamide was mentioned only once (Table 3).

Concerning the recommendation of lamotrigine for myoclonic epilepsy [20], there are no studies or reports about the application of lamotrigine in MERRF syndrome available. On the contrary, there are studies showing that lamotrigine may even aggravate myoclonus [21]. Other AEDs which have been reported to aggravate myoclonus include phenytoin, carbamazepine,