Optical coherence tomography findings in chronic progressive external ophthalmoplegia

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Abstract

Background: Chronic progressive external ophthalmoplegia (CPEO) is a mitochondrial encephalomyopathy caused by multiple mtDNA abnormalities. There is little information about the changes of ocular fundus with CPEO. The aim of this work was to measure and evaluate changes in the macular retinal thickness and optic nerve head in patients with CPEO using spectral-domain optical coherence tomography and to compare the findings with those of healthy individuals.

Methods: Totally, 18 CPEO patients were enrolled in this study. Healthy volunteers matched for gender, age, and diopter settings were included as a control group. The retinal thickness of macular central fovea, inner and outer retinal layer thickness of perifoveal macular, optic nerve head parameters, and peripapillay retinal nerve fiber layer thickness (pRNFLT) for all included cases were measured using spectral-domain optical coherence tomography. A paired *t* test was used to compare the differences in the studied parameters between the two groups. The correlations between macular retinal thickness, pRNFLT, disease duration, and age of onset were also analyzed.

Results: Among the macular parameters, retinal thickness of macular central fovea ($t = -2.135$, $P < 0.05$) and outer retinal layer thickness ($t = -1.994$, $P < 0.05$) of patients in the CPEO group were statistically significant lower than those of patients in the normal control group. For the optic nerve head parameters, the patients in the CPEO group showed a larger rim volume ($t = -2.499$, $P < 0.05$) and nerve head volume ($t = -2.103$, $P < 0.05$). The overall pRNFLT of patients in the CPEO group was statistically significant lower than that of patients in the control group ($t = -4.125$, $P < 0.05$). The comparison of pRNFLT in eight sectors showed that the pRNFLT of patients in the CPEO group was statistically significant lower than that of the control group mainly in the inferior and temporal sectors. The degree of pRNFL defect negatively correlated with the disease duration ($r = -0.583$, $P < 0.05$).

Conclusions: The retinal thickness of patients with CPEO was significantly thinner, which was mostly the outer retina. The patients' optic discs had a low volume and the loss of the retinal nerve fiber layer was obvious. With the extension of the disease duration, the retinal nerve fiber layer defect was even more significant.

Keywords: Optical coherence tomography; Chronic progressive external ophthalmoplegia; Retina; Nerve fiber layer

Introduction

Mitochondrial encephalomyopathies (MEs) are a group of diseases involving the central nervous system, skeletal muscle, myocardium, endocrine system, and optic nerves. Caused by mitochondrial dysfunction, MEs include Leber hereditary optic neuropathy, lactic acidosis, stroke-like episodes, Leigh syndrome, chronic progressive external ophthalmoplegia (CPEO), and Kearns-Sayre syndrome. CPEO is one of the common types of MEs. The main clinical manifestations of CPEO include ptosis and extraocular muscle paralysis. CPEO is also known as Kearns-Sayre syndrome if it is accompanied with retinitis pigmentosa and a myocardial conduction defect.[1] Pathologically, muscular biopsies of CPEO patients show changes in ragged-red fibers and cytochrome oxidase activity and abnormal mitochondria on electron microscopy.[2] Etiologically, CPEO is associated with the deletion of mitochondrial DNA fragments.[1]

In this disease, the defective function of oxidative phosphorylation may affect evidently in highly oxidative tissues like ocular muscle and retina. Although ocular motility abnormalities[3,4] and ptosis have been commonly observed in patients with CPEO,[5-8] not much researches on the measurement of changes in the ocular fundus structure of CPEO patients have been reported. The effects

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.1097/CM9.0000000000000262

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Chinese Medical Journal 2019;132(10)

Received: 27-12-2018 **Edited by:** Yuan-Yuan Ji

of CPEO on the fundus structure may include changes in the retina and optic nerve head morphology. Some existing studies only performed a qualitative observation using ocular fundus radiography. The advent of optical coherence tomography (OCT) has made it possible to observe the changes of retinal thickness and optic nerve head rapidly in a high resolution and conduct an accurate analysis and measurement. In this study, spectral-domain OCT (SD-OCT) was used to scan and measure the changes of fundus structure in pathologically confirmed CPEO patients to observe whether they were abnormal. In addition, we aim to evaluate whether the changes correlate with the disease duration and onset age.

Methods

Ethical approval

The research adhered to the *Declaration of Helsinki* and the protocol was approved by the Ethics Committee of Peking University First Hospital (No. 2012[542]). Written informed consent was obtained from each patient and each comparison individual before examination.

Participants

From July 2012 to June 2016, 18 patients diagnosed with CPEO who had a muscular biopsy and gene test in the Department of Neurology at Peking University First Hospital were included in this study. Patients with any other systemic disease and any other ocular condition affecting retina and optic nerve, such as glaucoma or macular degeneration, were excluded from this study. Healthy volunteers were selected as the control group. The patients in the two groups were matched for gender, with the same age or a difference of no more than 2 years, and the same diopter group. All the patients with different diopters were grouped based on the spherical equivalent refraction. The grouping method was as follows: the cases with +0.50 D to −0.50 D were in the normal group, the cases with −0.50 D to −3.00 D were in the mild myopia group, the cases with −3.00 D to −6.00 D were in the moderate myopia group, and the cases with greater than −6.00 D were in the severe myopia group.

Ophthalmologic examination

The right eyes of all the patients were selected to evaluate and each eye underwent a detailed ophthalmic examination, including the visual acuity, anterior and posterior segmental biomicroscopic examination, and intraocular pressure measurement.

All OCT examinations were carried simultaneously by a single experienced physician and the examinations were performed using Optovue OCT (RTVue-100, Optpvue Inc., Fremont, CA, USA), a kind of SD-OCT. Only the images with a scan score index >35 were obtained.

The built-in analysis software for OCT was used to measure and the measures consisted of two parts: macular structural examination and optical nerve head examination. Macular examination was performed employing Optovue OCT software for *Macular Thickness Map* protocols and optical nerve head examination for *Nerve head Circle* protocols.

The *Macular Thickness Map* protocol consists of a series of 6 to 24 equally spaced line scans through a common central axis. The diameter of aiming circle is fixed at 6 mm. This protocol calculated retinal thickness, which is the distance measured between the vitreoretinal interface and the junction between the inner and outer segment of the photoreceptors, which is just above the retinal pigment epithelium. The thickness at foveal center point is defined as macular foveal retinal thickness (RTm), and the average perifoveal retinal thickness examination in the macular area within 6 mm × 6 mm was also calculated [Figure 1A].

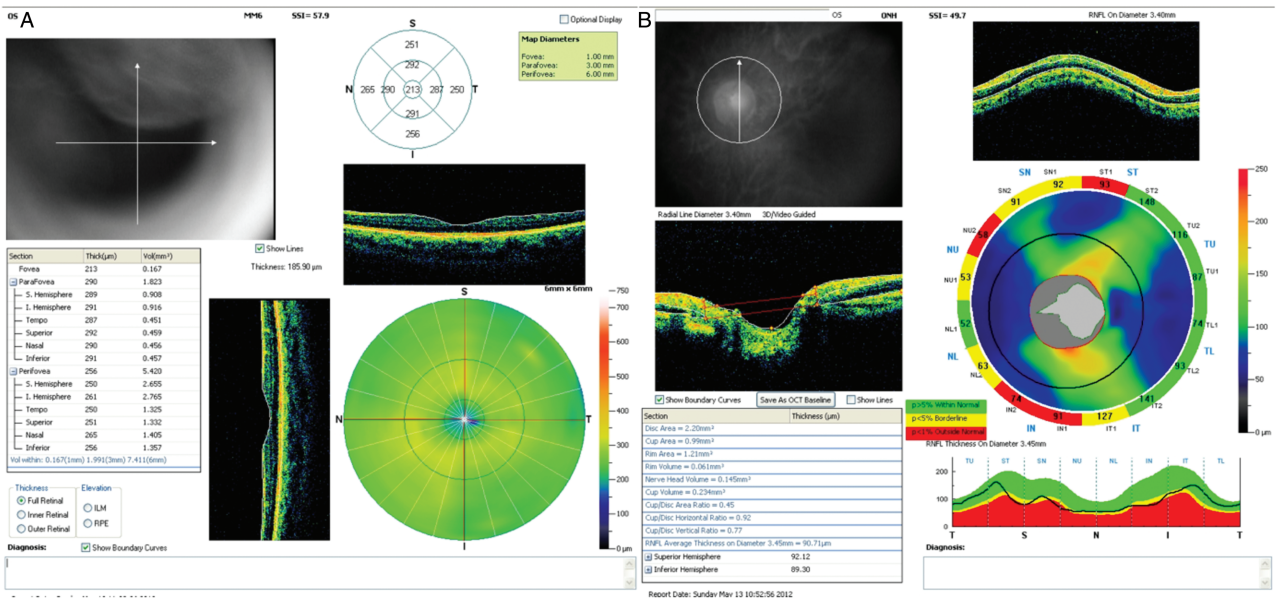

Figure 1: (A) Output of retinal thickness at macula in CPEO patients. (B) Output of optic nerve head analysis of CPEO patients. CPEO: Chronic progressive external ophthalmoplegia.

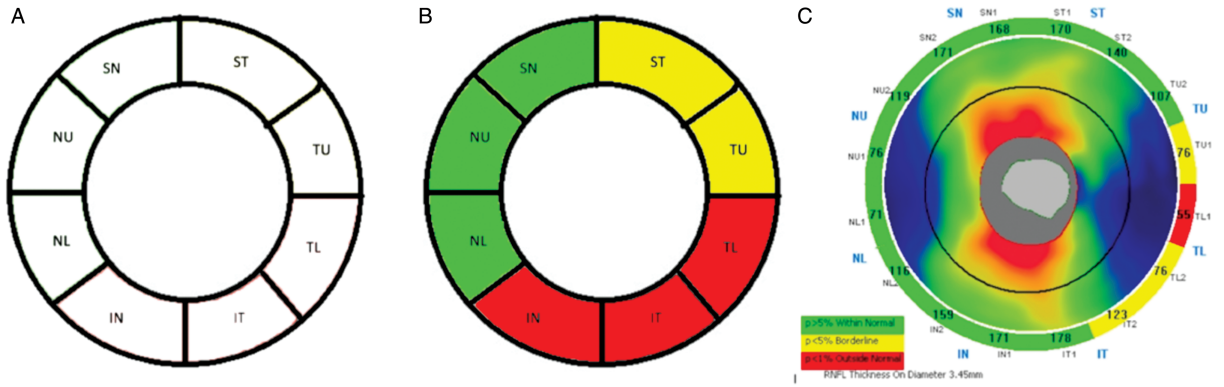

Figure 2: (A) Eight-sector division diagram of pRNFL. (B) The statistical difference between the two groups in eight sectors (red: $P < 0.01$; yellow: $P < 0.05$; green: $P > 0.05$). (C) The implementation of eight sectors on OCT. OCT: Optical coherence tomography; pRNFL: Peripapillay retinal nerve fiber layer.

Table 1: Comparison of the thickness of macular and ONH parameters between CPEO and control groups.

Parameters of macular structure	CPEO group ($n = 18$)	Control group ($n = 18$)	t	P
RTm (μm)	222.33 ± 29.57	240.06 ± 18.43	−2.135	0.04
IRL (μm)	63.06 ± 17.87	65.78 ± 9.72	−0.565	0.57
ORL (μm)	162.61 ± 21.34	173.56 ± 9.31	−1.994	0.05
Disc area (mm^2)	2.531 ± 0.495	2.343 ± 0.558	0.941	0.36
Cup area (mm^2)	1.178 ± 0.713	0.863 ± 0.548	1.160	0.26
Rim area (mm^2)	1.368 ± 0.473	1.512 ± 0.383	−0.924	0.36
Rim volume (mm^3)	0.125 ± 0.075	0.216 ± 0.105	−2.499	0.02
Nerve head volume (mm^3)	0.248 ± 0.124	0.367 ± 0.159	−2.103	0.05
Cup volume (mm^3)	0.331 ± 0.360	0.252 ± 0.239	0.651	0.52

IRL: Inner retinal layer; ONH: Optic nerve head; ORL: Outer retinal layer; RTm: Retinal thickness of macular central fovea.

Using the instrument's segmentation software, the perifoveal retinal macula was divided into the inner retinal layer (IRL) and the outer retinal layer (ORL) with the interface of inner nuclear layer and outer plexiform layer as boundary, and measurements of average inner retinal layer thickness (IRLT) and outer retinal layer thickness (ORLT) were done, respectively.

The *Nerve Head Circle* protocol was used to acquire a single circle scan around the optic disc. The diameter of circle was 3.46 mm and the retinal never finer layer (RNFL) thickness was calculated automatically. Six ONH parameters such as the optic disc area, cup area, rim area, rim volume, optic nerve head volume, and cup volume were collected, including overall average peripapillay RNFL thickness (pRNFLT) [Figure 1B]. The protocol calculated the pRNFLT as the distance between the vitreoretinal interface and RNFL posterior boundary. The full thickness of RNFL was divided into eight sectors, labeled superior temporal, temporal upper, temporal lower, inferior temporal, inferior nasal, nasal lower, nasal upper, and superior nasal [Figure 2A], and the data of each sector were collected separately.

Statistical analysis

All data were statistically analyzed using software IBM SPSS Statistics 14.0 version (SPSS, Inc., Chicago, IL, USA) and the measurement data were represented as the mean ± standard deviation. All parameters of CPEO eyes and control eyes were compared by using paired t tests. The significance of correlations between the OCT parameters of CPEO eyes, disease duration, and the age of onset were determined by Pearson correlation coefficient test. A difference of $P < 0.05$ was considered statistically significant.

Results

Among the included patients, there were six males and 12 females. The patient's age ranged from 15 to 52 years, and the average age was 32.9 ± 11.4 years. The control group also included six males and 12 females, with the age ranging from 14 to 52 years and an average age of 31.0 ± 12.3 years.

The RTm and ORLT of patients in the CPEO group were significantly thinner than those of control group ($P < 0.05$). Also, the IRLT were found to be thinner in the CPEO group, although it did not reach statistical significance ($P > 0.05$) [Table 1].

Among all the parameters of the optic disc, the volume parameters (rim volume and nerve head volume) showed a statistically significant difference, and no abnormalities in the other parameters were found between the two groups [Table 1].

The pRNFLT in the CPEO group was significantly thinner than those of the normal control group, and the difference

Table 2: Comparison of general pRNFLT and pRNFLT at every section between CPEO and control groups.

pRNFLT	CPEO group ($n = 18$)	Control group ($n = 18$)	t	P
General (μm)	100.99 ± 10.61	114.85 ± 9.53	−4.125	0.00
ST (μm)	135.81 ± 21.45	150.25 ± 16.91	−2.488	0.02
TU (μm)	82.16 ± 14.33	96.38 ± 18.95	−2.126	0.05
TL (μm)	74.38 ± 13.97	90.41 ± 20.25	−2.892	0.01
IT (μm)	140.27 ± 18.68	168.16 ± 20.32	−4.871	0.00
IN (μm)	118.11 ± 20.10	133.64 ± 17.11	−2.722	0.01
NL (μm)	66.13 ± 10.61	71.25 ± 11.88	−1.263	0.22
NU (μm)	74.11 ± 13.97	82.66 ± 12.10	−1.263	0.07
SN (μm)	113.44 ± 20.72	125.05 ± 21.86	−1.840	0.08

CPEO: Chronic progressive external ophthalmoplegia; IN: Inferior nasal; IT: Inferior temporal; NL: Nasal lower; NU: Nasal upper; pRNFLT: Peripapillay retinal nerve fiber layer thickness; SN: Superior nasal; ST: Superior temporal; TL: Temporal lower; TU: Temporal upper.

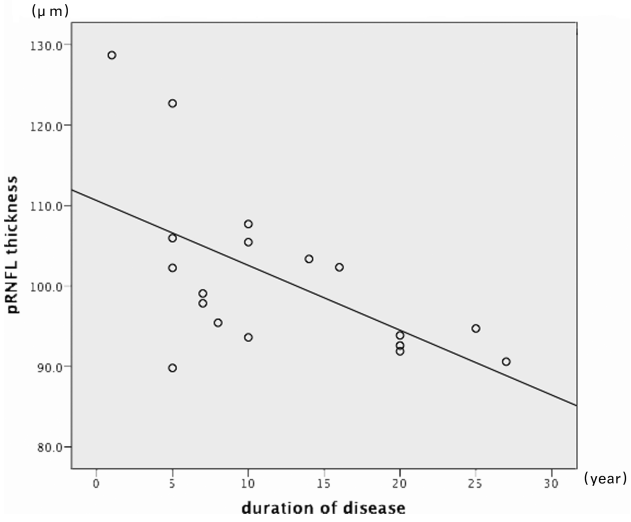

Figure 3: pRNFL thickness of CPEO eyes were correlated with the duration of disease and the correlation was statistically significant ($n = 18$, $r = -0.583$, $P < 0.05$). CPEO: Chronic progressive external ophthalmoplegia; pRNFL: Peripapillay retinal nerve fiber layer.

was statistically significant. After dividing the patient's optic parapapillary nerve fiber layer thickness into eight sectors, a statistically significant difference between the two groups was mainly found in the temporal and inferior sectors [Table 2, Figure 2B].

The onset age ranged from 4 to 45 years, and the average age of onset was 18.6 ± 10.5 years. The duration of the disease ranged from 1 to 27 years, and the average disease duration was 11.9 ± 7.6 years. According to the Pearson correlation analysis, the pRNFLT negatively correlated with the disease duration ($r = -0.583$, $P < 0.05$) [Figure 3], but there was no clear correlation with the age of onset. We also evaluated the correlation between disease duration and pRNFLT of every section. The correlations between the duration and sectional pRNFLT were statistically significant in pRNFLTtl, pRNFLTit, and pRNFLTsn [Table 3].

Discussion

ME is a group of cellular respiratory chain and energy metabolism disorders caused by deletions or mutations of mitochondrial DNA.[9] CPEO is one of the representative disease types. Skeletal muscle and nerve tissue are highly aerobic tissues in the human body that are prone to be affected by CPEO. Specifically for the eye, the extraocular muscles (including the levator palpebrae muscle) and the retina are easily involved. The involvement of the extraocular muscles manifests as symptoms such as ptosis and paralysis of the external ophthalmoplegia, which can easily catch the patient's attention and become the most common complaint and the first symptom of the disease. The changes in the structure of the retina and optic nerve head are generally not considered to be the clinical features of CPEO and are therefore frequently ignored.

In fact, retinal changes are common signs of mitochondrial diseases affecting the eye.[10] In the existing literature, retinal pigmentation was the only signs found in some CPEO patients.[11] Till now, structural changes in ocular fundus of CPEO patients has not yet been reported. The observation of changes in the structure of the retina requires more accurate examination methods. The development of SD-OCT equipment provides us with such an opportunity to observe the fine structure of the ocular fundus.

We performed OCT scans in 18 patients with mitochondrial disease with extraocular ophthalmoplegia as the main manifestation. Healthy individuals matched for gender, age, and diopter-level group served as the controls to measure and compare the parameters of macula and optic nerve head morphology. The results showed significant changes in these parameters.

The common diseases that result in decreased pRNFLT are ophthalmic diseases, including open-angle glaucoma and myopia. The pattern of RNFL loss in open-angle glaucoma corresponds to the changes of optic nerve head rim, and the most frequently affected areas are the inferior and superior temporal areas,[12] which is related to stress-induced retinal ganglion cell apoptosis.[13] Myopia, with the increase in refraction, can cause RNFL thinning in the nasal sector as well as the inferior and superior sectors. This change was positively correlated with the patient's equivalent spherical refraction and was more pronounced in the cases with moderate–severe myopia. Age and gender are also the influence factors of pRNFLT. It had been reported that the pRNFLT decreases with normal aging[14]

Table 3: Correlation between OCT findings and the age of onset, disease duration.

OCT findings	The age of onset		Disease duration	
	r	*P*	*r*	*P*
RTm	−0.122	>0.05	−0.084	>0.05
IRLT	0.461	>0.05	−0.277	>0.05
ORLT	0.034	>0.05	−0.033	>0.05
pRNFLT	−0.056	>0.05	−0.583	<0.05
pRNFLTst	0.258	>0.05	−0.420	>0.05
pRNFLTtu	−0.023	>0.05	−0.175	>0.05
pRNFLTtl	0.110	>0.05	−0.463	<0.05
pRNFLTit	0.075	>0.05	−0.491	<0.05
pRNFLTin	−0.245	>0.05	−0.300	>0.05
pRNFLTnl	−0.149	>0.05	−0.417	>0.05
pRNFLTnu	−0.053	>0.05	−0.359	>0.05
pRNFLTsn	−0.010	>0.05	−0.523	<0.05

IRLT: Inner retinal layer thickness; OCT: Optical coherence tomography; ORLT: Outer retinal layer thickness; pRNFLT: Peripapillay retinal nerve fiber layer thickness; RTm: Retinal thickness of macular central fovea.

and male sex is a significant predictor of increased foveal thickness.[15] Therefore, in addition to the exclusion of eye diseases, age, gender, and diopter degree also should be considered well in the selection of comparative individuals.

For the parameters provided by OCT that are accurate to detect various changes of retina and optical nerve head, this technique has also been applied in several areas in neurology in the last decade. Some neurodegenerative diseases such as Alzheimer disease (AD),[16-19] cognitive impairment,[20,21] dementia,[19,22,23] and Parkinson disease (PD) [24,25] are all found to affect the ocular fundus structure. AD is the most frequent neurodegenerative disease. Although foveal thickness is not considered a useful parameter to detect the atrophy,[17] reduction of IRL, including ganglion cell layer and inner plexiform layer, was observed in the patients of AD.[26] Moreover, the damage of IRL is associated with disease duration and severity.[27] Patients with AD also presented a reduction of pRNFLT,[28] especially in inferior sectors, which were suggested as the earliest sign of AD.[29] PD is another common neurodegenerative disorder, and the macular retinal thickness, especially the IRLT, was found to be reduced in the perifoveal area of PD patients compared to healthy individuals.[30] General pRNFLT, especially in temporal sectors, was affected by PD and reduced significantly.[31] There is a correlation between these ocular findings and the severity of the disease and there OCT parameters were considered as biomarkers of such neurodegenerative diseases. In our study, we found that CPEO, a kind of mitochondrial disease, also had a significant reduction in macular and RNFL.

Unlike these neurodegenerative diseases, in which the loss of the RNFL is more significant in the superior[16,24,29] and temporal sector,[31] the RNFL defect of CPEO is more significant in the inferior sector, followed by temporal sector. Due to the highest density of nerve fibers in the inferior–temporal sectors, the thickness of RNFL may be more affected by degeneration. RNFL thinning of temporal sector was also affected by the damage of photoreceptors at macula and the papillomacular bundle, which was the reason of RTm thinning. Additionally, the thinner layer in retinal thickness of neurodegenerative diseases was IRL, but in CPEO was ORL. The inner retina is comprised of ganglion cell and axon and the outer retina is mainly the cell bodies of the photoreceptor cells. The damages of IRL presented a degenerative disorder of nerve fiber, whereas the reduction of the ORL thickness was mainly caused by the hypogenesis of the photoreceptor cell. Such difference reflects the difference in the effect of these two types of diseases, mitochondrial disease and degenerative disease, on the nerve fiber layer. We suggest that the retinal thickness measured by OCT may be a helpful parameter for the evaluation of mitochondrial disease such as CPEO.

There was significant difference in the rim and nerve head volume between the CPEO group and the control group. The decrease of such volume parameters may be resulted by the low quantity of optical never axon, which was caused by hypogenesis of photoreceptors. Lots of mitochondrial diseases may lead a full axonal loss and the optic disk may turn pale and atrophic, whereas the optical head only had a mild volume decrease in CPEO patients and it may be one of the characters of CPEO.

CPEO is a relatively rare disease and we took nearly 5 years to collect these cases. It is difficult to collect the medical data because of the paralysis of the patients' eye movement. Most of the patients in this study had severe ptosis, and it was difficult to perform a visual field examination. The lack of visual field results did not allow us to determine whether the changes in RNFL thickness resulted in changes in visual function. The sample size was relatively small and there may be some bias in the selection of the samples. These findings in OCT need to be corroborated in a larger cohort.

In further studies, functional changes should be considered to further refine the study design in a larger sample.

Funding

This study was supported by a grant of Beijing Municipal Science and Technology Commission (No. Z15110000 3915126).

Conflicts of interest

None.

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How to cite this article: Wu Y, Kang L, Wu HL, Hou Y, Wang ZX. Optical coherence tomography findings in chronic progressive external ophthalmoplegia. Chin Med J 2019;132:1202–1207. doi: 10.1097/CM9.0000000000000262