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READERS' COMMENTS

Exophthalmos associated with chronic progressive external ophthalmoplegia

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To the Editor

We read with interest the article by Takeda et al. on a case series of seven patients with chronic progressive external ophthalmoplegia (CPEO) due to a single mtDNA deletion who also developed exophthalmus [1]. It was found that exophthalmus is a common finding in PEO with an incidence of 70% and can be hidden by ptosis [1]. The study is appealing but raises concerns that should be discussed.

The aim of the study to calculate the incidence of exophthalmus in Japanese CPEO patients is discordant with the study design. First, it is a single center study which does not cover all Japanese patients with CPEO. Second, only patients with CPEO due to single mtDNA deletions were included. Therefore, the aim of the study cannot be reached.

A further limitation of the study is that heteroplasmy rates of the causative mtDNA deletions were not provided [1]. Because mtDNA deletions were detected in different tissues such as buccal mucosa cells, saliva, or extra-ocular muscles (EOMs), variable heteroplasmy rates can be expected, as heteroplasmy rates frequently correlate with the severity of organ affection [2]. In CPEO EOMs are usually more severely affected than buccal mucosa cells.

CPEO may not only be due to single mtDNA deletions but also due to multiple mtDNA deletions, mtDNA depletions, and point mutations in mtDNA or nDNA located genes. CPEO with multiple mtDNA deletions has been particularly reported with variants in *POLG1*, *POLG2*, *TWNK*, *RRM2B*, *TK2*, *C1QBP*, or *RNASEH1*.

Exophthalmus in CPEO may not only be explained by atrophy of EOMs, thyroid ophthalmopathy, orbital mass lesion, or increased axial length [1], but also due to a number of other causalities. Other possible explanations for exophthalmus in CPEO patients could be weakness of the extraocular muscles, facial dysmorphism resulting in narrow orbitae, sinus cavernous thrombosis, and pituitary adenoma [3]. Facial dysmorphism is a common feature of mitochondrial disorders, and some of these patients may develop pituitary adenoma. All these differentials should be appropriately ruled out before starting genetic work-up for single or multiple mtDNA deletions.

Because 4% of single mtDNA deletions are inherited [4], it is crucial to acquire a profound and extensive family history. Knowing the family history is not only crucial for genetic counselling of these patients but also to assess intrafamilial phenotypic heterogeneity of CPEO, which can be considerable between family members [5].

Patients with a mitochondrial disorder may manifest with keratoconus. Keratoconus may lengthen line "B" and may lead to a false positive diagnosis of exophthalmus.

Overall, the interesting study has some limitations that call the results and their interpretation into question. Clarifying these weaknesses would strengthen the conclusions and could improve the study.

Sincerely,

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Author's reply

Thank you for your interest in and the comments on our paper titled "Exophthalmos associated with chronic progressive external ophthalmoplegia".

Please find a reply to your inquiries below.

As you correctly pointed out, we designed our study as a single-center study, so it does not represent the incidence of exophthalmos in all Japanese CPEO patients. Until now, the association between exophthalmos and CPEO has rarely been noted. Therefore, although the present study was conducted at a single institution, we believe that exophthalmos should not be used as a diagnosis to rule out CPEO, and conclude that future data collection at multiple institutions is needed.

We did not screen for mutations in nuclear gene variants, such as POLG, TWNK, RPM2B, TK2, and the whole mitochondrial genome.

To detect the mitochondrial mutations in the present study, our laboratory performed the analysis. We did not determine accurate heteroplasmy rates, which is why we cannot provide them.

In our study, only case 5 was diagnosed with CPEO based on a muscle sample taken during strabismus surgery. Muscle biopsy was not performed in our study due to its invasiveness. The percentage of deleted mtDNA has increased over time. Therefore, for patients in whom no mutations were detected in buccal mucosa cells or saliva, we plan retests within a few years. We believe that the detection of mitochondrial mutations in buccal mucosa cells is sensitive and that we diagnosed mild cases of CPEO without missing any patients.

Cases 1, 2, 3, 4, 6, and 7 underwent head MRI or CT to rule out intracranial diseases such as sinus thrombosis or pituitary adenoma, and these abnormalities were ruled out. Case 5 underwent head MRI or CT at other hospitals and a general checkup by a neurologist to ensure that no other disorders were present except fatigue and ocular paralysis. We hope that data from Westerners will be reported, as the orbit of Japanese patients may be narrower than that of Westerners.

Patients were asked about family history, but none had any.

We agree with Dr. Finsterer's comment that "Patients with a mitochondrial disorder may manifest with keratoconus. Keratoconus may lengthen line "B" and may lead to a false positive diagnosis of exophthalmus". As described in this study, only superficial punctate keratopathy was observed in four patients (cases 1, 2, 5, and 7). No cases of corneal opacity or ulceration were observed and no keratoconus was present.

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