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MELAS reflects a clinical concept with heterogeneous genetic background

A MELAS reflete um conceito clínico com antecedentes genéticos heterogêneos

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We read with interest the excellent review article by Lorenzoni et al.[1] about definition, pathogenesis, genetic background, clinical manifestations, diagnosis, and treatment of mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS). We want to stimulate the discussion by adding the following points.

The term MELAS reflects a clinical condition and, therefore, should not be diagnosed upon the presence of a specific mutation, as proposed by the Japanese criteria[2]. For defining this condition, it is essential to select specific clinical constituents of the syndrome. The most specific constituent of the syndrome is the stroke-like episode (SLE). Though first described in association with MELAS[3], SLEs occasionally also occur in myoclonic epilepsy with ragged red fibers, Kearns-Sayre syndrome, Saguenay Lac St-Jean cytochrome oxidase (COX) deficiency, Leigh syndrome[4], and nonspecific mitochondrial disorders due to mutations in the *FASTKD2* gene[5]. However, SLEs are the hallmark of MELAS and should be included in its definition. Lactic acidosis, encephalopathy, and epilepsy are non-specific terms and frequently occur in other mitochondrial disorders as well. Mitochondrial myopathy is also non-specific but may present heterogeneously. Predominantly, the extra-ocular eye muscles may be affected in chronic progressive external ophthalmoplegia or Kearns-Sayre syndrome, whereas in MELAS, the limb muscles are most frequently affected by myopathy. Ragged-red fibers occur in many mitochondrial disorders but together with succinate-dehydrogenase (SDH)-hyper-reactive vessels and normal COX activity, they are typical for MELAS[6]. Canonical features defining MELAS are thus SLEs, together with ragged-red fibers, SDH-hyper-reactive vessels, absence of COX deficiency, and lactic acidosis.

Concerning the vascular hypothesis of SLEs, it is not conceivable that macro-angiopathy is responsible for SLEs, since all stroke-like lesions, the morphological equivalent of an SLE, are by definition not confined to a particular vascular territory. However, it is conceivable that during the development of the primary metabolic defect, not only are neurons and astrocytes involved but, secondarily, so too are local medium- and small-sized arteries, and veins. This would explain why parts of stroke-like lesions can appear as an ischemic lesion in certain stages of the stroke-like lesion. Affection of the arteries is supported by muscle biopsy findings showing SDH-hyper-reactive vessel walls and by primary macro- or microangiopathy in mitochondrial disorders[7]. Mitochondrial macroangiopathy may manifest as atherosclerosis, ectasia of arteries, aneurysm formation, dissection, or spontaneous rupture of arteries[7]. Mitochondrial microangiopathy may manifest as leukoencephalopathy, migraine-like headache, or retinal vasculopathy[7].

Concerning treatment, it has to be mentioned that the ketogenic diet (low glycemic, high fat content) may be beneficial in individual MELAS patients[8]. The ketogenic diet may be particularly effective for seizures and SLEs[9]. The ketogenic diet increases the production of ketone bodies, a side effect of which may be metabolic acidosis, which again increases the propensity of seizures[10]. However, by modifying the diet by monitoring the protein intake and by maximizing consumption of alkaline mineral-rich, low carbohydrate green vegetables, metabolic acidosis can be spared[10].

In summary, we propose to define MELAS upon the presence of a stroke-like lesion on MRI, upon ragged-red fibers, SDH-hyper-reactive muscular arteries, and normal COX staining on muscle biopsy, and lactic acidosis, to differentiate MELAS from myoclonic epilepsy with ragged red fibers syndrome and other mitochondrial syndromes. The pathogenicity and distribution of mutations associated with MELAS can be assessed reliably only if there is general agreement on what can be diagnosed clinically as MELAS and what is not MELAS.

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