MELAS – a genetico-phenotypic continuum

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Letter to the Editor

In a recent article, El-Hattab et al. provided and interesting, and comprehensive review about the management of MELAS-syndrome1. We have the following comments and concerns.

We disagree with classifying ophthalmoparesis as an ophthalmologic manifestation1. Ophthalmoparesis is due to affection of the extra-ocular eye muscles and thus clearly attributable to myopathy of these muscles. We also disagree with the classification of pulmonary hypertension as a pulmonary manifestation. Since the lung is hardly affected in mitochondrial disorders (MIDs), pulmonary hypertension is usually a cardiac manifestation of MELAS.

Several phenotypic manifestations of MELAS were not mentioned. These include mitochondrial arteriopathy with carotid artery dissection2,3 and aortic rupture4, pituitary adenoma [personal communication], atrial fibrillation5, sudden cardiac death6, status epilepticus7, dystonia8, cerebellar dysfunction9, and maculopathy10.

The authors mention that seizures respond to traditional antiepileptic drugs (AEDs). Traditional AEDs also include mitochondrion-toxic medication such as valproate (VPA), phenytoin (PHT), phenobarbital (PB), and primidone (PRM). Particularly VPA may impair mitochondrial functions at various levels and should be avoided in MIDs. Fatalities due to severe liver toxicity have been reported together with VPA11. Though VPA is particularly mitochondrion-toxic in mitochondrial depletion syndrome (MDS), it is potentially mitochondrion-toxic also in MELAS. Alternative AEDs with low mitochondrion-toxic potential, or even beneficial effects to mitochondria should be applied such as lamotrigine (LTG), zonisamide (ZNS), levetiracetam (LEV), or gabapentin (GBT)12. The authors do not mention the beneficial effect of ketogenic diet in some types of mitochondrial epilepsy.

MELAS may also manifest as status epilepticus7,13 usually requiring intravenous application of AEDs. It should be mentioned that in such case LEV, lacosamide (LAC) or benzodiazepines should be initially preferred over VPA, PHT, and PB. Only in case of non-effectivity VPA, PHT, or PB may be added. For mitochondrial migraine or migraine-like headache tryptanes are an effective alternative to non-steroidal analgetic drugs (NSAD). LTG should be avoided in case of subaortic type of hypertrophic cardiomyopathy, since it may worsen cardiomyopathy14.

Concerning the cardiac therapy, application of vitamin-K-antagonists for atrial fibrillation or severe systolic dysfunction is mandatory. In case of severe ventricular arrhythmias, an implantable cardioverter defibrillator (ICD) should be implanted. In case of heart failure with a left bundle branch block (LBBB) a cardiac resynchronization therapy (CRT) system can be considered. A pacemaker is indicated in case of bradycardious rhythm abnormalities. Ablation of certain supraventricular arrhythmias is another therapeutic option which should be mentioned.

What is missing in this review is a paragraph about prenatal diagnosis and genetic counselling. What should be recommended to patients who carry a silent mutation? What should be recommended to a MELAS patient with a clinically manifesting mutation? Should pregnant females with MELAS be recommended to terminate their pregnancy prematurely? There is no mentioning about preimplantation therapy in which mitochondria are removed from eggs and replaced by mitochondria from a healthy donor.

Overall, this review could profit from extending the discussion about clinical manifestations of the disease, about the treatment of epilepsy and cardiac involvement in MELAS, and how mutation carriers should be counselled with regard to transmitting their disease.

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References


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