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ABSTRACT

Purpose Chronic progressive external ophthalmoplegia (CPEO) is a mitochondrial disease characterized by slowly progressive ptosis and limitations in ocular motility. Although exophthalmos is not considered to be a common feature of CPEO, this study focused on the incidence of exophthalmos in patients with CPEO.

Study design Retrospective observational case series

Methods We reviewed the clinical charts of patients who received a diagnosis of CPEO sometime during the period between January 2010 and December 2018. CPEO was diagnosed on the basis of detection of a deletion of mitochondrial DNA (mtDNA) from saliva, buccal mucosa, or extraocular muscle specimens obtained during strabismus surgery. Horizontal MRI/CT images or Hertel ophthalmometry was used in determining exophthalmos.

Results Seven patients (4 males) were identified. The mean age at diagnosis was 32.6 years (range, 13–53 years). mtDNA deletion mutations were detected in the buccal mucous membrane DNA in 5 patients and in the saliva and extraocular muscle DNA in 2 patients. MRI/CT was recorded in 6 patients, four of whom showed exophthalmos (cases 1–4), and case 5 was determined as exophthalmos on the basis of a Hertel ophthalmometer reading.

Exophthalmos was bilateral in 4 of the patients (cases 1, 2, 4, and 5) and unilateral in 1 patient (case 3). Exophthalmos was the chief concern of 2 of the patients; however, it was not clinically significant in the other patients.

Conclusions Although exophthalmos may not be recognized by either the patient or the clinician, it may be one of the common features of CPEO. A large multiethnic study should be performed.

Introduction

Chronic progressive external ophthalmoplegia (CPEO) is a mitochondrial disease characterized by a slowly progressing ptosis and limitations in ocular motility. The diagnosis of CPEO is based on the results of a muscle biopsy including ragged-red fibers or of Southern blot analysis to verify alterations in the mitochondrial DNA (mtDNA) of skeletal muscle [1, 2]. Hwang and colleagues [3] proposed the efficacy of long-range polymerase chain reaction (PCR) for the diagnosis of CPEO mtDNA deletions in buccal cells in 2 patients with confirmed CPEO mtDNA deletions in the medial rectus muscle. Investigation of CPEO mtDNA deletions in buccal cells is a minimally invasive method, and we have been using this technique for the diagnosis of CPEO and have reported on its consistency in terms of its results [4].

Exophthalmos is not generally considered to be a feature of CPEO and should prompt evaluation for alternative etiologies [5]. On the basis of a literature search in PubMed with the keywords *proptosis*, *exophthalmos*, and *CPEO*, only 2 case reports were found [6, 7]. The authors of those studies suggested that CPEO with exophthalmos was caused by loss of support due to atrophy of the extraocular muscles (EOMs). We recently encountered several patients with a chief concern of exophthalmos; hence, we were interested in the incidence of

exophthalmos in patients with CPEO. This study aimed to report the incidence of exophthalmos in Japanese patients.

Patients and methods

In this study, we reviewed the electronic medical records of the CPEO patients who received a diagnosis of mtDNA deletion mutation sometime during the period from January 2010 to December 2018 at the Hamamatsu University School of Medicine. All the study procedures were approved by the institutional review board of the Hamamatsu University School of Medicine (no. 14-040). All the study procedures adhered to the guidelines of the Helsinki Declaration. Written informed consent was obtained from all the patients and guardians after detailed information on the procedures had been explained to them.

Patient age, sex, family history, past ocular surgeries, chief concern, ocular clinical symptoms, angle of deviation, findings of the anterior segment, sample materials, and amount of exophthalmos measured with a Hertel ophthalmometer were retrieved. The amount of exophthalmos was determined using a horizontal image of the orbit obtained with magnetic resonance imaging (MRI) or computed tomography (CT). When both Hertel ophthalmometer and MRI/CT measurements were obtained, the MRI/CT measurement was used. When a

patient's MRI/CT data were not available, the Hertel ophthalmometer reading was used for the evaluation. Exophthalmos measurements on MRI or CT were conducted by two of the authors (Y.T. and H.S.) in a blind manner, and the averages of those measurements were used. The measurement technique was indicated in the *Treatment Guide for Thyroid-Associated Ophthalmopathy* [8] and is shown in Figure 1. We chose the axial plane in which the lens was best seen on T1-weighted images of orbital MRI or CT. The images included the corneal apex, optic nerve head, and lens. A horizontal line between the lateral orbital rims on the axial plane was drawn (line A); then, a perpendicular line toward the posterior surface of the cornea was drawn (line B) [9]. The length of line B was measured on the image-viewing system SPINE-2 (Fujifilm Holdings Corporation). Standard patient positioning, with both eyes on the axial plane without a head tilt or eye deviation, was adopted to ensure precise measurements. The estimated mean exophthalmometric values in the Asian population are 15.35 ± 2.31 mm for men, 15.31 ± 2.31 mm for women [10], and 13.49 ± 1.11 mm for children aged 8 to 13 years [11]. Following the severity index of the thyroid ophthalmopathy treatment guidelines published in 2020 in Japan, we considered exophthalmometric values to indicate exophthalmos at >18 mm for adults [8] and at >16 mm for children under the age of

13 years [12]. Moreover, an asymmetry of more than 2 mm was considered as unilateral exophthalmos [13].

DNA was extracted from sample materials (saliva, extraocular muscle specimen obtained during strabismus surgery, blood, or buccal mucous membrane) with the consent of the patients. The saliva samples were collected from the patients using the Oragene DNA collection kit (DNA Genotek), and genomic DNA was isolated following the manufacturer's instructions. Genomic DNAs from the blood, extraocular muscle, and buccal mucous membrane samples were isolated using the QIAamp DNA Blood kit (Qiagen), the NucleoSpin Tissue kit (Takara), and the Buccal Quick, Buccal Cell DNA Extraction kit, (TrimGen), following the manufacturer's instructions of each. The NCBI reference sequence accession number NC_012920.1 was used as the reference mitochondrial sequence in this study. To screen the mtDNA deletion mutations, an mtDNA fragment of about 12-kb (m.4621–m.16449) covering the previously reported mtDNA deletion regions (m.8470–m.13447 and m.9649–m.15983) of CPEO patients was amplified using a long-range PCR assay [3, 4]. Long-range PCR was performed using the TKs Gflex DNA Polymerase kit (Takara) with the following primer set: forward primer 5′-GTTCCACAGAAGCTGCCATCAAGT-3′, located in m.4621–m.4644, and reverse primer

5′-GAGGAGAGTAGCACTCTTGTGCG-3′, located in m.16427–m.16449. The amplification conditions were 1 minute at 94 °C for 1 cycle, followed by a total of 30 cycles at 98 °C for 10 s and at 68 °C for 6 min in an automated thermal cycler.

Results

Seven cases of CPEO were retrieved. The patients' characteristics are listed in Table 1. The mean age at diagnosis was 32.57 years (range, 13–53 years), and the onset of symptoms was between 9 and 20 years of age. The duration of symptoms since onset and diagnosis was more than 10 years for most patients. In cases 1, 2, 3, 6, and 7, mtDNA deletion mutations were detected in the buccal mucous membrane DNA. In cases 4 and 5, the deletion mutations were detected in the saliva and extraocular muscle DNA, respectively. No deletion mutations were detected in the blood DNA obtained from the patients in this study. None of the patients had a positive family history of mitochondrial diseases. Most of the patients requested consultation for ptosis and ophthalmoplegia, and 2 patients were referred to our hospital because of exophthalmos (cases 2 and 4). Visual acuities were better than 20/20 in 6 patients and 20/40 in 1 patient because of cataract. No patients showed myopia more than -3.50 D. None of the patients had night blindness or an abnormal retinal appearance associated with

retinitis dystrophy. ERGs were recorded in 4 patients (cases 2, 4, 5, and 6) and showed no abnormal response. Bilateral superficial punctate keratopathy was observed in 4 patients (cases 1, 2, 5, and 7).

MRI or CT was recorded in 6 patients. MRI and CT images showed exophthalmos in 4 of these patients (cases 1–4). One patient without an imaging study received a diagnosis of bilateral exophthalmos based on measurements obtained with a Hertel ophthalmometer (case 5). Exophthalmos was bilateral in 4 patients (cases 1, 2, 4, and 5) and unilateral in 1 patient (case 3). The incidence of exophthalmos in this series was around 70%. Nine gaze positions and the MRI of case 2 are shown in Figure 2.

Discussion

CPEO is not generally considered as a causative factor of exophthalmos. None of the widely used ophthalmology textbooks reported exophthalmos as a characteristic finding in patients with CPEO [14–16].

This survey began after the patients of cases 2 and 4 were referred to us with chief concerns of exophthalmos. The patient of case 2 was a 15-year-old boy with a 3-year history of bilateral ptosis and exophthalmos; the patient of case 4 was a 13-year-old girl with a 4-year

history of unilateral ptosis and exophthalmos. Both patients had been intensively studied for thyroid function and myasthenia gravis, in addition to other causative diseases of exophthalmos without any conclusive results, and finally received a PCR-based diagnosis of CPEO at our hospital.

The etiologic factors and predisposing conditions recognized as leading to exophthalmos include the following: enlargement of EOMs, such as in thyroid ophthalmopathy or ocular myopathy; space-occupying lesions in the orbit, such as orbital tumors; increased axial length or high myopia; and lack of mechanical support to the globe by EOMs. Chehade and colleagues [17] described exophthalmos secondary to third nerve palsy. The authors suggested that neuropathic atrophy and/or lack of tonus in multiple rectus muscles allows the globe to prolapse. Maeda and colleagues [6] described a case of CPEO with exophthalmos and suspected that it was caused by a loss of tension in the EOMs after atrophy and lack of globe support. Jenna and colleagues [7] reported a case of Kearns-Sayre syndrome with bilateral exophthalmos that showed atrophy of all EOMs. In the conditions of the above-mentioned 3 cases, the EOMs in CPEO have been reported to frequently undergo atrophy [18–20], except in 1 report [21]. This may lead to insufficient EOM tension and loss of globe support, resulting in exophthalmos. In the current study, we did not measure the muscle

volume, but the coronal T1-weighted MRI images or CT images showed atrophy of the EOMs independently from exophthalmos (cases 1, 2, 3, 4, 6, and 7). We did not find any relationships between the severity of EOM atrophy or limitation of eye movement and the severity of exophthalmos.

In addition to exophthalmos, 4 patients had superficial punctate keratopathy with or without blepharoptosis surgery. Daut and colleagues [22] reported 3 cases and Cohen and Waiss [23] reported 1 case with CPEO and secondary chronic keratopathy following blepharoptosis surgery. They suggested that the myopathy of the levator palpebrae superioris and orbicularis oculi muscles leads to ptosis and poor lid closure. The cornea is susceptible to chronic exposure, coupled with the loss of the Bell phenomenon. We suspect that unrecognized exophthalmos may increase the risk of exposure keratitis. Unlike thyroid ophthalmopathy, which presents with exophthalmos and lid retraction, CPEO usually presents with ptosis, and consequently, exophthalmos may remain undetected. Exophthalmos associated with CPEO may have a different etiologic aspect from that of thyroid ophthalmopathy or other ocular myopathies. Clinicians should consider CPEO when progressive symptoms of exophthalmos, ptosis, and ophthalmoplegia occur, whether alone or in combination, and continue observations.

Our study had several limitations, including the retrospective observations and a small sample size. We used various measurement technics such as MRI, CT, and Hertel ophthalmometry, and thus, the values may have differed according to the examiners, strabismus angle, or orbital bony asymmetry. Slice thickness and other conditions for obtaining MRI or CT images were not controlled. Owing to severe eye movement restrictions, the eyes of most patients were fixed at the lateral position, and the exophthalmos measurements with MRI/CT or with a Hertel ophthalmometer were not well controlled. Moreover, the definition of exophthalmos may vary according to ethnicity. Regardless of these limitations, this is the largest series reporting exophthalmos in patients with CPEO. We believe that exophthalmos is one of the common features of CPEO, with an incidence of up to 70% of cases, and it may be often concealed by ptosis. A large multiethnic study should be performed.

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Fig. 1 Exophthalmos measurements on T1-weighted images of orbital magnetic resonance imaging or computed tomography. A horizontal line is drawn between the lateral orbital rims on the axial plane in which the lens is best seen (line A), following which, a perpendicular line is drawn forward to the posterior surface of the cornea (line B). The length of line B was measured by using the built-in calipers on the monitor

Fig. 2 Nine gaze positions and the horizontal slice of magnetic resonance imaging in case 2. Magnetic resonance imaging shows significant exophthalmos and atrophic horizontal extraocular muscles. The patient provided permission for use of this photograph

Table1

Table 1 Patients' profiles and findings

Case no.	Sex	Age at onset, y	Age at diagnosis, y	Chief concern	mtDNA deletion mutation[a]	Previous surgery	Angle of deviation, PD	Ophthalmoplegia	Anterior segment	Exophthalmos R/L mm (method)
1	F	10s	38	Bilateral ophthalmoplegia	BMM (+) Blood (-)	R-R for XT	80XT	OU; SPD (-2), ABD (-2), INF (-1), ADD (-2)	Bilateral SPK	20.0/20.8 mm (MRI)
2	M	10s	15	Bilateral exophthalmos, ptosis, and ophthalmoplegia	BMM (+) Blood (-)	None	18XT	OU; SPD (-2), ABD (-1), INF (-1), ADD (-2)	Bilateral SPK	19.5/19.0 mm (MRI)
3	M	20s	47	Bilateral ptosis and ophthalmoplegia	BMM (+) Blood (-)	Ptosis	65XT, 5LHT	OD; SPD (-1), ABD (-1), INF (-1), ADD (-1) OS; No limitation	Normal	18.7/16.2 mm (MRI)
4	F	9	13	Bilateral exophthalmos, ptosis, and ophthalmoplegia	Saliva (+) Blood (-)	None	5-15XT, 5LHT	OD; SPD (-1), ADD (-1) OS; INF (-1), ADD (-1)	Normal	16.0/18.2 mm (MRI)
5	F	27	53	Bilateral ptosis and ophthalmoplegia	EOM (+) Saliva (-) Blood (-)	None	110XT	OU; All directions (-4)	Bilateral SPK	18/18 mm (Hertel)
6	M	11	26	Bilateral ptosis and ophthalmoplegia	BMM (+)	Ptosis	90XT	OU; All directions (-4) except ABD	Normal	15.2/14.0 mm (MRI)

7	M	11	36	Bilateral ptosis and ophthalmoplegia	BMM (+)	None	30XT	OU; SPD (-3), ABD (-1), INF (-2), ADD (-3)	Bilateral SPK	15.0/13.9 mm (CT)

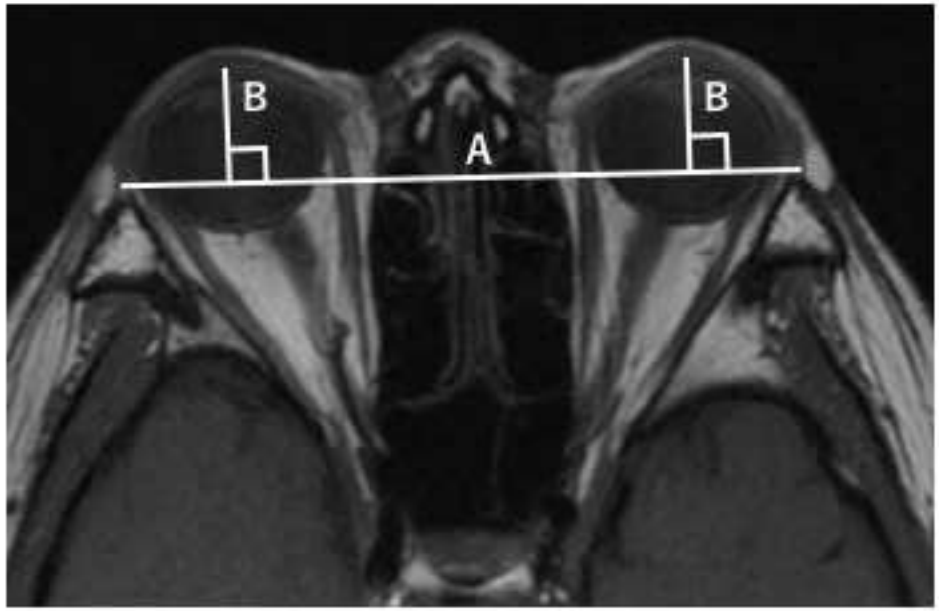
10s teens, *BMM* buccal mucous membrane, *R-R* recess and resect, *XT* exotropia, *LHT* left hypertropia, *OU* both eyes, *OD* right eye, *OS* left eye, *EOM* extraocular muscle, *PD* prism diopter, *SPD* supraduction, *ABD* abduction, *INF* infraduction, *ADD* adduction, *SPK* superficial punctate keratopathy

[a]mtDNA deletion analysis was performed with long-range PCR using the DNAs extracted from sample materials obtained at the onset of symptoms.

(+): Sample material DNAs in which mtDNA deletion were detected.

(-): Sample material DNAs in which mtDNA deletion were not detected.

Figure1



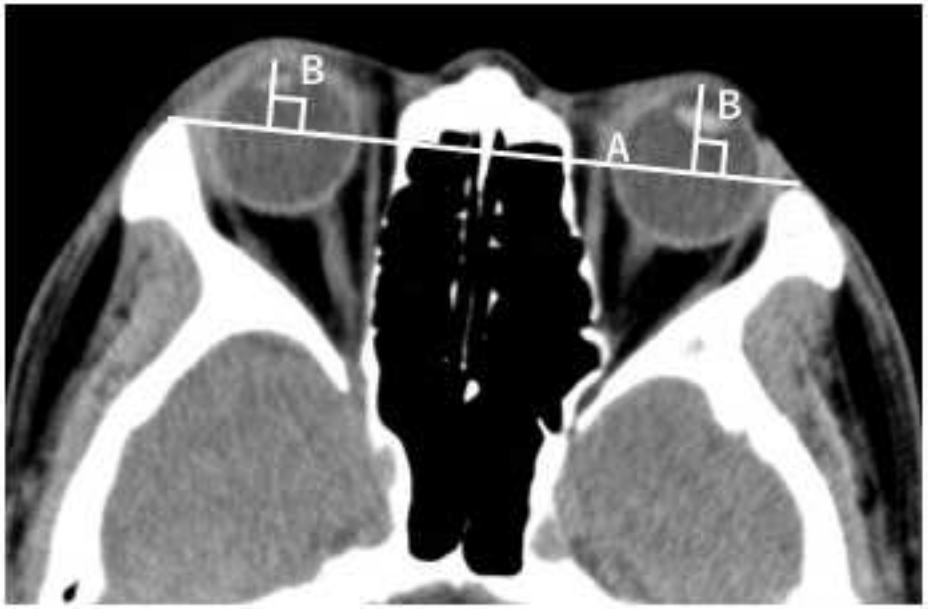


Figure2

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