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Letter to the Editor

The m.13513G>A Variant is Unlikely to Manifest as Non-Arteritic Ischemic Optic Neuropathy

¹ Sounira Mehri, ² Josef Finsterer

¹ Biochemistry Laboratory, LR12ES05 "Nutrition-Functional Foods and Vascular Health", Faculty of Medicine, Monastir, Tunisia

² Department of Neurology, Neurology & Neurophysiology Center, Vienna, Austria

Corresponding Author: **Josef Finsterer**

Letter to the Editor

We read with interest the article by Mathot *et al.* regarding a 47-year-old man with non-arteritic anterior ischemic optic neuropathy (NAION) attributed to the m.13513G>A variant in the MT-ND5 gene [1]. The authors concluded that mtDNA mutations can represent an independent vascular risk factor and that mitochondrial disease (MID) should be considered in patients with atypical optic neuropathy, particularly those lacking cardiovascular risk factors [1]. While the study is noteworthy, several points warrant discussion.

First, the differential diagnoses for NAION were not adequately ruled out [2]. Key differential diagnoses include inflammatory and demyelinating optic neuropathies, such as optic neuritis associated with multiple sclerosis (characterized by painful eye movements and early onset), myelin oligodendrocyte glycoprotein (MOG) antibody-associated disease, neuromyelitis optica spectrum disorder, temporal arteritis, and infectious optic neuritis (e.g., due to syphilis or sarcoidosis). In addition to inflammatory causes, optic neuropathies can result from compressive or infiltrative processes, such as orbital tumors, Graves' disease, leukemia, lymphoma, or metastases. Finally, potential causes of optic neuropathy include diabetes mellitus, central retinal artery thrombosis, arterial hypertension, optic disc drusen, and elevated intracranial pressure. Were all these differential diagnoses appropriately ruled out?

A second point is that the critical parameters determining the phenotype of mtDNA variants were not reported [1]. Factors essential for understanding the phenotypic expression include heteroplasmy levels in the affected tissues, mtDNA copy number, haplotype, the specific phenotypic threshold above which cells can no longer tolerate mutated mtDNA, the random distribution of mutated and wild-type mtDNA within the tissue, nuclear genetic modifiers, and environmental factors. Knowledge of these determinants of mtDNA variants is crucial to explaining why the m.13513G>A variant manifested exclusively as NAION in the index patient.

A third point is that the patient was not systematically evaluated for mitochondrial vasculopathy [1]. Although rare, there is no doubt that MIDs can manifest in the arterial vascular system [3]. In a patient suspected of having mitochondrial vasculopathy, it would therefore have been imperative to specifically screen for atherosclerosis, stenoses, dissections, vascular malformations, and spasms affecting the brain, internal organs, or extremities. If the mitochondrial vasculopathy manifested exclusively in the optic nerve, an explanation would be required as to why this did not occur in other vascular regions.

A fourth point is that the patient was not systematically evaluated for multisystem disease [1]. Given that the m.13513G>A variant has previously been described in association with Leigh syndrome [4], mitochondrial encephalopathy, lactic acidosis and stroke-like episodes (MELAS) syndrome, cardiomyopathy [5], and renal disease, it would have been crucial to screen for subclinical or mild multisystem disease.

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