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ADVANCES IN MEDICAL RESEARCH

# External ophthalmoplegia requires genetic work-up prior to strabismus surgery

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## Letter to the Editor

We read the article by Chatzistefanou et al. about 2 adults undergoing surgery for strabism due to Chronic Progressive External Ophthalmoplegia (CPEO) [1]. There are a number of issues that raised concerns and require comments and discussion.

The main shortcoming of the study is that the cause of CPEO was not provided, neither for patient-1, a 26 year male nor for patient-2, a 36-year female. CPEO is, in the vast majority of the cases, a genetic disorder due to a single deletion of the mitochondrial DNA (mtDNA), due to mtDNA point mutations, due to multiple mtDNA deletions, or due to depletion of the mtDNA [2]. Single mtDNA deletions manifest phenotypically as CPEO, Kearns-Sayre Syndrome (KSS), or Pearson syndrome. KSS usually goes along with CPEO and Pearson syndrome may turn into a multisystem disease, including CPEO during the disease course [3]. Single mtDNA deletions are sporadic in the vast majority of the cases and maternally inherited in only 4% of the cases. mtDNA point mutations associated with CPEO include m.3243A>G, m.8340G>A, m.960delC, m. 2835C>T, m.12294G>A, m.5613T>C, and m.3291T>C, to mention only the most recently detected. Multiple mtDNA deletions or mtDNA depletion follows a Mendelian trait of inheritance. Multiple mtDNA deletions associated with CPEO are due to mutations in *POLG1, POLG2, TK2, DGUOK, MPV17, RRM2B, ANT1,* and *TWINKLE (C10orf2)* [4]. MtDNA depletion associated with CPEO is due to mutations in *POLG1, TK2*, or *TWINKLE*, Knowing the genetic cause of CPEO is crucial for genetic counseling, for guiding treatment, and for assessing the prognosis.

A second shortcoming is that the family history was not provided. We should be informed if any of the first degree relatives also manifested with CPEO or other typical manifestations of a Mitochondrial Disorder (MID) and if any of the manifesting relatives was genetically investigated.

CPEO may not only occur as an isolated feature but also together with phenotypic manifestations in other organs (CPEO-plus) [5]. Two presented patients systematically and prospectively investigated for CPEO plus, in particular involvement of the brain, endocrine organs, heart, ears, gastrointestinal tract, or kidneys?

Lacking is also a long-term follow-up. As with surgical correction of ptosis, surgical correction of strabismus may be initially beneficial but may be complicated by relapse after a shorter or longer period of time. This is why these patients need to be thoroughly followed up to assess the long-term outcome of the intervention.

It would be also interesting to know if a biopsy of any external bulb muscles was taken and which abnormalities were found. Typically, myopathic features, reduced oxidative enzymes, ragged red fibers, ragged blue fibers, COX-negative fibers, and

morphologically abnormal mitochondria can be found. Biochemical investigations of the muscle homogenate may show a deficiency of single or multiple complexes of the respiratory chain.

In conclusion, this case study could be more meaningful if the genetic cause of CPEO would have been provided if the family history would have been taken thoroughly, if the patients would have been investigated for multisystem involvement, and if results of histological and biochemical investigations of the extra-ocular eye muscles would have been provided.

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