LHON plus due to the variant m.3460G>A requires extensive investigation and close monitoring

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LHON plus due to the variant m.3460G>A requires extensive investigation and close monitoring

Short title: LHON plus requires extensive work-up

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Letter to the Editor

We read with interest the article by Hey et al. about two patients with Leber's hereditary optic neuropathy (LHON) who also presented with hypertrophic cardiomyopathy (hCMP) [1]. The underlying genetic defect was identified as the variant m.3460G>A in *ND1* in both the index patient and his sister, who had a similar phenotype but no ophthalmologic impairment [1]. The study is appealing but raises concerns that should be discussed.

A limitation of the study is that heteroplasmy rates of the m.3460G>A variant were not reported [1]. Knowledge of heteroplasmy rates is crucial as the amount of mutated mtDNA in a tissue can strongly determine the phenotypic expression of the variant [2]. It would be also helpful to know the patient's haplotype and the mtDNA copy number as these factors can contribute to phenotypic expression. In this respect, sequencing of the entire mtDNA is missing.

The discussion about LHON plus is also missing. Not only is LHON a mono-system disease affecting retinal ganglion cells, but it is increasingly recognised that LHON can affect systems/organs other than the eyes (LHON plus) [3]. Organs other than the eyes that are most commonly affected by LHON plus are the myocardium and brain [4]. Cerebral imaging can show multiple sclerosis-like features, also known as Harding's disease. We should know if cerebral MRI showed any cerebral abnormalities in addition to optic nerve demyelination.

There is no discussion of the association between LHON due to the variant m.3460G>A and left ventricular hypertrabeculation (LVHT), also known as non-compaction [4]. In a previous report of two brothers carrying this variant, both presented with hCMP plus LVHT [4]. One of them died of sudden cardiac death (SCD) [4]. Similar to the index patient, these two brothers had Wolff-Parkinson White syndrome [4].

Since patients with hCMP tend to develop ventricular arrhythmias, it should be discussed whether implantation of a reveal recorder would be useful in order to assess over a longer period of time whether there is an indication for the implantation of an implantable cardioverter defibrillator (ICD). Both, supra-ventricular and ventricular arrhythmias can be complicated by syncope or SCD, so we should know if the index patient's history or family history was positive for syncope or SCD.

Overall, the interesting study has limitations that challenge the results and their interpretation. Patients with LHON plus require comprehensive evaluation for subclinical/clinical multisystem disease and appropriate protective measures in the case of cardiac compromise.

Declarations

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Consent for publication: was obtained from the patient

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Code availability: not applicable

Author contribution: JF: design, literature search, discussion, first draft, critical comments, final approval, FS and A-CA: literature search, discussion, critical comments, final approval,

References

1 Hey TM, Nielsen SK, Eriksen U, Hansen F, Mogensen J. Leber's Hereditary Optic Neuropathy and Hypertrophic Cardiomyopathy. CJC Open. 2022 Jun 17;4(9):813-815. doi: 10.1016/j.cjco.2022.06.005.

2 Yang M, Xu L, Xu C, Cui Y, Jiang S, Dong J, Liao L. The Mutations and Clinical Variability in Maternally Inherited Diabetes and Deafness: An Analysis of 161 Patients. Front Endocrinol (Lausanne). 2021 Nov 25;12:728043. doi: 10.3389/fendo.2021.728043.

3 Lackey E, Lefland A, Eckstein C. Leber's Hereditary Optic Neuropathy Plus Causing Recurrent Myelopathy due to an MT-DN1 Mutation at G3635A. Case Rep Neurol Med. 2022 Jan 11;2022:1628892. doi: 10.1155/2022/1628892.

4 Finsterer J, Stollberger C, Gatterer E. Wolff-Parkinson-White syndrome and noncompaction in Leber's hereditary optic neuropathy due to the variant m.3460G>A. J Int Med Res. 2018 May;46(5):2054-2060. doi: 10.1177/0300060518765846.