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Letter to Editor

OPA1 Variant Carriers Require Prospective Investigations for Multisystem Disease

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Abstract:

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Letter to the Editor

In a recent article, Maeda-Katahira *et al.*, reported about four patients with dominant optic atrophy (DOA)-plus due to 4 different variants in *OPA1* (Maeda-Katahira, A. *et al.*, 2019). "Plus" manifestations included vestibular dysfunction (patient 2), muscle weakness (patient 2), cerebellar atrophy (patient 2), and external ophthalmoplegia (patients 2 and 3) (Maeda-Katahira, A. *et al.*, 2019). It was concluded that extra-ocular manifestation should be considered in patients carrying *OPA1* variants (Maeda-Katahira, A. *et al.*, 2019). The study has a number of shortcomings.

We do not agree with the classification of DOA-plus in all four patients. Patient 1 manifested only with deafness and optic atrophy but no other clinical manifestations according to table 2 and the case description. Also patient 4 presented without involvement of other structures than the optic nerve and the ears (Maeda-Katahira, A. *et al.*, 2019). Only patient 2 manifested additionally with vestibular dysfunction and muscle weakness. However, it was not specified in the case description if weakness was due to cerebral, spinal cord, peripheral nerve, or muscle involvement. "Plus" manifestations in patient 3 included affection of the extra-ocular eye muscles, resulting in progressive external ophthalmoparesis (Maeda-Katahira, A. *et al.*, 2019). Thus, the conclusions are not well supported and investigations of organs seemingly unaffected or only mildly affected need to be carried out.

The main shortcoming of the study is that the four patients were not prospectively investigated for multi-system disease. Patients carrying *OPA1* mutations may not only manifest in the brain, ears, vestibular organs, eyes, muscle, or nerve but also in the heart (Ham, M. *et al.*, 2019; & Burke, N. *et al.*, 2015). Thus, we should be informed about the results of the standard or long-term electrocardiograms and echocardiography or other cardiac investigations, to rule out or confirm cardiac involvement. Assessment of cardiac functions in *OPA1* mutation carriers is crucial, as cardiac involvement may strongly determine the outcome of these patients. *OPA1* variants may also manifest with migraine or dysmorphism (Finsterer, J., & Laccone, F. 2019).

Missing in this study are the cerebral MRIs of each patient. Since patient 2 had ataxia and the authors did not specify if ataxia was due to cerebellar dysfunction, spinal cord affection, or sensory neuropathy, cerebral MRI results should be presented to rule out or confirm the cerebellar origin of ataxia.

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Since mutations in *OPA1* show wide intra-familial phenotypic heterogeneity (Napolitano, F. *et al.*, 2020), we should know if there was phenotypic heterogeneity in the family of patient 4, in which another family member was affected in addition to the index case.

Some patients with Leber's hereditary optic neuropathy respond to the application of idebenone. We should be informed if any of the included patients received idebenone or any other type of treatment and if any beneficial effect could be observed.

Overall, this interesting study has a number of shortcomings which need to be addressed before drawing supported conclusions. Two patients need to be re-classified as DOA-, all patients need to be prospectively investigated for multisystem disease, particularly cardiac involvement, and all patients need to undergo cerebral MRI for assessment of subclinical cerebral involvement and for identifying the origin of ataxia and muscle weakness in patient 2. .

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