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Letter to the Editor Open Access

Pathogenicity of low heteroplasmic m.3243A>G variants requires confirmation

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In a recent article, Yee et al. reported about a 31 years old Caucasian male with non-specific mitochondrial multiorgan disorder syndrome (MIMODS) due to the mtDNA variant m.3243A>G [1]. Phenotypic manifestations attributed to the mtDNA variant included diabetes, gastro-intestinal dysmotility, gastro-intestinal pseudo-obstruction, facial dysmorphism, pectus excavatus, nystagmus, ophthalmoparesis, cataract, hypoacusis since childhood, migraine, retinopathy, right retinal detachment (ablatio retinae), and sinus tachycardia [1]. We have the following comments and concerns.

A shortcoming of the study is the low heteroplasmy rate of 30% in blood lymphocytes. The low heteroplasmy rate hardly explains the phenotype why tissues other than blood, such as hair follicles, skin fibroblasts, buccal mucosa cells, muscle cells, or urinary epithelial cells should be investigated for the mutation load. In case heteroplasmy rates are similarly low, functional tests should be carried out to confirm or exclude pathogenicity of the variant. Additionally, clinically affected first-degree relatives should be genetically investigated.

We do not agree that mitochondrial disorders (MIDs) only manifest in organs or tissues with high energy demand. MIDs rather manifest in organs or tissues with a high mutation load or

low mtDNA copy number. Additionally, clinical manifestations may depend on the drugs patients are regularly taking. Particularly mitochondrion-toxic are antiepileptic drugs (AEDs), such as valproic acid, phenytoin, carbamazepine, phenobarbital, and some anesthetics [2], but from most of the drugs it is not well known if they are mitochondrion-toxic or not. Thus, we should be informed about the medication the index patient was regularly taking and if there were any drug intolerabilities.

We do not agree with the diagnosis of MELAS/MIDD overlap syndrome. MELAS is characterized by encephalopathy, lactic acidosis, stroke-like episodes and seizures. Except for occasionally and mildly elevated serum lactate, the patient did not present with any of the key clinical manifestations of MELAS. He had not developed stroke-like episodes, seizures, or encephalopathy.

Not mentioned as a treatment of stroke-like episodes is the ketogenic diet [3], antioxidants, particularly idebenone, edaravone, and coenzyme-Q [4], AEDs [5], and steroids [5]. The ketogenic diet may exhibit a beneficial effect also on phenotypic manifestations other than epilepsy. Coenzyme-Q is highly effective in primary coenzyme-Q deficiency but may also exhibit beneficial effects in m.3243A>G carriers. Idebenone has been shown particularly effective in patients with Leber's hereditary optic neuropathy and is approved in this indication by several health authorities worldwide. AEDs may not only be effective in case of epilepsy, but also in case of stroke-like episodes with paroxysmal activity on EEG. Steroids may be effective in stroke-like episodes as they may reverse the breakdown of the blood-brain barrier, which is made responsible for the vasogenic edema characterizing a stroke-like lesion.

Though diabetes occurs frequently in MELAS patients, it may also occur in other specific MIDs, such as MERRF [6], Kearns-Sayre syndrome [7], MIDD, Leigh syndrome [8], NARP [9], LHON [10e], and in MIMODS [11i].

The patient was described as having sinus-tachycardia at initial presentation [1]. It should be discussed if this was due to sympathetic over-activity, exsiccosis, hyperthyroidism, sinus node dysfunction, or a cardiomyopathy. We should be informed about the cardiologic investigations of the index case, particularly the results of echocardiography and the long-term ECG recordings.

Finally, narrowing of the aorto-mesenteric angle may not be the only explanation of the gastro-intestinal complaints. The genetic defect itself may explain the clinical manifestations [12].

In summary, this case could be more meaningful if the pathogenicity of the mtDNA variant would have been confirmed, if other clinically affected family members would have been genetically tested, if the current medication would have been mentioned, and if a thorough cardiologic work-up would have been carried out.

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