

# Psychological morbidity in Leber's hereditary optic neuropathy depends on phenotypic, social, economic, and genetic factors

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## Dear editor

We have read with interest the article by Garcia et al<sup>1</sup> about the effect of visual impairment on psychological well-being with regard to mood, interpersonal interactions, and career-related goals.<sup>1</sup> Among the 103 Leber's hereditary optic neuropathy (LHON) patients, half became depressed with negative impacts on interpersonal relations and career goals. At diagnosis, older age corresponded to higher depression prevalence than young age. We have the following comments and concerns.

The main disadvantage of the study is that the included patients were not categorized according to the underlying genetic defect. The genetic cause of LHON is quite heterogeneous.<sup>2</sup> The three primary LHON mutations m.11778G>A, m.3460G>A, and m.14484T>C, located in the ND4, ND1, and ND6 mtDNA genes of the mitochondrial DNA (mtDNA), respectively, account for 90% of the LHON cases.<sup>2</sup> In addition, a number of other mtDNA mutations, such as m.3434T>C, m.3483G>A, m.3635G>A, m.3866T>C, m.9011T>C, m.11253T>C, m.11696G>A, or m.13042G>A, may be implicated in the pathogenesis of LHON.<sup>3</sup> Did the results vary between the three primary LHON mutations? Differentiation between the three mutations is of particular importance since spontaneous recovery of visual compromise has been reported in a small number of cases with LHON.<sup>4</sup> Remission is most pronounced in patients carrying the m.14484T>C mutation.<sup>2</sup> How many among the 103 included patients carried this particular mutation and how many showed improvement in visual dysfunction during the disease course? The type of mutation may also determine the risk of mutation carriers to develop symptoms.<sup>2</sup>

LHON is frequently not only a monoorgan disorder affecting the optic nerve and the retinal ganglion cells (pure LHON) but also usually a multisystem disease, additionally involving the brain (epilepsy, leucoencephalopathy, migraine, ataxia, chorea, dementia, and posterior reversible encephalopathy syndrome [PRES]), the ears (hypoacusis), endocrine organs (diabetes, thyroid dysfunction, and pituitary adenoma), the heart (cardiomyopathy, noncompaction, arrhythmias, heart failure, and sudden cardiac death), the kidneys, the bone marrow (anemia), the arteries (aortic stiffness), or the peripheral nerves (polyneuropathy) (LHON plus).<sup>3</sup> How many patients had pure LHON and how many LHON plus? Did the results differ between those with pure LHON and those with LHON plus?

Idebenone has been shown to partially improve visual compromise and has been approved as a supporting remedy for LHON in some countries.<sup>5</sup> How many of the

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included patients were under a therapy with idebenone when filling out the questionnaire? Were those under idebenone less frequently depressed than those without this therapy?

Mean interval between conversion and time of survey was  $5 \pm 1.3$  years.<sup>1</sup> Did the results differ between those asked shortly after conversion and those asked long after visual loss?

Overall, this interesting study may be more meaningful if the cohort would be divided according to the underlying genetic cause, the length of the interval between conversion and questionnaire, the clinical presentation (pure LHON vs LHON plus), and the treatment applied.

## Disclosure

The authors report no conflicts of interest in this communication.

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## Authors' reply

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## Dear editor

We appreciate Dr Finsterer and Dr Zarrouk-Mahjoub's interest in our article<sup>1</sup> and regret that many of their questions cannot be addressed by the nature of our study. Their most salient inquiries were as follows: did mutation affects visual prognosis, risk of vision loss, or psychological morbidity? Were systemic health associations associated with psychological morbidity? Did idebenone therapy affects psychological morbidity? Did the recency of vision loss affects psychological morbidity? Our study was not designed to collect data on these questions.

Among our respondents, the self-reported mutations were 55% m.11778G>A, 11% m.14484T>C, 11% m.3460G>A, 20% unknown, and 3% other. This demonstrates that nonprimary mutations are very uncommon in Leber's hereditary optic neuropathy (LHON). Mutation clearly affects visual prognosis.<sup>2</sup> Mutation type also affects the risk of conversion, but this is harder to measure.<sup>3</sup> In our anonymous questionnaire study, participants self-reported their visual acuity and did not describe the course of vision loss, so we could not analyze whether mutation affected visual prognosis in this cohort. We did not find significant differences in depression symptoms between mutations. There are several reasons why mutation, vision, and depression were not clearly interrelated

in our participants – most notably selection bias, small subgroups, and the pitfalls of post hoc analysis.

We disagree that systemic associations are common in LHON. In support of their contention, Dr Finsterer and Dr Zarrouk-Mahjoub cite their own literature review, which considers ~22 case reports of others. Without a “denominator,” and in the face of such ascertainment bias, it is impossible to demonstrate whether an associated finding has a raised prevalence among the rare patients with LHON. Indeed Orphanet, maintained by a consortium of institutions lead by Inerm, estimates the prevalence of LHON plus at less than one in a million, considerably lower than that of LHON, which is estimated at 1:50,000.<sup>4,5</sup> Our respondents were not asked specifically about systemic illnesses or idebenone therapy, and these did not appear to play a role in qualitative analyses of their psychological morbidity.<sup>6</sup>

The recency of vision loss did appear to be associated with psychological morbidity in a parallel study.<sup>6</sup> Predictably, those who lost vision many years earlier were more likely to have made a psychological recovery. Even so, it was noteworthy that many participants had severe psychological symptoms years after vision loss.

We note that Dr Finsterer and Dr Zarrouk-Mahjoub have published ~60 letters to editors in the last 6 months. We believe that readers should be aware that high-volume letter writing has the potential to be superficial and off point, failing to reflect on the nature of the studies in question or on previously published findings.

## Disclosure

The authors report no conflicts of interest in this communication.

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