Management of MERRF patients including myoclonic epilepsy

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INTRODUCTION

The acronym MERRF stands for myoclonic epilepsy with ragged-red fibers, which is a rare mitochondrial disorder (MID) due to mutations in mtDNA located genes or due to mutations in the *POLG1* gene. Phenotypically, MERRF presents as either classical MERRF or as MERRF plus, the latter characterised by the canonical features myoclonus, generalised epilepsy, ataxia, and myopathy plus additional features. This study focuses on the diagnostic and therapeutic management of MERRF patients with particular regard to myoclonic epilepsy.

METHODS

Systemic literature search.

RESULTS

Genotype

MERRF is due to 22 variants in 13 mtDNA located genes or due to variants in the *POLG1* gene. In about 80% of the cases, MERRF is due to the variant m.8344A>G in the *MT-TK (tRNA(Lys))* gene. Another 10% of the cases are due to other *MT-TK* mutations.

Phenotype

Classical MERRF is characterised by the presence of the canonical features myoclonus, generalised epilepsy, ataxia, and mitochondrial myopathy. In addition to the canonical features, MERRF plus presents with psychiatric disorders, migraine, cerebellar atrophy, tremor, stroke-like episodes, optic atrophy, pigmentary retinopathy, hypoacusis, hypothyroidism, diabetes, cardiomyopathy, GI abnormalities, single or multiple lipoma, or lactic acidosis (fig. 1).

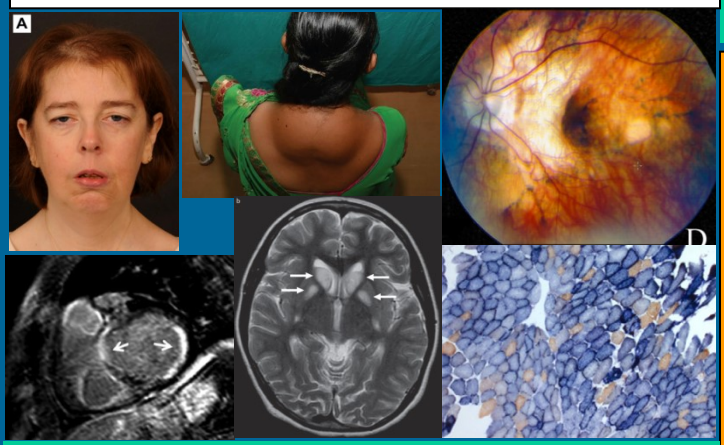

Fig. 1. MERRF phenotype: myopathic face (u. left), lipoma (u. middle), retinitis (u. right), LGE (l. left), putaminal lesion (l. m.), myopathy (l. r.)

Diagnosis

MERRF is diagnosed upon the history, clinical exam, blood/urine tests, LST, EMG, biopsy, MRI, and genetic investigations.

Treatment

No causative treatment is available. Supportive measures are applied for myopathy, epilepsy, hypoacusis, lactic acidosis, migraine, respiratory dysfunction, psychiatric disease, cardiac disease, lipoma, ptosis, hypothyroidism, diabetes, and gastrointestinal involvement.

Epilepsy

Seizures types in MERRF include focal (myoclonic, clonic, atonic) or generalised seizures (myoclonic, tonic-clonic, atonic, myoclonic-atonic seizures or absences). Myoclonus may be associated with epileptic activity (fig. 2) or due to cerebellar or spinal cord dysfunction.

Treatment of epilepsy

AEDs recommended for myoclonus respectively seizures include LEV, CZP, TPM, ZNS, and PIR. AEDs enhancing myoclonus or being potentially mitochondrion-toxic (CBZ, VPA, PHT, PB) should be avoided.

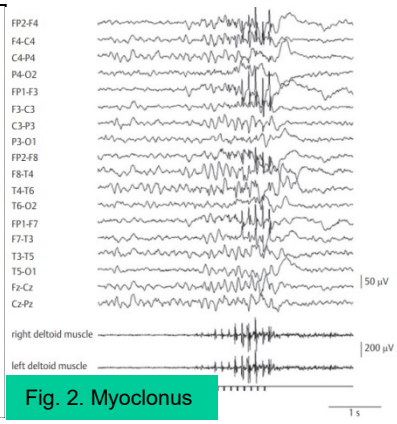

Fig. 2. Myoclonus

AED	Acronym	Effect (MERRF)	Effect (non-MERRF)	Reference
Levetiracetam	LEV	Bf	Bf	[56,108]
Clonazepam	CLZ	Bf	Bf	[1,108,109]
Topiramate	TPM	Bf	Bf (only add-on)	[108]
Zonisamide	ZNS	Bf	no	[1,108]
Piracetam	PIR	Bf	Bf	[28,110]
Valproic acid	VPA	Mixed*	Bf, myoclonus ↑	[1,108]
Lamotrigine	LTG	Mixed*	Bf, myoclonus ↑	[108]
Carbamazepine	CBZ	nr	myoclonus ↑	[108]
Oxcarbazepine	OXC	nr	myoclonus ↑	[108]
Phenytoin	PHT	nr	myoclonus ↑	[108]
Phenobarbital	PB	nr	Bf	[108]
Primidon	PRM	nr	Bf	[52]
Ethosuximide	ESM	nr	Bf	[111]
Gabapentin	GBP	nr	no, myoclonus ↑	[10,108]
Felbamate	FBM	nr	Bf	[112]
Tiagabine	TGB	nr	myoclonus ↑	[10,108]
Vigabatrin	VGB	nr	myoclonus ↑	[10,108]
Pregabalin	PGB	nr	myoclonus ↑	[10,108]
Lacosamide	LAC	nr	Bf	[113]
Rufinamide	RFM	nr	Bf	[114]
Perampanel	PER	nr	Bf	[115]

Tab. 1. AEDs recommended for myoclonic epilepsy and those enhancing myoclonus

CONCLUSIONS

Myoclonic epilepsy is a hallmark of MERRF, although there are patients without ever developing epilepsy. Myoclonic epilepsy in MERRF is difficult to treat since myoclonic seizures may be resistant to various AEDs. AEDs recommended for the treatment of myoclonic epilepsy include LEV, CZP, TPM, ZNS, and PIR. The combination of LEV with CZP may have the strongest beneficial effect on myoclonic seizures in MERRF