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Letter to the Editor

Retinal Nerve Fiber Layer Thickness in Progressive External Ophthalmoplegia Not Only Reflects the Disease Trajectory

Josef Finsterer, MD, PhD*

Neurological Department, Krankenanstalt Rudolfstiftung, Messerli Institute, Vienna, Austria

*Corresponding Author
Josef Finsterer, MD, PhD

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With interest we read the article by Wu *et al.*, about 18 patients (6 males, 12 females) with the diagnosis chronic progressive external ophthalmoplegia (CPEO), established upon findings on muscle biopsy and genetic testing who underwent measurement of the peripapillary retinal nerve fiber layer thickness (pRNFLT) (Wu, Y*et al.*, 2019). pRNFLT was significantly lower in CPEO patients than in an age- and sex-matched controls (Wu, Y*et al.*, 2019). We have the following comments and concerns.

The main shortcoming of the presented study is that the genetic background of the included patients was not provided. Knowing the genetic cause of CPEO patients is crucial as disease course, development of ocular involvement, degree of multisystem involvement (CPEO plus) prognosis, and outcome may strongly depend on the genotype.

From the genetic point of view it is crucial to differentiate CPEO due to point mutations, such as in the *tRNA (Ala)* or *POLG1* genes from CPEO due to mtDNA deletions. CPEO due to mtDNA deletions can be due to a single deletion or due to multiple mtDNA deletions. Single mtDNA deletions occur most frequently sporadically, whereas multiple mtDNA deletions are due to mutations in nDNA located genes, such as *C10Orf2* (twinkle), *SLC25A4*, *TK2*, *ANT-1*, or *POLG1* (McClelland, C *et al.*, 2016).

Since CPEO is not a homogenous disease entity but genetically heterogeneous, traits of inheritance may follow a maternal, autosomal dominant, or autosomal recessive transmission. A factor that needs to be considered with regard to the variability of phenotypic expressions among CPEO patients carrying a single mtDNA deletion or an mtDNA point mutation is the heteroplasmy rate. Heteroplasmy rates are responsible for variable mutation loads in different cells and tissues, between affected probands of a single family and between different families carrying the same mutation. Variability of the ophthalmologic findings may be attributable, at least in part, to variant heteroplasmy rates in retinal ganglion cells, Amacrine cells, bipolar cells, horizontal cells, or receptor cells.

Another shortcoming of the study is that no follow up investigations were carried out and that the current medication these patients were regularly taking was not provided. Knowing the current medication is crucial as it may not only influence disease trajectory but also the pathophysiology of affected mitochondria. Follow-up investigations are crucial to know the course of the disease and the pattern and progression of organ involvement. In the majority of the cases CPEO is not restricted to the extra-ocular eye muscles, but a multisystem disease (CPEO plus) (Jackson, C.B *et al.*, 2014).

Missing in this study is also the family of the 12 included patients. Since mtDNA point mutations or single mtDNA deletions are inherited in 75% respectively 4% of the cases, (Poulton, J *et al.*, 2017), we should be informed in how many of the patients the variant was inherited or occurred spontaneously.

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Overall, this interesting study could profit from providing the genetic background of the included patients, the family history, heteroplasmy rates, and the current medication. There is also a need to prospectively investigate all patients for subclinical or mildly manifesting multisystem disease (CPEO plus).

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