Letter to the Editor

Comment on “Role of Mitochondrial Genome Mutations in Pathogenesis of Carotid Atherosclerosis”

Josef Finsterer ¹ and Sinda Zarrouk-Mahjoub²

¹Krankenanstalt Rudolfstiftung, Vienna, Austria

²University of Tunis El Manar and Genomics Platform, Pasteur Institute of Tunis, Tunis, Tunisia

Correspondence should be addressed to Josef Finsterer; fipaps@yahoo.de

Received 3 October 2017; Accepted 2 January 2018; Published 28 March 2018

Academic Editor: Giuseppe Cirillo

Copyright © 2018 Josef Finsterer and Sinda Zarrouk-Mahjoub. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

We read with interest the article by Sazonova et al. about their study of 700 patients with atherosclerosis who were investigated for the presence or absence of 11 mtDNA variants [1]. The authors found that the mtDNA variants m.652delG, m.3336C>T, m.12315G>A, m.14459G>A, and m.15059G>A could serve as biomarkers for the assessment of future atherosclerotic risk in the general population [1]. We have the following comments and concerns.

We do not agree with the statement that the above-mentioned mtDNA variants could be useful as a biomarker of atherosclerosis [1] for several reasons. First, heteroplasmy rates were determined only in blood lymphocytes [1]. It is well known that heteroplasmy rates vary considerably between different tissues and that heteroplasmy rates in lymphocytes do not reflect the mutation load in clinically or instrumentally affected tissues. Were the heteroplasmy rates determined in tissues other than lymphocytes? Heteroplasmy rates from vascular endothelial cells or vascular smooth muscle cells would be of interest, at least in an animal model of atherosclerosis.

Second, it is not mentioned how many of the included patients had arterial hypertension, diabetes, and hyperlipidemia or how many were smoking. Since these classical risk factors for atherosclerosis were not assessed, it cannot be excluded that plaque burden in the carotid arteries is in fact attributable to any of the classical risk factors and has nothing to do with the amount of mtDNA variants.

Third, more specific risk factors for atherosclerosis, such as high-sensitivity C-reactive protein, the telomere length, lipid oxidation products (MDA-modified collagen type IV IgM and IgG antibodies), hyperuricemia, TNF-alpha, and IL-15 polymorphism, were not assessed. They also can have a significant influence on the severity and progression of atherosclerosis.

Fourth, we need to be informed about the medication these patients were regularly taking, since there are a number of compounds which potentially increase the risk of atherosclerosis such as anabolic androgen steroids, testosterone gel, antiretroviral agents, proton pump inhibitors, leptin, or anti-epileptic drugs, particularly valproate and carbamazepine [2].

It would be also interesting to know how many of those who carried an mtDNA variant also suffered from a mitochondrial disorder (MID) at inclusion or how many developed a MID during follow-up. It is well appreciated that MIDs manifest not only in the arteries but also in the brain, spinal cord, eyes, ears, endocrine organs, heart, lungs, intestines, kidneys, blood, bones, or skin [3]. In the included patients, were any of these organs or tissues affected alone or in combination? In the included patients, was the family history positive for a MID?

It is also well known that large and small arteries may be affected in MIDs manifesting as dissection of the carotid arteries [4–6], aneurysm formation [5], ectasia of the aorta [7], microangiopathy of the retinal arteries [8], spontaneous

rupture of the aorta [9], premature atherosclerosis [10], arteriovenous malformations [11], and arterial hypertension [12]. How many of the included patients manifested with arteriopathy other than atherosclerosis?

Overall, this interesting study could profit not only from more widespread genetic studies but also from the assessment of common and uncommon risk factors for atherosclerosis to exclude influences other than the amount of mtDNA variants tested on the atherosclerotic risk in the general population.

Conflicts of Interest

There are no conflicts of interest.

Authors' Contributions

Josef Finsterer is responsible for the design, literature search, and discussion and for the first draft. Sinda Zarrouk-Mahjoub is responsible for the literature search, discussion, and critical comments. Both authors contributed equally.

References

- [1] M. A. Sazonova, V. V. Sinyov, A. I. Ryzhkova et al., "Role of mitochondrial genome mutations in pathogenesis of carotid atherosclerosis," *Oxidative Medicine and Cellular Longevity*, vol. 2017, Article ID 6934394, 7 pages, 2017.
- [2] Q. Lai, C. Shen, Y. Zheng, Y. Zhang, Y. Guo, and M. Ding, "Effects of antiepileptic drugs on the carotid artery intima-media thickness in epileptic patients," *Journal of Clinical Neurology*, vol. 13, no. 4, pp. 371–379, 2017.
- [3] J. Finsterer and S. Zarrouk-Mahjoub, "Mitochondrial vasculopathy," *World Journal of Cardiology*, vol. 8, no. 5, pp. 333–339, 2016.
- [4] A. V. Sakharova, L. A. Kalashnikova, R. P. Chaikovskaia et al., "Morphological signs of mitochondrial cytopathy in skeletal muscles and micro-vessel walls in a patient with cerebral artery dissection associated with MELAS syndrome," *Arkhiv Patologii*, vol. 74, no. 2, pp. 51–56, 2012.
- [5] R. C. C. Ryther, Y. A. Cho-Park, and J. W. Lee, "Carotid dissection in mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes," *Journal of Neurology*, vol. 258, no. 5, pp. 912–914, 2011.
- [6] L. A. Kalashnikova, L. A. Dobrynina, A. V. Sakharova et al., "The A3243G mitochondrial DNA mutation in cerebral artery dissections," *Zhurnal Nevrologii i Psikiatrii Imeni S.S. Korsakova*, vol. 112, no. 1, pp. 84–89, 2012.
- [7] N. Brunetti-Pierri, R. Pignatelli, N. Fouladi et al., "Dilation of the aortic root in mitochondrial disease patients," *Molecular Genetics and Metabolism*, vol. 103, no. 2, pp. 167–170, 2011.
- [8] I. Martin-Kleiner, J. Gabrilovac, M. Bradvica et al., "Leber's hereditary optic neuroretinopathy (LHON) associated with mitochondrial DNA point mutation G11778A in two Croatian families," *Collegium Antropologicum*, vol. 30, no. 1, pp. 171–174, 2006.
- [9] S. H. K. Tay, D. R. Nordli Jr, E. Bonilla et al., "Aortic rupture in mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes," *Archives of Neurology*, vol. 63, no. 2, pp. 281–283, 2006.
- [10] J. Finsterer and C. Stöllberger, "Leriche-syndrome despite regular sport and non-compaction suggest neuromuscular disease," *International Journal of Cardiology*, vol. 191, pp. 15–17, 2015.
- [11] J. Fujitake, H. Mizuta, H. Fujii et al., "Leber's hereditary optic neuropathy with intracranial arteriovenous malformation: a case report," *Acta Neurologica Belgica*, vol. 102, no. 2, pp. 82–86, 2002.
- [12] L. Wang, Z. Dong, W. Lin, R. Gao, C. Chen, and J. Xu, "Molecular characterization of a pedigree carrying the hypertension-associated mitochondrial tRNA^{Gln} T4363C mutation," *Molecular Medicine Reports*, vol. 16, no. 5, pp. 6029–6033, 2017.