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Letter to the Editor

Carriers of Heterozygous POLG1 and GBA Variants Require Prospective Investigations for Multisystem Disease

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In a recent article, Hsieh *et al.*, reported about two related males with Parkinson's disease (PD) being attributed to a variant in the *POLG1* and *GBA* gene respectively (Hsieh, P.C. *et al.*, 2019). The 70yo father of the 59yo index case developed diabetes, chronic insomnia, lower limb pain, and anxiety disorder in addition to PD and the index case presented with cognitive decline, rapid eye movement sleep behaviour disorder, orthostatic dizziness, and visual hallucinations in addition to PD (Hsieh, P.C. *et al.*, 2019). We have the following comments and concerns.

POLG1 mutations usually cause multisystem disease (Finsterer, J., & Scorza, F.A. 2018). Multisystem disease may be present already at onset of the clinical manifestations or may develop during the further disease course. During the disease trajectory more and more organs/tissues become affected. Often, however, organs/tissues are only subclinically affected, depending on the stage of the disease and the degree of involvement. Thus, patients with *POLG1* mutations need to be prospectively investigated for subclinical involvement of organs/tissues other than the brain. Particularly, we should be informed about subclinical involvement of the eyes, ears, endocrine organs, myocardium, gastrointestinal tract, the kidneys, cartilage, the haematological system, the lungs, and the skin (Finsterer, J., & Scorza, F.A. 2018).

We do not agree with the notion that *POLG1* mutations damage mtDNA (Hsieh, P.C. *et al.*, 2019). POLG1 dysfunction leads to a deficient replication of the mtDNA, thus the generation of the molecule is impaired and there is no damage of an intact molecule. *POLG1* mutations may not only lead to multiple mtDNA deletions but more frequently to depletion of the entire mtDNA (Finsterer, J., & Ahting, U. 2013). Thus, we should be informed if the amount of mtDNA was reduced in the two described patients or not.

Concerning the visual hallucinations in the index case we should be informed if they were attributable to epileptic activity, a stroke-like episode (SLE), to psychiatric disease, or to a side effect of the anti-Parkinson medication. Particularly, we should know if the patient ever required antiepileptic drugs (AEDs), if cerebral imaging ever suggested the presence of a stroke-like lesion (SLL), the morphological equivalent of a SLE, or of visual hallucinations had developed already before onset of PD.

Missing is a discussion about the pathogenicity of the *POLG1* and *GBA* variant. Since both variants have been reported in association with PD (Hsieh, P.C. *et al.*, 2019; Kim, C.Y., & Alcalay, R.N. 2017), we should know if both variants contributed equally to the phenotype or if either of the two was the causative factor. From *GBA* variants it is only known that they represent a risk factor of developing the disease but it is unclear, which factors need to be present to trigger the development of PD.

Missing in this report is also the description of cerebral imaging. Since both patients presented not only with PD but also with insomnia, visual hallucinations, rapid eye movement sleep behaviour disorder, and cognitive decline, it is crucial to present and discuss the

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MRI findings of both patients. Of particular interest is if any of the described phenotypic manifestations was attributable to a SLL or due to epileptogenic seizure activity. In this respect, we also need to know the results of EGG recordings in the father.

Overall, this interesting case study could be more meaningful if mtDNA content in both patients was quantified, if multiple mtDNA deletions were excluded, if both patients were prospectively investigated for subclinical or mildly manifesting multisystem disease, and if the nature of visual hallucinations was clarified.

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