Diagnosis of keratoconus in a young male after the hint of electrophysiological test: A Case Report and Review of the Literature

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Case report

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Abstract

Background: Keratoconus (KCN) is a bilateral and usually asymmetrical disease in which the ectatic cornea becomes conical. Diagnosis of unimproved visual acuity (VA) as KCN might sometimes be missed out due to lack of consideration. However, combination of the electrophysiology test and other common ophthalmological examinations could help to locate the lesion for the unimproved VA and realize the possibility of the existence of KCN, which could be diagnosed via corneal topography. The purpose of this report is to describe the diagnosis process of a case of KCN after the hint of lesion location by electrophysiological tests. Case presentation: A 23-year-old young male presented to our ophthalmology clinic complaining of decreased visual acuity in the left eye for 5 months. Clinical evaluation showed best corrected visual acuity of 1.0 OD, and 0.06 OS. The dilated fundus examination revealed no specific abnormality. Spectral-domain optical coherence tomography (SD-OCT) of macular revealed no obvious change on macular and the thickness of peripapillary nerve fiber layer on both eyes. No leakage of fluorecein was found under Fluorescein angiogram (FFA) of both eyes. Indocyanine green angiography (ICGA) did not showed abnormality. The full-field electroretinogram (ffERG) revealed no obvious changes of amplitudes in all responses. Pattern visual evoked potentials (PVEP) detected a reduced amplitude and delayed phase in P100-wave in both eyes. The amplitude and latency of P2-wave in Flash VEP (FVEP) were comparable in both eyes and were within normative ranges. Corneal topography was finally performed and KCN was diagnosed with the presence of asymmetrical bowtie pattern in both eyes, which was worse in the OS. Conclusions: The hint of lesion location by electrophysiological studies (ffERG, PVEP and FVEP) could be of favor to diagnose the conditions with unimproved VA, such as KCN. Consideration of KCN should be suspected in patients with unimproved VA and significant irregular stigmatism, while no obvious lesion exists in other parts of the eye.

Background

Keratoconus (KCN) is a common corneal ectasia with the characterized features of corneal thinning and protrusion. It is usually presented as bilateral, asymmetric and non-inflammatory corneal disorder. KCN would lead to decreased vision and significant visual impairment with the development of irregular astigmatism. Usually, correction with glasses could not be achieved. KCN starts usually at puberty, occurs in the second decade of life, progresses and stabilizes until the third or fourth decade of life[1]. Its prevalence and incidence vary widely with both genders and all ethnicities affected. Approximately, the incidence is estimated to be between 50 and 230 per 100,000 in some studies[2, 3].

Under normal slit lamp, the conical protrusion of cornea in KCN caused by the corneal thinning and distortion might be not easily observed in some cases[4]. In these circumstances, KCN patients with unimproved visual acuity may go undiagnosed or delayed in disgnosis unless the clinician come up with the idea of using corneal tomography, which could assess the corneal surfaces and make the detection of early or subclinical KCN available[5].
Electrophysiological examinations have been used in clinical ophthalmology for centuries, which are especially popular when undiagnosed cases present[6]. Full-field electroretinogram (ffERG) and visual

evoked potentials (VEP) are two of the most common-used electrophysiological methods. Specifically, ffERG is a widely used electrophysiologic test of retinal function, especially the outer and middle retinal layers, induced by flash stimuli of series strength[7]. Visual evoked potentials (VEP) with stimuli of pattern-reversal checkboard (PVEP) or flash (FVEP), can provide assessment of functional integrity of the visual system, including the ocular media, the retina, the optic nerve, and visual cortex[8]. Application of ERG and VEP could provide clues on the location of ocular lesions, which would aid to the definite diagnose of ocular diseases in combination of other advanced examinations[9, 10].

In this report, a case of KCN by the final diagnosis via corneal topography after hint of possible location of lesion by electrophysiological tests, especially the help of FVEP, is described. In addition, this report provides a review of the current literature regarding the application of electrophysiology in KCN patients.

Case Presentation

A 23-year-old young male presented to our clinic complaining of decreased visual acuity in the left eye over 5 months. He had neither history of ocular disease nor previous eye surgery. Besides, he reported no subjective symptoms, such as itching, redness, photophobia, tearing.

Clinical evaluation showed that his best corrected visual acuity (BCVA) was 1.0 with -4.50 sph -0.75 cyl 40° in the right eye (OD). The BCVA was 0.06 in the left eye (OS), which could not be improved by correcting the refractive error (-19.00 sph -4.25 cyl 45°). Intraocular pressures detected by non-contact tonometer (NTC) were 6 mmHg OD and 6 mmHg OS, which were within normal limits in both eyes.

His anterior segment was unremarkable. No obivous abnormolities were found under slit lamp. The cornea and lens are clear, with no sign of inflammation in the anterior chamber. Pupils were equal, reactive to light and accommodation. No relative afferent pupillary defect was found. On dilated fundus examination, no retinal edema or other fundus abnormalities were found elsewhere. (Figure 1) Spectral-domain optical coherence tomography (SD-OCT, Spectralis HRA + OCT, Heidelberg Engineering, Germany) of macular revealed no detachment, schisis or hole on macular. The foveal thickness was 259 μm in OD and 352 nμm in OS. In addition, OCT scanning of peripapillary retinal nerve fiber layer (RNFL) with a radial spoke pattern centered on the foveola in a length of 6 mm, revealed that the thickness of peripapillary RNFL in both eyes were within normal limits according to the reference data (European Descent 2009). (Figure 2)

No leakage of fluorecein was found under FFA throughout all the phases of both eyes. ICGA did not show any abnormality on both eyes, either (Figure 3). Furthermore, no obviously morphological changes were found under B-scanner of both eyes (data not shown)

Electroretinogram was performed with the Ganzfeld (Roland, Germany) according to the International Society for Clinical Electrophysiology of Vision (ISCEV) standard after 30 min of dark adaption with dilated pupil. ERG data revealed no obvious changes of parameters in all responses. In addition, the data were comparable in both eyes. (Figure 4)

The pattern visual evoked potential (PVEP) was recorded according to the ISCEV standard. The reproducibility and reliability were obtained by performing the recording twice. PVEP detected a reduced amplitude and delayed phase in P100-wave of both the 1 degree (1°) and the 0.25° PVEP in both eyes. The delayed phase of P100-wave was more obvious in the right eye, while the reduced amplitude of P100-wave was more obvious in the left eye. (Figure 5)

Flash visual evoked potential (FVEP) was later on performed according to the ISCEV standard with twice recording to ensure the reproducibility and reliability. Reproducible and reliable waveforms of FEVP existed in both eyes. The amplitude and latency of P2 component were comparable in both eyes, which were within common normative ranges. (Figure 6)

Corneal topography was finally performed and KCN was diagnosed in both eyes with the asymmetrical bowtie pattern, which was worse in the OS (Figure 7). The patient was finally diagnozed as bilateral keratoconus and was referred to our superior hospital for transepithelial corneal collagen cross-linking immediately.

Discussion And Conclusions

KCN is characterized by a asymmetrical bilateral central or paracentral corneal stromal thinning, leading to alteration in the corneal curvature. In the initial stage, KCN may be asymptomatic, but its progression causes visual morbidity due to high astigmatism and anisometropia. Patients with KCN usually complains about decreased visual acuity, which could not be improved after correcting the refrative error[11, 12].
Diagnosis of KCN, even in the initial stage, is feasiblly available with specific methods, such as corneal topography, corneal tomography, Holladay map display, and Belin/Ambrosio Enhanced Ectasia Display[13-15]. In paritcular, high astigmatism or an asymmetrical bowtie pattern deteced in corneal topography maps are clinically suggestive of KCN[16, 17]. Different patterns of astigmatism would lead to asymmetrical bowtie pattern with different shapes, such as superior steep, inferior steep, round or oval. All these patterns indicate corneal ectatic disorders. As in our case, the corneal topgraphy reveals an asymmetrical bowtie patterns in the left eye, which is inferior steepening. The refractive error of high mypia and high astigmatism in the left eye lead to an unimproved visual acuity. Thus, the left eye is definitely diagnozed as KCN. As for the right eye, we found that the refractive error is much lower than that of the left eye and the BCVA is 1.0 even though there is also an asymmetrical bowtie patterns in corneal topography maps. The reason might be that the KCN of the right eye is in its early stageand the central point of cornea could still retains intact corneal curvature after correcting the refractive error[18]. Therefore, the right eye should also be diagnozed as KCN. The anisometropia between the right and left eye of our case, to some exent, demontrates the phenomena of asymmetrical bilateral progression of KCN[19].

Decreased vision, which could not be improved by correcting the refractive error is usually associated with lesion in the posterior segment of the eye, such as retinal diseases, macular diseases, optic nerve

diseases[20]. Progress in ocular imaging techniques, particular OCT and FFA, allows high-resolution observation of subtle morphological changes of the retina. However, as the lesion of KCN lies in the cornea, no pathologic changes would be found in the posterior segment by fundus picture, OCT, FFA or ICGA, unless other systemic diseases accompany[21]. In the present case, we do not get positive clues from all the above examinations. In the first begining, we did not bring about KCN as the reason for the unimproved visioin acuity, as we did not find obvious changes of the cornea under slit-lamp. Commonly, electrophysiological tests might be of great usefulness in hinting on the position of lesion in case of unknown reasons for the decreased visual acuity or unimproved visual acuity[9, 10]. Fortunately, we got the hint of lesion location after analyzing the combined results of eletrophysiological investigations, i.e. ffERG, PVEP and FEVP.

ffERG is a mass potential of the summed electrical activity of the retina, which evaluats the global retinal function reflecting the whole retinal function. The influence of ocular media would not be so impressive as the stimuli for ffERG is a series of flash, unless the opaque media is so severe that it reduces the flash strength reaching the retina[22]. In this condition, the Dark-adapted 10 ERG of ISCEV ffERG may give more reliable responses in patients with opaque media, as the strong flash strength is as strong as 10 photopic cd s m-2[7]. In our case, the ERG parameters did not reveal obvious abnormaility in both dark-adapted and light-adapted ERG, in both a-wave and b-wave, indicating the global function of outer and middle layer of retina is intact. Our OCT scaning along with the FFA and ICGA could in some extent exclude the possibility of lesion in macula although we do not perform multifocus (mf) ERG to provide a topographic measure of electrophysiological activity for macula[23].
VEP, recorded from the overlying scalp, are visually evoked electrophysiological signals in the visual cortex that extract from the electroencephalographic activity. Normal VEP waveforms rely on the functional integrity of central vision at all levels of the visual pathway, as visual cortex is activated primarily by the central visual field. PVEP, getting the waveform with the pattern-reversal checkboard stimuli, is less variable in waveform and timing than the VEP elicited by other stimuli. In great details, P100 is usually a prominent peak that shows relatively little variation between subjects, minimal within-subject interocular difference, and minimal variation with repeated measurements over time[8]. Herein, PVEP has been very popular in clinic. Usually, abnormalities of PVEP parameter, particular the latency of P100, are associated with optic nerve diseases when patients get an unimproved visual acuity[24, 25]. We found reduced amplitude and delayed latency of P100-wave in both eyes in the present case. We first assumed that the lesion might lie in the optic never or the pathway latter. However, peak time of P100 is affected by nonpathophysiologic parameters such as refractive error, ocular media, poor fixation[8]. The reduced amplitude in PVEP might be cuased by the the light scatter from the irregular astigmatism, as light scatter has an effect on the mfERG amplitudes[26]. In addition, Geng, W. J. et al. reported that PVEP is susceptible to the influence of visual attention[27]. Thus, PVEP data alone could not ensure whether the lesion lies in the ocular media or on the posterior segment.

FVEP, which are more variable than PVEP across typical subjects, usually remain similar between eyes of an individual subject. Patients who are unable or unwilling to cooperate for PVEP, or with optical factors, such as media opacities, that prevent the valid use of pattern stimuli, FVEP can give useful clinical

information to complement that available from PVEP. Usually, the most consistent and robust components in FVEP from typical adults are the P2 peaks[8]. In our case, the latency and amplitude of P2-wave in both eyes are comparable. In addition, there parameters are all within normative ranges[28].

The abnormal PVEP parameters and the normal FVEP parameters lead us to focus the lesion on the on the ocular media. We confirmed the abnormality of PVEP by asking the patient to count the times of pattern reversal as to focus his attention. In addition, we excluded the possibility of malingering as the reason for the unimproved VA. Furthermore, the ocular media of the patient including the anterior chamber, the lens and the vitreal body, are clear in general. Considering the above situations, we assumed that the lesion might happened in the cornea, which lead us to come up with the ideal of KCN and was finally confirmed a by corneal topography, as noted before.
KCN, commonly arising as an isolated disorder, might also be associated with systemic disease, such as Down's syndrome and Turner's syndrome [29, 30]. In some cases, KCN may be accompanied by other ocular disorders, such macular dysfunction, retinitis pigmentosa, Leber's congenital amaurosis[21]. Usually in this case, eletroretinographic tests are of great use in evaluating potential diseases, especially when visualization of the posterior segment might not be visible ophthalmoscopically due to the high refractive error and the corneal opacities. There are several reports that KCN is accompanied by other diseases found by ERG or VEP. Moschos et al. reported that the retinal response density in mf-ERG differed significantly between some KCN patients and controls, implying that impaired macular function might coexist in some KCN patients[31]. They also applied ERG and VEP in a series of 233 KCN patients and revealed the existence of a diffuse tapetoretinal degeneration or a macular lesion in many cases[32]. Nguyen, D. Q. et al. diagnosed a 35-year-old male of KCN associated with congenital stationary night blindness type 1, whose ERG recording revealed no response to the dim flash in the dark and a "negative" waveform to the standard flash with near absence of b-wave[33]. In such circumstances, the low visual acuity of these KCN might not only be attributed to the corneal abnormality, but also to the retinal dysfunction. Furthermore, the preoperative electrophysiological studies of such KCN cases could provide valuable prognostic information and are crucial to avoid a needless treatment, such as corneal transplantation. Fogla, R. et al. discovered an unimproved BCVA after uneventful penetrating keratoplasty in the left eye of a bilateral KCN case, whose postoperative ERG results indicated the coexistence of cone-rod dystrophy[34]. Actually, we do not find any significant dysfunction of retinal function and the visual pathway through ERG and VEP in our case. Thus, we could predict in some extent that the patient could gain a good vision quality after successful treatment in the cornea.

In summary, we present the diagnostic process of a case of KCN after the hint of lesion location by electrophysiological studies in combined with other morphological examinations. The availability of electrophysiology could help to gain a deeper understanding of clinical picture and prognostic outcome of treatment for KCN. In addition, KCN should be suspected in any patient with significant irregular stigmatism, especially if unstable and increasing over time and when no obvious lesion exists in other parts of the eye.

Abbreviations

KCN: Keratoconus; VA: visual acuity; SD-OCT: Spectral-domain optical coherence tomography; FFA: Fluorescein angiogram; ICGA: Indocyanine green angiography; ffERG: full-field electroretinogram; PVEP: Pattern visual evoked potentials; FVEP: Flash visual evoked potentials; BCVA: best corrected visual acuity; NCT: non-contact tonometer; RNFL: retinal nerve fiber layer; ISCEV: International Society for Clinical Electrophysiology of Vision; mfERG: multifocus electroretinogram.

Declarations

Ethics approval and consent was granted by the ethics committee of the 900th Hospital of The Logistic Team of Chinese PLA.

Consent for publication

Written consent for publication was obtained from the patient

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests

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Author's contributions

W.Y., Y.W., Y.C and M.C. analyzed and interpreted the patient data. W.Y. and M.C. wrote and edited the paper. All authors read and approved the final manuscript

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Figures

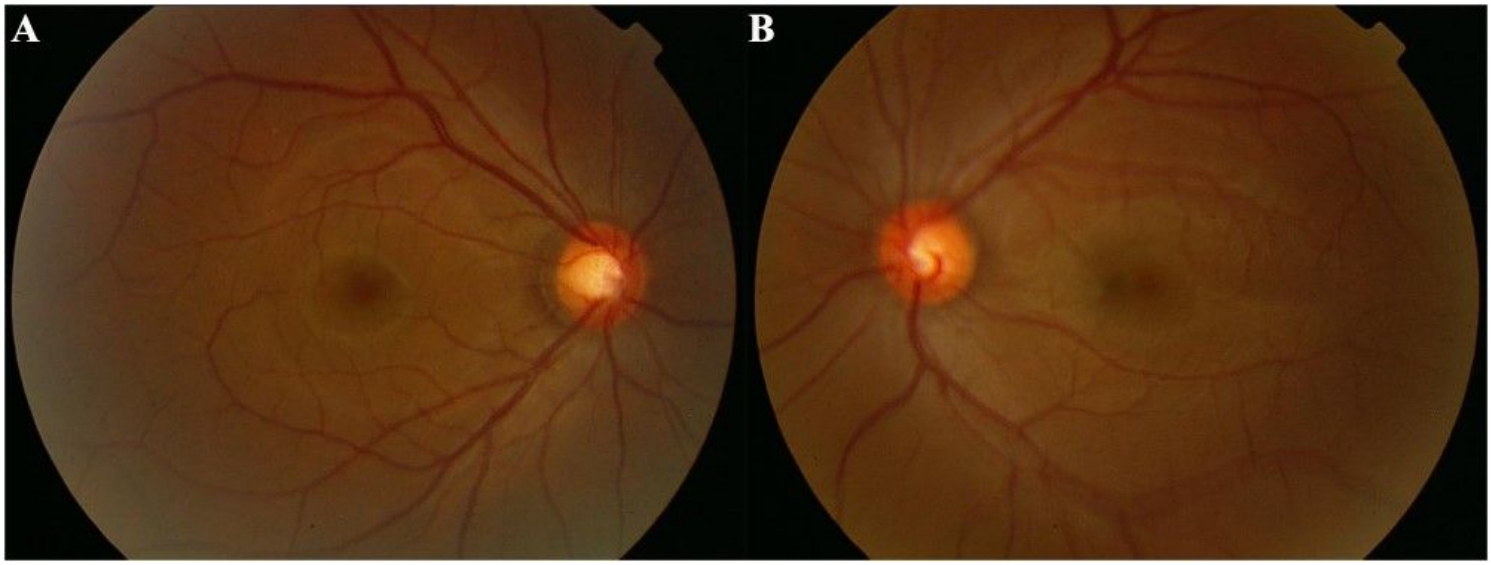

Figure 1

Fundus photograph of both eyes (A: the right eye, OD; B: the left eye, OS). No obvious fundus abnormalities were present in both eyes.

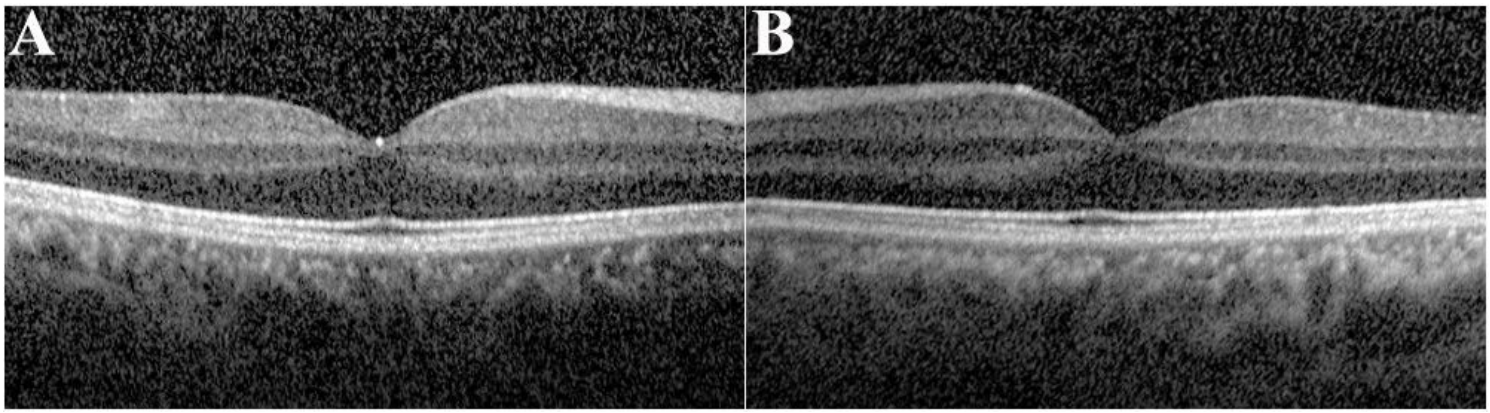

Figure 2

SD-OCT scans of both eyes (A: the right eye, OD; B: the left eye, OS). No obvious changes of macula morphology were found on both eyes under SD-OCT scanning. The thickness of fovea was within normal range.

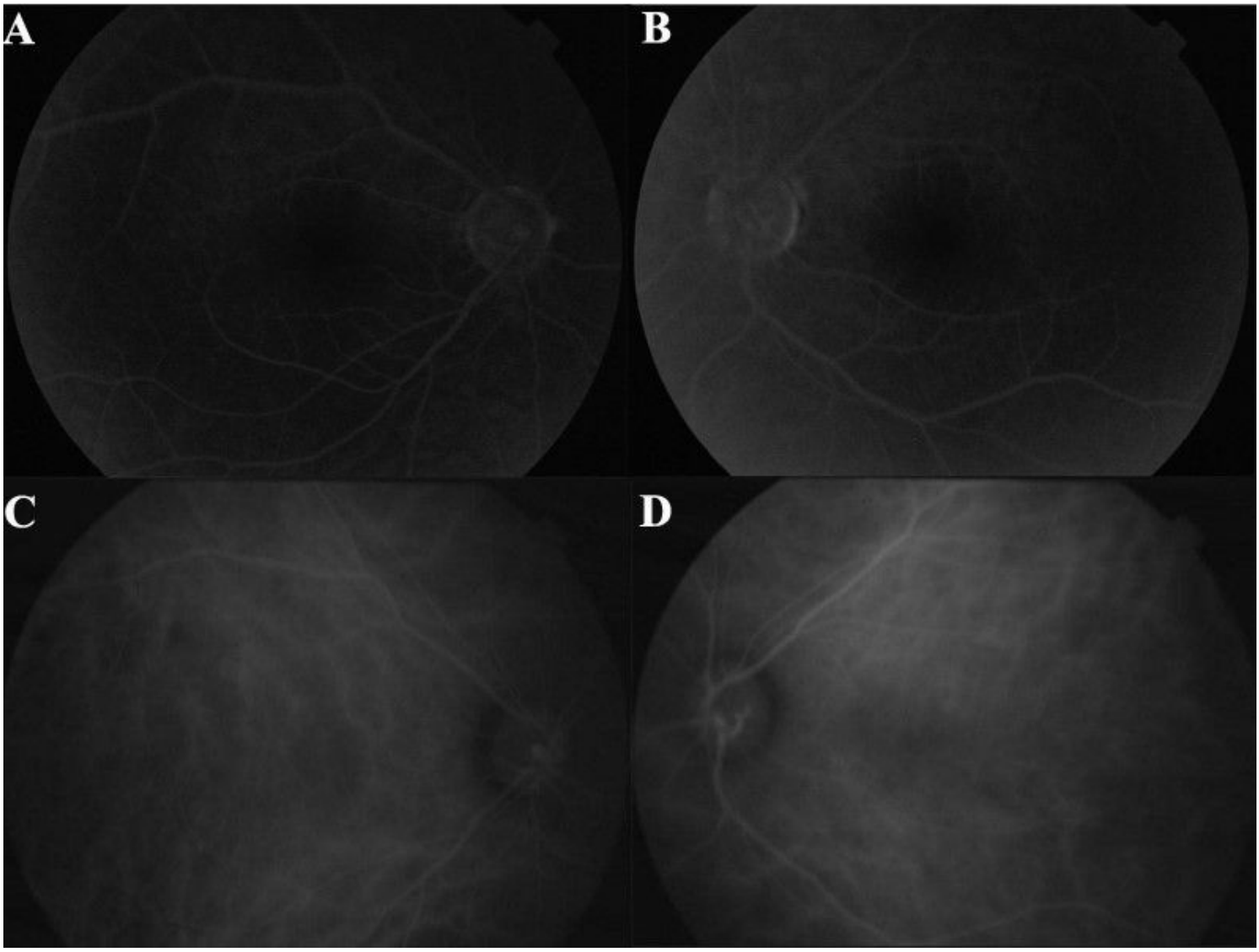

Figure 3

Fluorescein angiogram (FFA) and ICGA of both eyes (A: the right eye, OD of FFA; B: the left eye, OS of FFA; C: the right eye, OD of ICGA; D: the left eye, OS of ICGA). No leakage of fluorecein under FFA was found in both eyes throughout all the phases. No abnormality was found under ICGA.

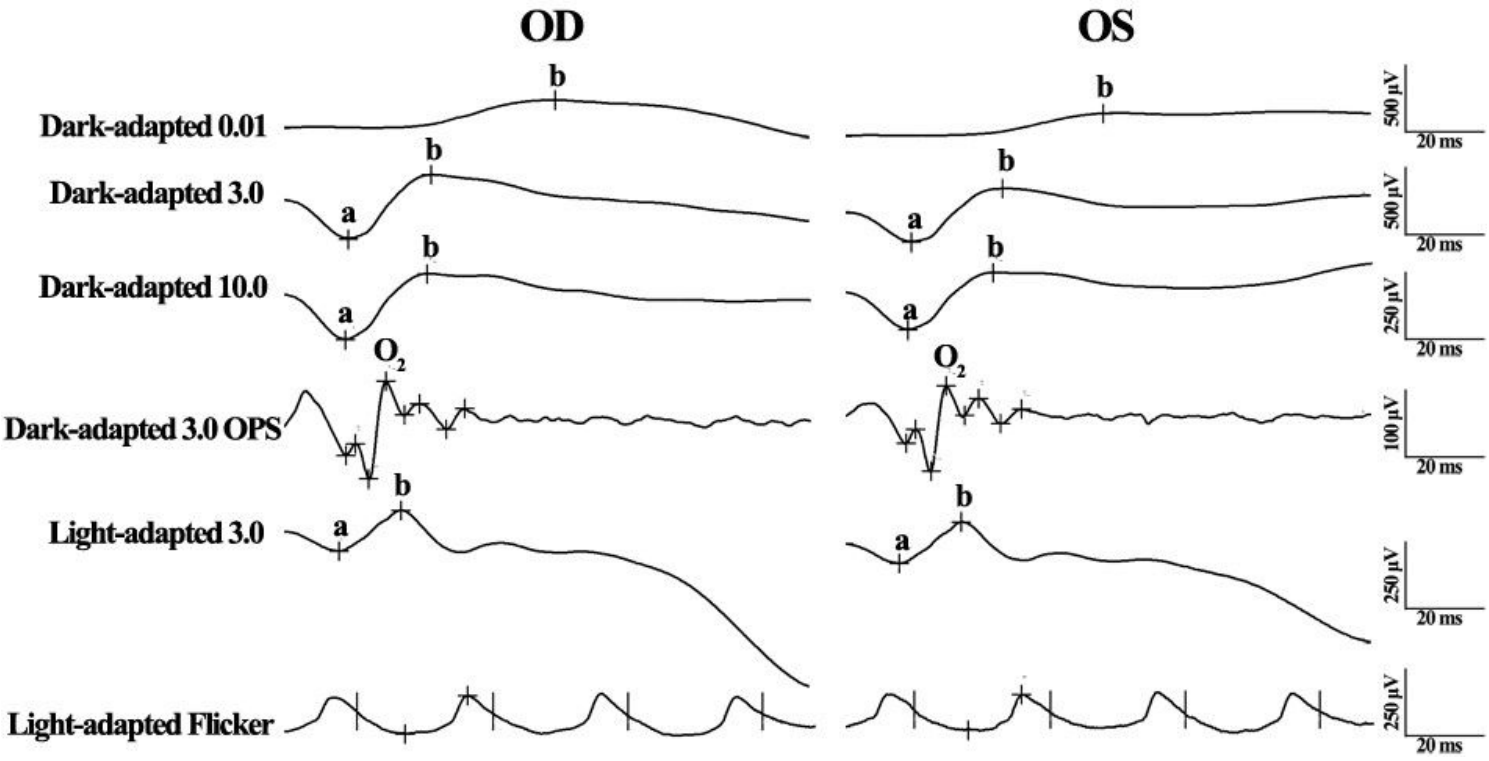

Figure 4

Full-field ERG of both eyes (OD: the right eye; OS: the left eye, OS). The parameters were comparable for both eyes, which were within normative range in general.

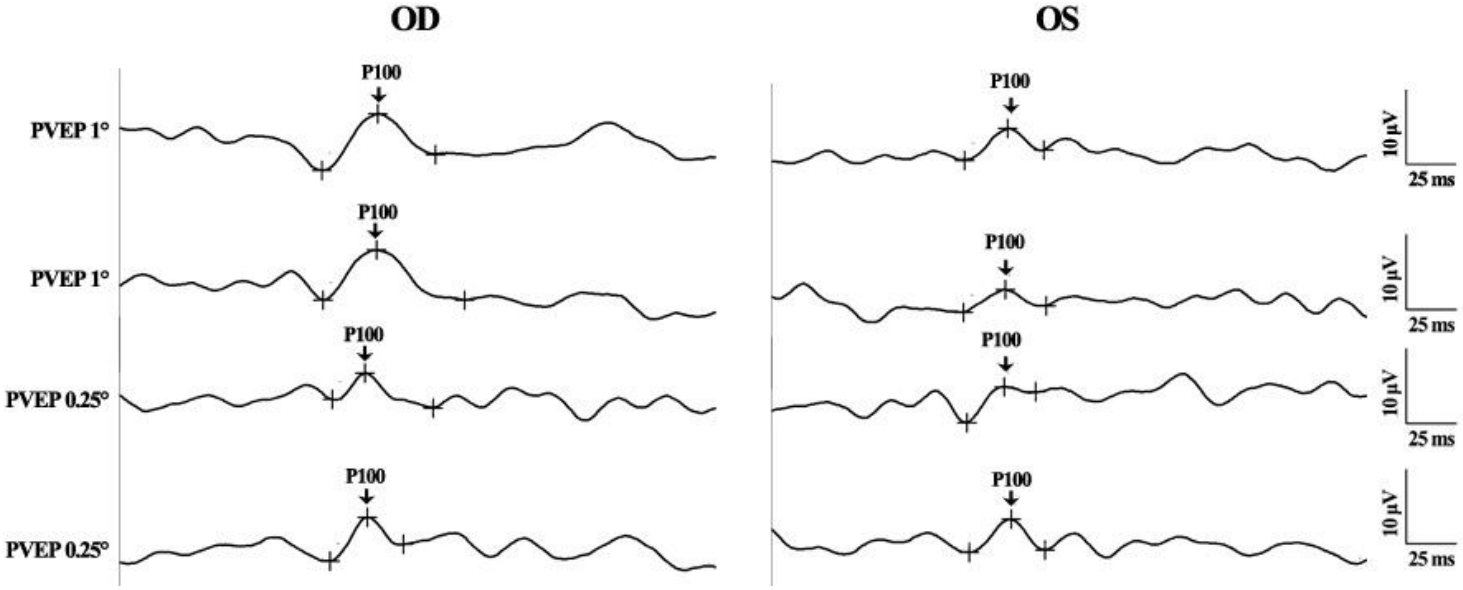

Figure 5

PVEP of both eyes (OD: the right eye; OS: the left eye, OS). A reduced amplitude and a delayed phase of P100-wave were found in both eyes. The delayed phase of P100-wave was more obvious in the right eye, while the reduced amplitude of P100-wave was more obvious in the left eye.

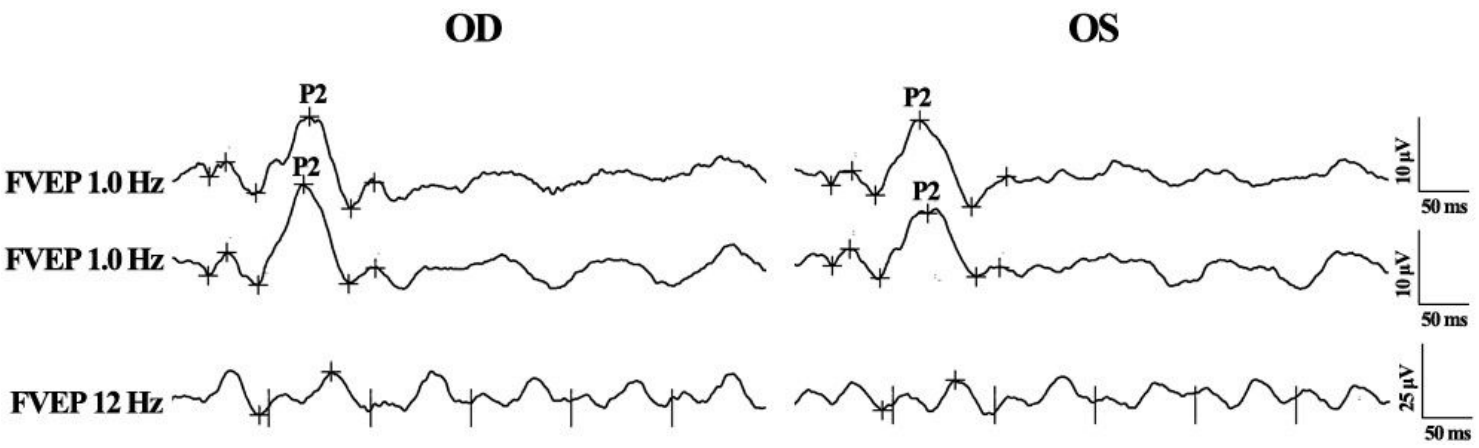

Figure 6

FVEP of both eyes (OD: the right eye; OS: the left eye, OS). The amplitude and latency of P2 component of FVEP were comparable between the right eye and the left eye, which were both within normative range.

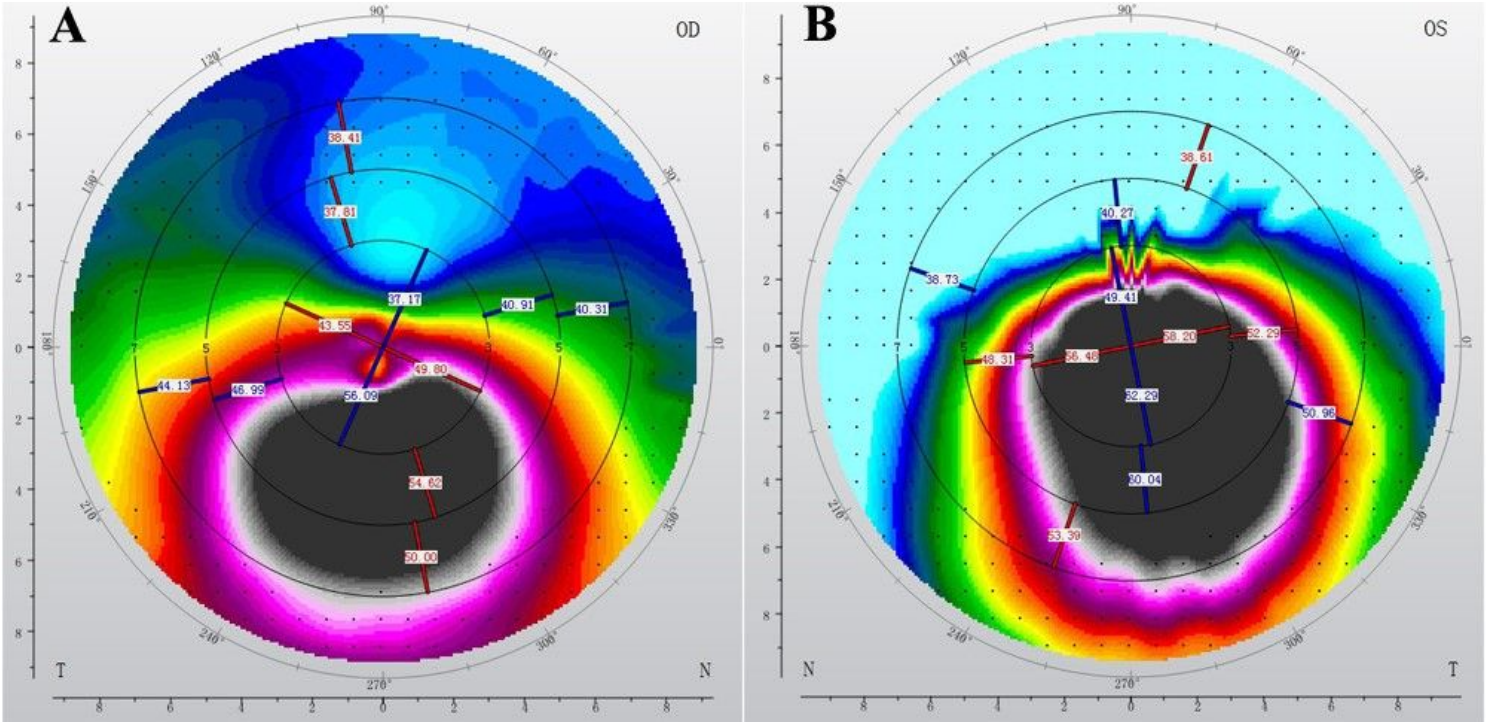

Figure 7

Corneal topography maps. (A: the right eye, OD; B: the left eye, OS). Typical bowtie pattern were revealded under corneal topography in both eyes, showing a inferior steep thinning cornea, characteristic of KCN.

Supplementary Files

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