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Letter to the Editor

Effect of Idebenone in Chronic Leber's Hereditary Optic Neuropathy

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In a recent article, Pemp *et al.*, reported about the therapeutic effect of idebenone started 5-50y after onset and given for 12 months in 7 patients with Leber's hereditary optic neuropathy (LHON) due to the mtDNA variants m.14484T>C (n=4), m.11778G>A (n=2), and m.13051G>A (n=1) (Pemp, B. *et al.*, 2019). It was concluded that 300mg/d idebenone improve visual acuity even in patients with chronic LHON and a disease duration >5y (Pemp, B. *et al.*, 2019). We have the following comments and concerns.

We do not agree with the conclusion that idebenone is beneficial for chronic LHON. This is due to several shortcomings of the study. The main shortcoming is the low number of patients. To conclude from 7 patients that idebenone has a beneficial effect in chronic LHON may be misleading as the size of the cohort is too small to draw such conclusions with certainty. Furthermore, no control group was included, no multicentre approach was chosen, and the investigated cohort was inhomogeneous with regard to the genotype.

A second shortcoming is that spontaneous recovery among those who improved during the observational period was not sufficiently considered. Particularly from pediatric patients carrying the variants m.3460G>A and m.14484T>C it is known that spontaneous recovery may occur (Majander, A. *et al.*, 2017; Acaroğlu, G. *et al.*, 2001). However, also in adult patients carrying the variant m.14484T>C (Hsu, T. K. *et al.*, 2014) or the variant m.11253T>Ct (Leo-Kottler, B. *et al.*, 2002) spontaneous recovery has been reported. In the present study 4 patients with pediatric (n=1) or adult onset (n=1) carried the m.14484T>C variant and thus may have experienced spontaneous recovery. Spontaneous recovery may even occur >5y after onset of the ophthalmologic compromise (Spruijt, L. *et al.*, 2006; Stone, E. M. *et al.*, 1992; & Riordan-Eva, P. *et al.*, 1995).

A third shortcoming is that heteroplasmy rates of the variants m.14484T>C, m.11778G>A, and m.13051G>A have not been reported. Mutations associated with LHON usually occur in the homoplasmic or near homoplasmic state. Knowing heteroplasmy rates of the included patients is crucial as it may determine not only the outcome but also an eventual therapeutic effect.

According to table 1 patient 5 had a previous treatment with "radial optic neuropathy". It should be explained which type of treatment for LHON patients this is.

A fourth shortcoming is that the current medication the 7 included were regularly taking was not provided and that factors triggering the manifestation of primary LHON mutations (e.g. smoking, environment) have not been provided. To assess an eventual therapeutic effect, it is crucial to exclude any change of the co-medication that could explain any influence on the outcome parameters.

A fifth shortcoming is that visual acuity of seven eyes was relatively good and that three patients had relatively little visual impairment, suggesting that there was continuous improvement already prior to starting idebenone or that these patients were in fact never severely affected.

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A sixth shortcoming of the study is the affiliation of the first author with company producing idebenone. A bias on the interpretation of the results cannot be excluded irrespective of the inappropriate design of the study.

Since phenotypically manifesting mtDNA variants are inherited from the mother's side in 75% of the cases (Poulton, J. *et al.,* 2017) we should be informed about the family history. Particularly, we should know if the culprit variants were maternally inherited or occurred spontaneously, We should also know if any other first degree relatives was clinically affected or carried the variant of their index relative as well.

Overall, this interesting study of 7 LHON patients with regard to the therapeutic effect of idebenone in the chronic stage of the disease has a number of shortcomings which need to be solved before final conclusions can be drawn. As long as these points have not been sufficiently addressed we cannot be sure that idebenone truly exerts a beneficial effect in chronic LHON.

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