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Letter to the Editor

Restoration of Vision in LHON may Depend not only on Therapy, but also on Heteroplasmy, mtDNA Copy Number, and Haplotype

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Letter to the Editor

We read with interest the article by Paranjpe *et al*. about a 21-year-old man with Leber's hereditary optic neuropathy (LHON) plus due to the m.14484C>T variant in MT-ND6, which manifested phenotypically as severely reduced visual acuity, tachycardia, arterial hypertension, and mitral valve prolapse syndrome. His visual acuity recovered completely from 6/60 OD and 3/60 OS within one year of treatment with coenzyme-Q (200 mg/day) and dietary supplements [1]. The study is interesting, but some points deserve discussion.

The first point is that the heteroplasmy rate of the m.14484C>T variant has not been reported [1]. Since heteroplasmy significantly determines the phenotype, it would have been important to know the heteroplasmy rates of different affected tissues. Heteroplasmy rates are not only important for predicting the severity of the phenotype and the course of the disease, but also for genetic counseling. Another important determinant of the phenotype is the mtDNA haplotype [2]. The mtDNA haplotype alters mitochondrial function through interaction with nuclear DNA (nDNA), thereby influencing cellular properties such as energy metabolism, differentiation, fusion, fission, and disease risk. Different haplotypes set different mitochondrial targets for energy production, thereby influencing the cellular stress response. This leads to different gene expression patterns and changes in DNA methylation in the nDNA, which ultimately shapes the phenotype [2]. The third important determinant of phenotype is mtDNA copy number [3]. MtDNA copy number influences the effect of an mtDNA variant by acting as a buffer or amplifier of the mutation [3]. Higher copy numbers can compensate for a pathogenic mutation and lead to milder symptoms, while lower numbers exacerbate the dysfunction and cause a more severe course of disease [3]. In order to assess whether the complete restoration of vision in the index patient was due to antioxidant treatment or occurred spontaneously, it is essential to know these three crucial determinants of the phenotype of an mtDNA variant.

The second point concerns the discrepancy between the description of the medical history as unremarkable and the description that the patient suffered from palpitations, sinus tachycardia, and arterial hypertension [1]. Since palpitations are a symptom that the patient noticed, his medical history cannot be unremarkable. Furthermore, since arterial hypertension is usually symptomatic, he should have recognized symptoms of arterial hypertension such as headache, shortness of breath, chest pain, dizziness, visual disturbances, numbness, weakness, nosebleeds, or speech disorders [4]. Did the patient require antihypertensive treatment for arterial hypertension? Did the funduscopy indicate a hypertensive fundus?

The third point concerns the lack of explanation for hyperhidrosis in the index patient [1]. Hyperhidrosis is usually either genetic or secondary due to hormonal changes (e.g., menopause, pregnancy, thyroid), hypoglycemia, infections, medications (e.g., antidepressants, antidiabetics), neuropathy of the autonomic nervous system, obesity, some types of cancer, or idiopathic [5]. Which of these causes explain the hyperhidrosis in the index patient?

The fourth point is that the patient received not only coenzyme-Q but also dietary supplements (B complex vitamins, vitamin-C, and alpha-lipoic acid) [1]. What was the dosage of these dietary supplements? How can we be sure that it was the dietary supplements and not coenzyme-Q that was responsible for the recovery? Did the patient ever discontinue treatment during the one-year follow-up period? Did vision deteriorate without treatment?

In summary, the complete recovery of impaired vision in LHON-plus patients due to the m.14484C>T variant may be related not only to treatment but also to genetic factors such as heteroplasmy, mtDNA copy number, and haplotype. Until these parameters have been determined, the cause of complete recovery cannot be definitively explained.

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