Mitochondrial Hypertension Due To The Mutations M.5655T>C And M.4401A>G

Josef Finsterer, MD, PhD [1], Sinda Zarrouk-Majhoub, PhD [2]
[1] Krankenanstalt Rudolfstiftung, Messerli Institute, Veterinary University of Vienna, Vienna, Austria
[2] University of Tunis El Manar and Genomics Platform, Pasteur Institute of Tunis, Tunisia

Abstract:- With interest we read the article by Xu et al. about a three-generation Han Chinese family with essential hypertension in 6 members, of whom 5 carried the homoplasmic mtDNA mutations m.5655T>C and m.4401A>G [1]. Arterial hypertension was attributed to the underlying mtDNA mutations and reported as the sole clinical manifestation of the genotype [1]. We have the following comments and concerns.

Key words: mtDNA, mitochondrial, arterial hypertension, cardiomyopathy, phenotype

Introduction:-

With interest we read the article by Xu et al. about a three-generation Han Chinese family with essential hypertension in 6 members, of whom 5 carried the homoplasmic mtDNA mutations m.5655T>C and m.4401A>G [1]. Arterial hypertension was attributed to the underlying mtDNA mutations and reported as the sole clinical manifestation of the genotype [1]. We have the following comments and concerns.

Expression of the phenotype of an mtDNA mutation may not only depend on the heteroplasmy rate but also on the haplotype and the mutation load in various tissues [2]. Which haplotypes did the verum and control group carry? Were the haplotypes the same in both groups? Was the mutation load determined only in blood lymphocytes or in other tissues, such as hair follicles, buccal mucosa, fibroblasts, muscle cells, or urinary epithelial cells as well?

The index case was diagnosed with essential hypertension at age 29y with normal findings on physical examination, laboratory assessment of cardiovascular risk factors, and routine electrocardiography (ECG) [1]. To exclude secondary hypertension it is essential to exclude hyperthyroidism, cardiomyopathy, pheochromocytoma, and renal artery stenosis [3]. Were all thyroid function parameters truly normal? What were the results of the echocardiographic examination, what were the superselective catecholamine values in the suprarenal veins? Did CT-angiography reveal renal artery stenosis?

From figure 1 it is unclear if the five individuals with a filled symbol represent the mutation carriers or those with essential hypertension, or both [1]. Not in accordance with figure 1, table 1 contains 6 patients and the family tree 5 patients. Did the 6 patients in table 1 all suffer from arterial hypertension? If this is the case how do the authors explain that patient III/1 had arterial hypertension but did not carry the mutation? What was the cause of arterial hypertension in patient III/1? Were causes of secondary arterial hypertension truly excluded in all patients carrying the mtDNA mutations?

Mitochondrial disorders (MIDs) are usually multisystem, syndromic conditions which manifest in organs such as the brain, eye, ear, endocrine system, heart, gastrointestinal tract, kidneys, bone marrow, and skin (mitochondrial multiorgan disorder syndromes (MIMODSs)) [4]. Was the index case or any of the other mutation carriers prospectively investigated for multiorgan involvement, particularly were mutation carriers investigated for cardiac or cerebral involvement?

The m.4401A>G mutation has been previously reported in association with arterial hypertension [5,6,7] but mutation carriers did not manifest with other phenotypic features typical for MIDs. The m.5655T>C mutation has been reported in association with lung cancer [8] and hearing impairment [9]. Was the family history positive for carcinoma or hearing impairment in any of the present mutation carriers or family members not tested for the mutations?
Overall, this interesting case study may profit from prospective investigation of organs thus far not affected by the underlying metabolic defect, from follow-up investigations to see if multiorgan affection had occurred during the disease course, and from thorough work-up for secondary arterial hypertension. The pathogenicity of the two mutations remains questionable and requires in-silico computational prediction, in-vitro biochemical methods such as decreased respiratory chain enzyme activity in muscle liver, or fibroblasts, cybrid studies, correlation of the mutation load with the histochemical phenotype, or in-vivo studies of knock-in transgenic animals [10].
References


