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Letter to Editor

Only Genetically Homogeneous Cohorts Allow Assessment of Cognitive Dysfunction in Progressive External Ophthalmoplegia

Josef Finsterer, MD, PhD

[1]Krankenanstalt Rudolfstiftung, Messerli Institute, Vienna, Austria

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Abstract:

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LETTER TO THE EDITOR

With interest we read the article by Zhang *et al.,* about global cogntition, executive functions, language, working memory, memory functions, and visuospatial functions in 28 patients with genetically heterogenous chronic progressive external ophthalmoplegia (CPEO) (Zhang, G. *et al.,* 2020). The authors found impairment of gobal cognition, executive functions, and language (Zhang, G. *et al.,* 2020). The study has several shortcomings.

The main shortcoming is that CPEO in the included patients was genetically heterogeneous (single mtDNA deletion (n=24), *RRM2B* mutation (n=2), *TK2* mutation (n=1), *POLG1* mutation (n=1)) (Zhang, G. *et al.,* 2020). Cerebral involvement may strongly depend on the underlying defect why genetically homogenous cohorts are warrented to draw global conclusions about cognitive impairment. Group homogeneity should not be determined by clinical features but the genetic defect.

The second shortcoming is that disease duration was heterogeneous limiting the comparability between patients. Since cognitive impairment strongly depends on the disease duration, patients with longer disease duration may perform at variance from patients with short disease duration, as has been found in the presented study.

A third shortcoming is that patients were tested only once and that neither long-term results were provided nor changes over time investigated. Since mitochondrial disorders progress over time (Finsterer, J. 2004), including cerebral functions, it is crucial to assess the speed of cognitive deterioration for determining genotype/phenotype correlations and for assessing the outcome.

A fourth shortcoming is that the authors did not differentiate between CPEO and CPEO plus (Jackson, C. B. *et al.,* 2014). Not only single mtDNA deletions but also *POLG1* variants and *RRM2B* variants may go along with multisystem disease (Finsterer, J., & Zarrouk-Mahjoub, S. 2018), which additionally may determine cognitive functions. Thus, we should know how many patients had diabetes, thyroid dysfunction, parathyroid dysfunction, hepatopathy, lactic acidosis, or cardiac involvement. Exercise intolerance may not only be attributable to muscle involvement but also to lactic acidosis (Schrank, B. *et al.,* 2017). According to table 1, 12 patients had CPEO plus but they were not compared with the 16 pure CPEO patients.

***Corresponding Author:** Josef Finsterer

We disagree with the statement that "in mitochondrial diseases, mutant mtDNA accumulates in the frontal lobe more than the parietal, occipital, or temporal lobes". These findings have been reported in a 20yo paper and cannot be generalised. Heteroplasmy rates may vary considerably between different cortical areas, depending on the underlying variant and the degree of cerebral involvement.

Test re-test reliability should be provided. Overall, the interesting study by Zhang *et al.,*. has a number of shortcomings which limit the conlcusions drawn. Evaluation of genetically homogenous cohorts may allow stronger conclusions than testing inhomogeneous cohorts.

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