



Mitochondrial Ophthalmoplegia Is Not Only due to mtDNA Deletions

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With interest, we read an article written by Lee, et al.¹ about a retrospective study of 16 patients with ophthalmoplegia as a manifestation of mitochondrial disorder (MID). Five patients were classified as Kearns-Sayre syndrome (KSS), three as KSS-like, and eight as chronic progressive external ophthalmoplegia (CPEO).¹ The authors found gastrointestinal abnormalities in five of KSS and KSS-like patients, but in none of CPEO patients; therefore, they concluded that gastrointestinal disease is a feature of KSS.¹ We have the following comments and concerns regarding this article.

The main shortcoming of the study was its retrospective design. This implies that certain investigations were not performed in each patient. Therefore, conclusions about the frequency of certain manifestations remain uncertain. If investigations were only carried out in cases where the patient became symptomatic, asymptomatic abnormalities would have gone unrecognized. For example, if cardiac arrhythmias remain asymptomatic or occur only during night, and no long-term ECG recordings were done in each patient, then indication for treatment may have been missed.² This particularly refers to cases with ventricular arrhythmias, which may be life-threatening if they go unrecognized and untreated. Comparison of the two groups is unreliable if the same investigations were not performed in either cohort. Differences between the two groups are not unexpected, as KSS more frequently presents with multisystem involvement than CPEO, which usually presents with exclusive affection of the extra-ocular muscles without multisystem disease.

A further shortcoming of the study was that diagnosis was

genetically confirmed in only four patients. Diagnosis of MID requires genetic confirmation, as muscle biopsy and biochemical findings can be secondary and thus misleading. Therefore, we should be informed about which genetic tests were applied. Failure to detect the genetic cause in 75% of the cases may be due to either the application of inappropriate tests or application of inappropriate methods. Since ophthalmoplegia frequently results from mutations in nuclear DNA (nDNA) located genes (e.g., *POLG1*, *twinkle*, *C10orf2*, etc.),³ we should be informed on whether the authors also looked for mutations in any of these genes. Particularly, CPEO may not only be due to single mitochondrial DNA (mtDNA) deletions, but also due to point mutations of mtDNA or nDNA. Mutations in nDNA located genes may secondarily cause multiple mtDNA deletions or even mtDNA depletion.³

We do not agree with the definition of KSS. Diagnostic criteria for KSS not only include ophthalmoplegia, onset <20 y, retinopathy, and cardiac conduction defects,¹ but also short stature, elevated CSF protein, and endocrine abnormalities.⁴

Since 12 patients had a family history of being negative for the disease, MID in these 12 index cases may have occurred sporadically or was inherited via an autosomal recessive mode. Since clinical manifestations in mutation carriers may be absent or mild, it is recommended to investigate all first-degree relatives prospectively for subclinical or mildly manifesting MID.

Nothing was reported on what type of treatment the 16 patients were receiving. This should be considered relevant information, as treatment may strongly influence the phenotype and thus the outcome of these patients.

Overall, the results of this study could be more meaningful if the following conditions were met: 1) if the included patients were prospectively investigated for multisystem manifestations; 2) if first-degree relatives were prospectively investigated for subclinical or mildly manifesting MID; 3) if genetic work-up was carried out more vigorously; and 4) if treatment of the 16 included patients received was provided.

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