CJC Open 5 (2023) 35

# Letters to the Editor

## LHON Plus Due to the Variant m.3460G > A Requires Extensive Investigation and Close Monitoring

### To the Editor:

We read with interest the article by Hey et al. about 2 patients with Leber 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 mitochondrial DNA (mtDNA) in a tissue can strongly determine the phenotypic expression of the variant.[2] Knowing the patient's haplotype and the mtDNA copy number also would be helpful, as these factors can contribute to phenotypic expression. In this respect, sequencing of the entire mtDNA is missing from this study.

Discussion about LHON plus is also missing from this article. LHON not only is a mono-system disease affecting retinal ganglion cells, but also is increasingly recognized as being able to 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 for these cases if cerebral magnetic resonance imaging showed any cerebral abnormalities in addition to optic nerve demyelination.

No discussion is presented of the association between LHON due to the variant m.3460G > A and left ventricular hypertrabeculation, also known as noncompaction.[4] In a previous report of 2 brothers carrying this variant, both presented with hCMP plus left ventricular hypertrabeculation.[4] One of them died of sudden cardiac death (SCD).[4] Similar to the index patient, these 2 brothers had Wolff-Parkinson-White syndrome.[4]

Given that patients with hCMP tend to develop ventricular arrhythmias, whether implantation of a reveal recorder would be useful should be discussed, in order to assess over a longer period of time whether implantation of an implantable cardioverter defibrillator is indicated. Both supraventricular and ventricular arrhythmias can be complicated by syncope or SCD, so we should know whether the index patient's history or family history was positive for syncope or SCD.

Overall, this 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.

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### Ethics Statement

The letter is in accordance with ethical guidelines and was approved by the institutional review board. Consent to participate and for publication was obtained from the patient.

### Funding Sources

The authors have no funding sources to declare.

### Disclosures

The authors have no conflicts of interest to disclose.

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https://doi.org/10.1016/j.cjco.2022.10.006