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Letter to the Editor

The m.13513G>A variant in *ND5* Affects Multiple Tissues, Including the Retinal Ganglion Cells

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In a recent article, Chen *et al.*, reported about a 28 years old Chinese male with a previous history of syncope at age 6y due to Wolf-Parkinson-White (WPW) syndrome who developed bilateral, painless visual loss at age 15 years being attributed to the variant m.13513G>A in *ND5* (Chen, B. S. *et al.*, 2019). Visual impairment resolved completely within 13 months but he developed hyper-CKemia since age 25 years and renal insufficiency since age 28 years (Chen, B. S. *et al.*, 2019). The study has a number of shortcomings, which require comments.

Though the authors mention that the m.13513G>A variant was heteroplasmic, we were not informed about the exact heteroplasmy rate. Knowing heteroplasmy rates in various tissues is crucial for assessing the pathogenicity of the variant and for genetic counselling (Galera-Monge, T. *et al.*, 2019).

The m.13513G>A variant has not only been reported in association with MELAS and Leigh-syndrome but also in association with MELAS/Leigh/LHON overlap syndrome (Blok, M. J. *et al.*, 2007), MELAS/progressive external ophthalmoplegia overlap syndrome (Blok, M. J. *et al.*, 2007), atherosclerosis (Sazonova, M. A. *et al.*, 2017), and neonatal death (van Karnebeek, C. D. *et al.*, 2011). We do not agree that the index patient did not have other neurological manifestations than impaired visual acuity. Obviously, the patient also had myopathy.

Since MIDs may occur more frequently in subjects originating form consanguineous marriages, we should know if father and mother of the index case were related or not.

The index patient had symptomatic WPW-syndrome since age 6 years. We should know if he developed further syncopes or other clinical manifestations during follow-up. We should also know if he underwent thermo-ablation of the conduction defect. Most patients require ablation to prevent aberrant conduction of supraventricular arrhythmias. It should be also mentioned if in addition to WPW-syndrome other manifestations were detected on echocardiography or cardiac MRI, such as hypertrophic cardiomyopathy, dilated cardiomyopathy, restricted cardiomyopathy, or noncompaction.

Since the m.13513G>A variant can manifest with hypertrophic cardiomyopathy, we should know the proBNP and troponine values and the results of the echocardiographic and cMRI studies.

The authors do not discuss why visual impairment completely resolved. Was this due to spontaneous resolution or due to any changes of the life-style. We should know if the patient changed his diet to a low glycemic diet (ketogenic diet), which is known to exhibit a beneficial effect on various manifestations of a mitochondrial disorder (MID), particularly on epilepsy (Finsterer, J., & Zarrouk-

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Mahjoub, S. 2018). Was there any indication for reduction of the heteroplasmy rate over time?

Since thickness of the retinal nerve fiber layer was diminished (Chen, B. S. *et al.*, 2019), it is conceivable that there was also optic atrophy. Were there any indications for optic atrophy on orbital MRI or the visually evoked potentials?

Overall, this interesting case could be more meaningful if heteroplasmy rates were provided, if echocardiography or cardiac MRI findings were reported, if follow-up data of cardiac involvement and treatment were provided, if consanguinity of parents was excluded, if results of visually evoked potentials were shown, and if improvement of visual acuity within 18 months after onset was explained.

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