

CHELATION OF BAND KERATOPATHY IN LONG-TERM OBSERVATION

Kristian P., Cholevík D.

Gemini Eye Clinic, Ostrava, Czech Republic

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MUDr. Petr Kristian
Gemini oční klinika Ostrava
Zdeňka Chalabaly 3041/2
Bělský Les
700 30 Ostrava
E-mail: kristian.petr@gmail.com

SUMMARY

Aim: To report the clinical results of chelation of band keratopathy in long-term follow-up.

Material and methods: The long-term results of 5 patients (5 eyes) with symptomatic band keratopathy with a follow-up period of at least 6 months, in whom 2% EDTA was chelated on the affected eye in the study period from April 2018 to March 2021, were retrospectively evaluated. The follow-up period was 9-37 months.

Results: In all patients, there was a significant improvement in the local findings and an increase in the transparency of the cornea. The effect of therapy was verified on a color photograph of the anterior segment and on AS-OCT by the disappearance of subepithelial hyperreflective foci and accompanying optical shadows. Postoperatively, this enabled a more detailed visualization of the deeper layers of the cornea and other structures of the anterior segment. In a patient with the potential to improve vision, it was also possible to significantly improve visual functions. In the other three patients with pain in the affected eye, the pain subsided, and they also benefited cosmetically from the operation.

Conclusion: Based on our experience and previously published reports, EDTA corneal chelation is able to causally resolve the pathology and improve vision in eyes with visual potential. At the same time, it reduces discomfort and has an analgesic effect in long-term irritated eyes. The operation is also suitable for amaurotic, cosmetically unsightly bulbs, as a successful intervention preserving the eye and improving the appearance of such eyes leads to satisfaction and a subjective increase in the quality of life of the patients.

Keywords: band keratopathy, chelation, ethylenediaminetetraacetic acid, EDTA, anterior segment optical coherence tomography, OCT

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INTRODUCTION

Band keratopathy ranks among degenerative diseases of the cornea, caused by the accumulation of calcareous ions in the Bowman's membrane and the anterior corneal stroma, in the interpalpebral aperture [1] (Fig. 1). The main mineral forming the deposits is hydroxyapatite, which is a complex composed primarily of calcium and phosphate [2]. This frequently concerns a complication of chronic inflammatory and degenerative ocular pathologies [3]. The mechanism of formation of the calcium deposits in the cornea is unknown [4,5]. The disease is usually initially asymptomatic, at the limbus in the horizontal meridians. Upon progression it gradually forms a horizontal band, extending through the centre of the cornea. The speed of progression of the pathology is variable, from months to several years, nonetheless a more rapid development has been observed in dry eyes [5,6]. Calcium salts are a regular component of blood

serum and other bodily fluids such as tears or chamber fluid. The precipitation of calcium in the cornea may be the consequence of greater evaporation of tears in the interpalpebral region, which increases the concentration of solutes, or a lower pH in this area. The pathology may appear at any age; thus children are no exception [5,7-9].

The etiology of this pathology may be ocular, age-related in otherwise healthy individuals, metabolic and hereditary. The ophthalmological causes include above all chronic inflammations of the anterior uvea (e.g. upon a background of juvenile idiopathic arthritis), chronic keratitis, long-term corneal edema, presence of silicone oil in the anterior chamber, post-traumatic state, or phthisis of the eyeball following repeated surgical procedures [1,10]. Chronic inflammations causing elevation of the pH of the ocular surface may facilitate the precipitation of calcium salts [9]. Of metabolic disorders it is necessary to consider above all pathologies which are associated with an increased level of calcium and phosphorus in blood serum,

for example hyperparathyroidism, sarcoidosis, hypervitaminosis D and disseminated tumors with metastases in bones. In addition, secondary hyperparathyroidism accompanying chronic kidney failure may trigger this disease [5,11]. Cases have also been described of band keratopathy caused by a raised level of calcium in serum upon a background of long-term immobilisation or osteoporosis [12]. Another potential risk factor is hyperuricemia [1]. Local factors triggering the disease include preservative agents in eye drops (benzalkonium chloride), or preservative agents with a content of mercury in pilocarpine [5,9]. Another presumed direct trigger of the disease is combined topical treatment using the beta blocker timolol with topical steroids [3]. Familial incidence of the pathology has been described, for example in association with the rare biallelic mutation SLC4A4, leading to a depositing of hydroxyapatite in the Bowman's layer [1,7,13].

Typical complaints of patients suffering from the disease are ocular discomfort, a feeling of a foreign body in the eye, lachrymation and photophobia. Opacification of the centre of the cornea causes a deterioration of visual acuity and glare [2,14]. The accumulation of calcium may damage the ocular surface and lead to recurrent erosion of the cornea [4].

The most frequent indications for surgery are deterioration of visual acuity and persistent discomfort. Other reasons for such an intervention include the impossibility of examining the posterior segment and a cosmetically unsightly eyeball [5,7,13].

In addition to the standard examination on a slit lamp and photographic documentation, in the diagnosis and precise assessment of the affliction it is also possible to use anterior segment optical coherence tomography (AS-OCT) [15].

Among therapeutic strategies we include chelation with diluted 1–2% ethylenediaminetetraacetic acid (EDTA), superficial keratectomy or laser treatment with the aid of phototherapeutic keratectomy (PTK) by excimer laser, following the removal of the corneal epithelium [15,16]. In the case of chelation, mechanical debridement is required at the end of the procedure.

The aim of this study is to present a retrospective evaluation of the postoperative results of a surgical solution of band keratopathy at our centre using the method of chelation.

MATERIAL AND METHODS

A retrospective evaluation was conducted of the long-term results of therapy on patients with band keratopathy, who were treated at our centre using the method of chelation with 2% EDTA. The authors studied the health documentation of all the patients with this diagnosis who were examined at our clinic within an observation period of three years, from April 2018 to March 2021. The cohort included all the symptomatic patients who were indicated for and underwent therapy by chelation, in which the observation period was set at a minimum of six months.

Upon entry a detailed medical history of all the patients was recorded, and in addition a comprehensive ophthalmological examination was conducted both before and after the procedure, including assessment of the condition in artificial mydriasis (tropicamide 1% gtt). Furthermore, colour photographic documentation of the finding on the anterior segment of the eye was produced, and an examination was conducted with the aid of anterior segment optical coherence tomography using a Fourier-Domain AS-OCT system (Optovue Inc., Fremont,

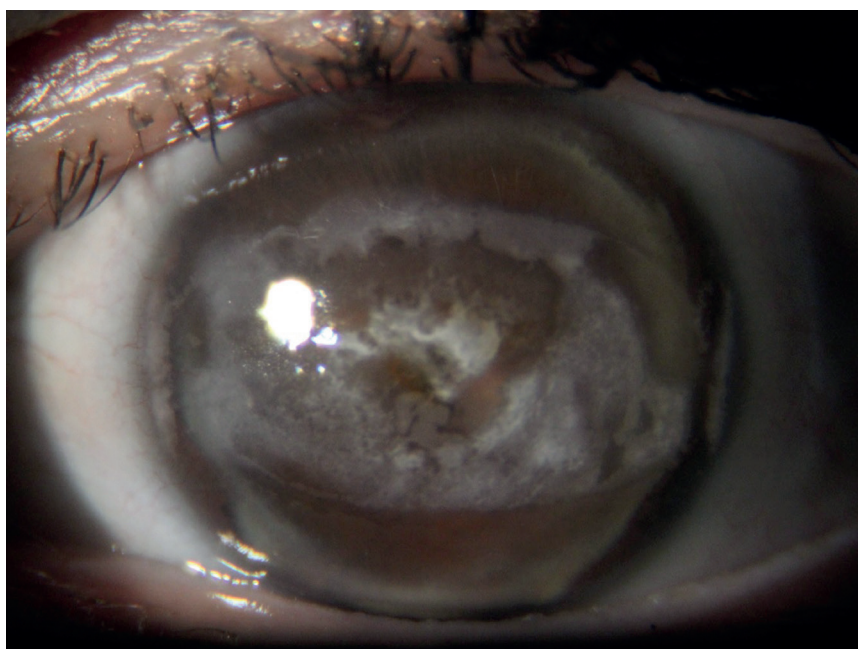


Figure 1. Band keratopathy in patient No. 4

CA, USA), with a corneal adaptor CAM-L attachment. Imaging of the raster was performed on all patients, in a total number of 17 horizontal scans of the central part of the cornea. The length of the individual incisions was 6 mm. The thickness of the identified pathological deposits was measured with the aid of inbuilt software, and the highest measured value was recorded.

All the procedures were performed by the same surgeon. The operations took place by the standard procedure under aseptic conditions in an operating theatre, under combined local topical and infiltration anesthesia with oxybuprocaine hydrochloride (Benoxi 0.4% gtt, Unimed Pharma) and artocaine hydrochloride + epinephrine hydrochloride (Supracain 4% inj., Zentiva). After the performance of mechanical abrasion of the epithelium within the scope of affliction, 2% ethylenediaminetetraacetic acid solution (prepared in a local pharmacy) was applied by topical drying (sugi) and rinsed repeatedly, until the opacification disappeared, and corneal transparency was restored. At the end of the procedure the affected eye was covered by a therapeutic contact lens in order to reduce postoperative pain, which was left until the re-epithelisation of the surface. As a prophylaxis for bacterial infection, levofloxacin hemihydrate (Oftaquin gtt, Santen Oy) was applied to the operated eye 4x per day for a period of 3 weeks.

Postoperatively, together with the clinical examination, the patients were questioned regarding their subjective feelings (presence of pain, cosmetic appearance of the eye and overall satisfaction with the procedure). In addition, the influence on visual acuity, objective appearance on a color photograph of the anterior segment, and the presence of hyperreflective deposits on OCT were evaluated.

The observation period following the procedure was within the range of 9–37 months.

RESULTS

Within the studied period a total of 18 patients with this diagnosis came for consultation, with an average age of 63 years (within the range of 18–85 years). We observed the pathology with twice the frequency in women, in five cases both eyes were afflicted. The main complaints in the majority of cases (72%) included cosmetic appearance and irreversible loss of visual functions.

Five symptomatic patients (five eyes) underwent therapy by means of chelation. Women predominated in this cohort within a ratio of 4:1.

Key factors for indication of surgical intervention were a significant deterioration of visual acuity in combination with a feeling of a foreign body beneath the eyelid of the affected eye in one patient (male), in the other cases (four women) this concerned long-term discomfort, and painful, cosmetically unsightly eyeballs.

In all the women this concerned a unilateral disease. In the sole man the affliction was bilateral, although only the symptomatic left (non-dominant) eye was treated. Bilateral damage to the cornea in this pathology was evident in association with the long-term local application of antiglaucoma agents with a content of benzalkonium chloride (timolol maleate + dorzolamide hydrochloride, Dorzogen combi, Famar). This patient was also treated for systemic hyperuricaemia, which may also have played a role in the etiology of the pathology.

The etiologies of band keratopathy in three of the four female patients included a medical history of repeated surgical procedures performed several years previously at other centres. In the majority of cases the health documentation was not available for consultation. One of the patients had suffered a penetrative injury of the cornea with subsequent suture following a severe fall. It was possible to preserve the eyeball, although visual functions

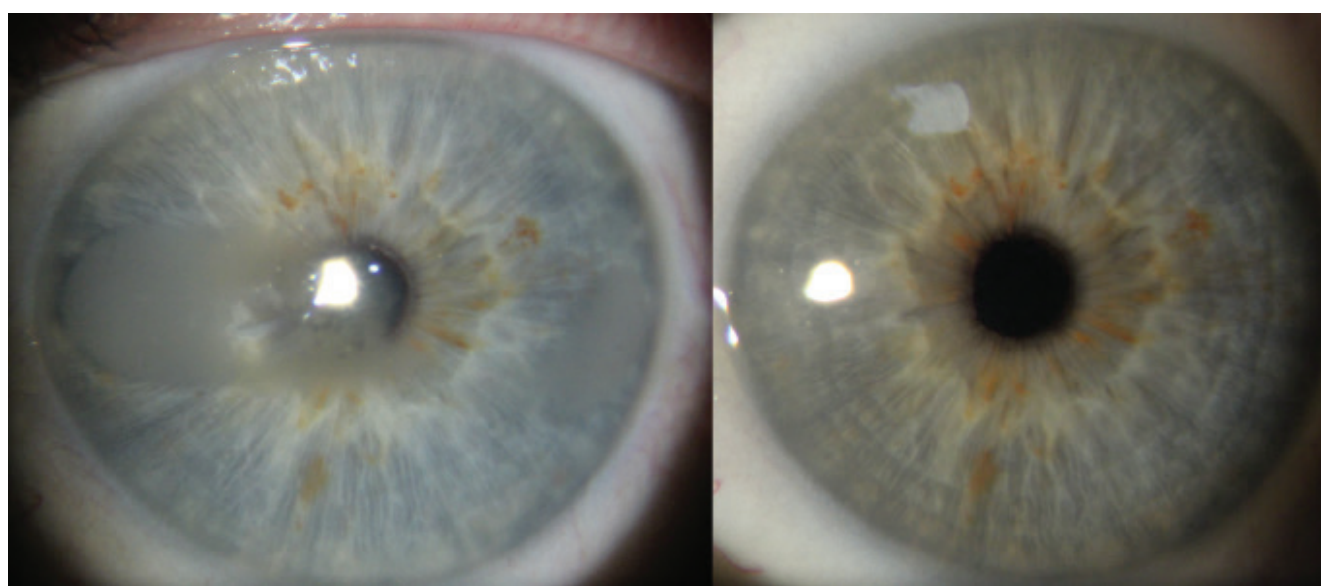


Figure 2. Left: preoperative finding in patient No. 1, right: complete remission – 3 years after surgery

remained on the level of blindness and post-traumatic phthisis occurred, which was evidently the cause of keratopathy. With the exception of this patient all of the eyes were treated with local preparations for glaucoma neuropathy. Two of the patients in the cohort were offered enucleation at other centres but refused this option. Brief demographic and clinical characteristics of our cohort are described in Table 1.

None of the procedures was complicated. In all cases an improvement was achieved, in three patients' complete remission of the pathology was induced and corneal transparency restored (Fig. 2). In the remaining two cases with deeper affliction of the stroma it was possible to remove the majority of the pathological deposits (Fig. 3). In all the patients, following re-epithelisation the procedure succeeded in eliminating pain and significantly reducing discomfort in the afflicted eye, which were among the most frequent preoperative complaints. At the same time as the disappearance of opacities and irritation of the eyeball, there was an improvement of the cosmetic appearance, which all the female patients evaluated hi-

ghly positively when questioned. In the sole patient with the potential of visual functions there was a significant improvement in visual acuity from 0.6 (logMAR) to 0.1 (logMAR), and the effect of this still persists three years after surgery.

In all the treated cases, upon imaging with the aid of AS-OCT a reduction of the scope or absolute disappearance of subepithelial hyperreflective deposits was achieved. Simultaneously with the disappearance of the optic shadow beyond the layer of calcium salts, imaging of the deeper layers of the cornea was made possible (Fig. 4). In three patients, in whom the maximum thickness of hyperreflective plaques did not exceed 70 µm on OCT, a complete remission of the disease was achieved. In the remaining two patients, in whom it was possible to remove only part of the pathological plaques, the maximum thickness was 118 and 133 µm respectively.

We did not observe any perioperative or postoperative complications of therapy in any of our patients. A comparison of the preoperative and postoperative condition is summarised in Table 2.

Table 1. Clinical and demographic characteristics of cohort. OD – right eye, OS – left eye, PPV– pars plana vitrectomy, LIRI – laser iridotomy

PATIENT	AGE	LATERALITY	ETHIOLOGY OF BAND KERATOPATHY	ANTI GLAUCOMATICS USED
male 1	79	OS	hyperuricaemia, combination of antiglaucoma drugs	Timolol + Dorzolamide (Dorzogen combi, Famar)
female 2	85	OD	posttraumatic phthisical eye	none
female 3	54	OS	amaurosis after retinal detachment years previously, secondary glaucoma	Timolol + Latanoprost (Xalacom, Pfizer)
female 4	34	OS	condition after repeated PPV 20 years previously, secondary glaucoma	Timolol (Timolol-POS, Ursapharm)
female 5	70	OS	absolute glaucoma, condition after repeated antiglaucoma operations (LIRI, trabeculectomy)	Latanoprost (Xalatan, Pfizer) + Brimonidine (Luxfen, Pharmstustulln)

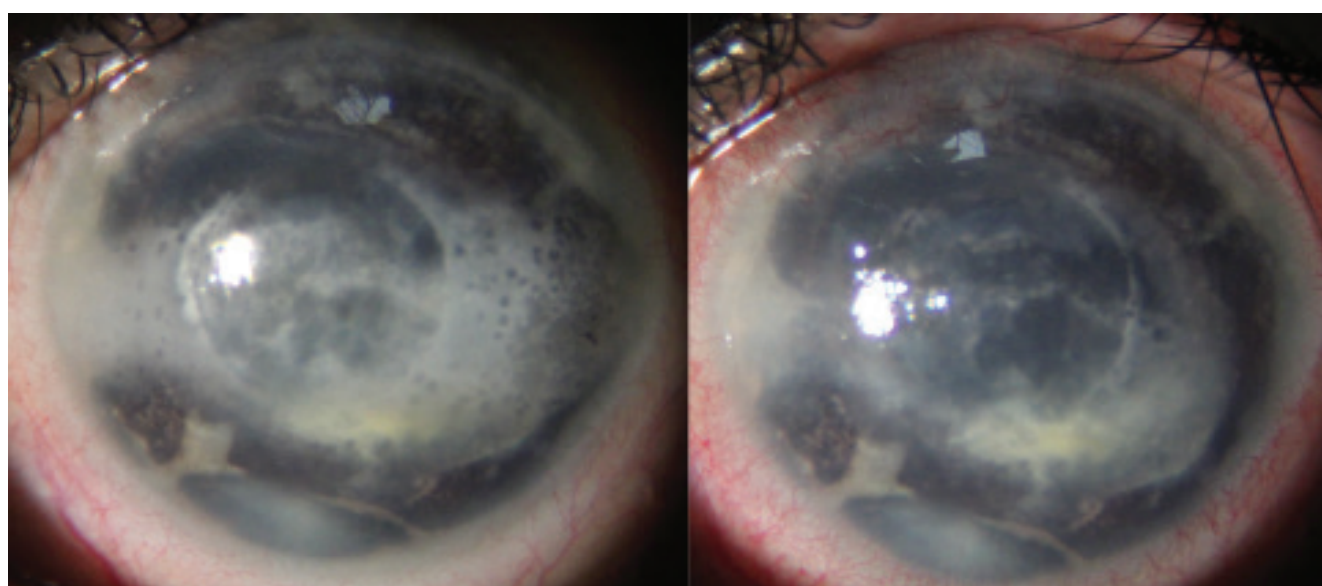


Figure 3. Left: preoperative finding in patient No. 3, right: postoperative finding in same eye

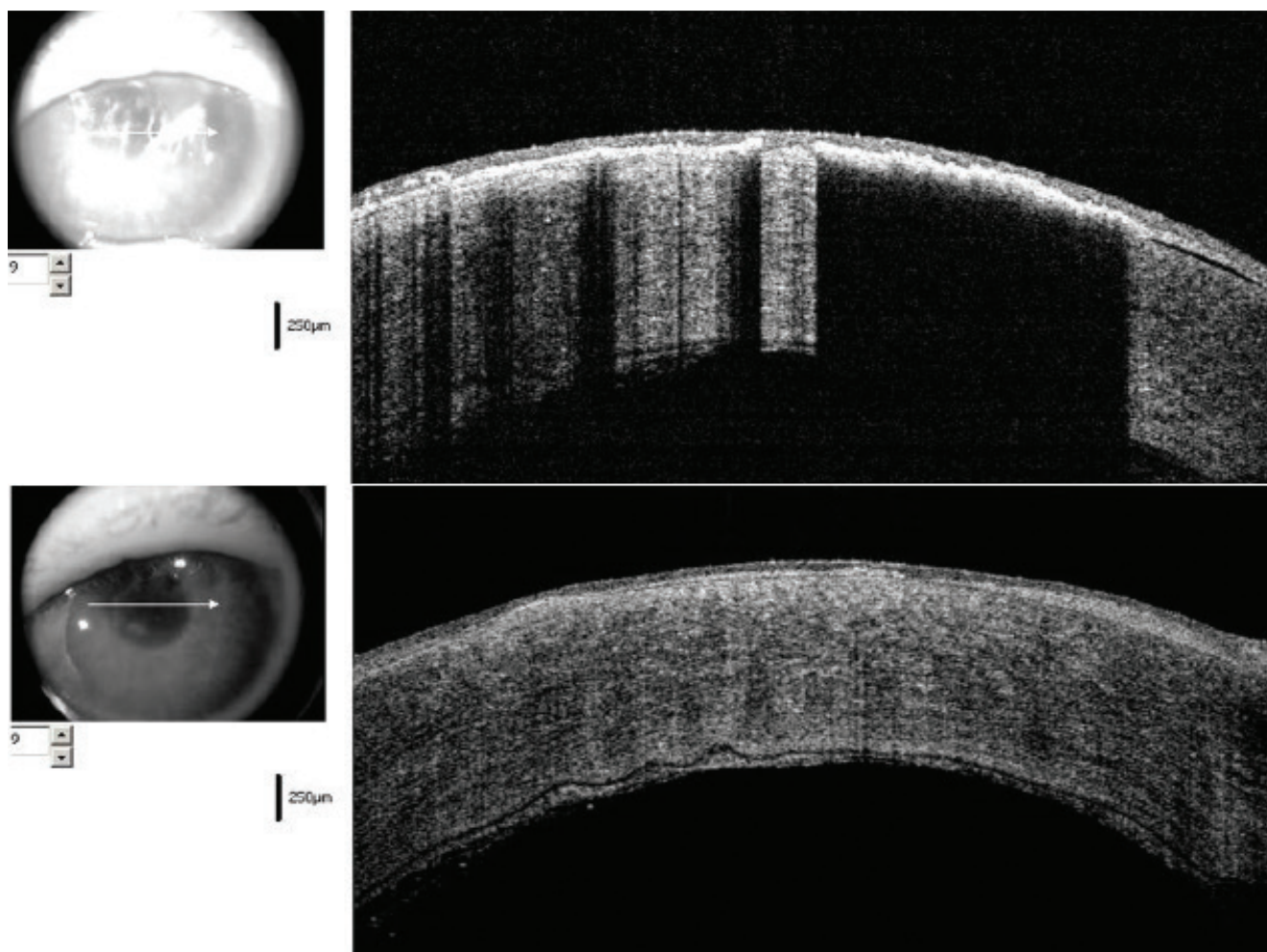


Figure 4. Comparative image of anterior segment OCT. Above: preoperative condition, below: finding six months after surgery

DISCUSSION

Band keratopathy was first described by Dixon in 1848 as a chronic degenerative disease, characterised by greyish-white opacities in the superficial layers of the cornea, in the interpalpebral aperture [12,13,17]. We usually observe a transparent region between the band of keratopathy and the corneal limbus. There is a typical appearance of "Swiss cheese", which is caused by the corneal nerves penetrating through the Bowman's layer [17]. Although this concerns a chronic disease, cases of acute incidence have also been described, for example rapid progression of the affliction following intracameral administration of Viscoat (chondroitin sulphate-sodium hyaluronate, Alcon), which was left in the anterior chamber during uncomplicated cataract surgery [18]. Sodium hyaluronate in topical administration (artificial tears) increases the risk of band keratopathy. Intraocular injection (for example of the tissue plasminogen activator – tPA) or penetrating keratoplasty can also lead to the acute onset and progression of this pathology (within a number of days) [3,10].

We verify the depth and degree of corneal affliction at our centre as standard before the procedure by means of anterior segment optical coherence tomography, and we monitor the condition throughout the entire period of postoperative observation. Calcium opacities are displayed as a superficial hyperreflective layer in the region of the Bowman's membrane, with a characteristic shadow. The method enables imaging of the precise extent of calcareous plaques, similarly to histological examination [15]. Postoperatively we can use this technique to examine the internal layers of the cornea and identify any applicable subclinical recurrence of the disease. However, to date no study has been published documenting the use of AS-OCT in a cohort of patients being treated for band keratopathy. Only a few case reports have appeared in the literature [15,19]. From our clinical experiences, this method appears to be capable of providing detailed imaging of the pathology of the individual corneal structures and measuring the maximum thickness of pathological plaques. This imaging can then help us better estimate the prognosis and effect of subsequent therapy. In our patients with a smaller scope of affliction (maximum thickness of plaque

Table 2. Preoperative and postoperative results of all patients. CDVA – corrected distance visual acuity, NLP – no light perception

Patient	Subjective symptoms	Subjective evaluation after surgery	Preoperative CDVA	Postoperative CDVA	Maximum thickness of hyperreflective layer preoperatively (µm)	Maximum thickness of hyperreflective layer postoperatively (µm)	Objective evaluation after operation	Observation period (months)
male 1	decrease in visual acuity, sensation of foreign body under eyelid	adjustment of visual functions, disappearance of sensation of foreign body	0.6	0,1	69	0	Complete remission	37
female 2	ocular discomfort, cosmetically unsightly eyeball	improvement in appearance of eye, satisfaction with procedure	light perception	light perception	67	0	Complete remission	25
female 3	pain, cosmetically unsightly eyeball	no pain, improvement in appearance of eye, satisfaction	NLP	NLP	133	34	Partial improvement	17
female 4	pain, cosmetically unsightly eyeball	no pain, improvement in appearance of eye, satisfaction	NLP	NLP	118	44	Partial improvement	12
female 5	pain, cosmetically unsightly eyeball	no pain, improvement in appearance of eye, satisfaction	NLP	NLP	69	0	Complete remission	9

69 µm) we succeeded in removing the corneal opacities completely, whereas in the two female patients with deeper affliction exceeding 100 µm we observed only a partial improvement. Similarly, Yang et al., who treated two patients with a maximum depth of the pathology at 96 µm with the aid of phototherapeutic keratectomy, induced a complete remission of the disease [19].

The most frequently used strategies of treating symptomatic patients include chelation with the aid of EDTA and laser therapy with the aid of PTK. Some surgeons use of combination of both of these techniques [20,21]. A possible accessory to this combined operation may be simultaneous covering of the defect with an amniotic membrane [20]. Other cited alternative methods are Nd:YAG or keratectomy with a diamond burr [2]. The aim of

the treatment is to remove opacities of calcium, to restore the smooth ocular surface [4,14], and thereby to enable an improvement of visual functions. In children the reason may also be to prevent the development of amblyopia [8]. Potential problems in connection with abrasion of the epithelium in these therapeutic approaches include postoperative pain, temporary deterioration of visual acuity, prolonged healing and the risk of recurrence [20]. In the case of PTK therapy it is also necessary to reckon with a hypermetropic shift of the refractive error. Some centres use repeat repositioning of the elevated epithelium as prevention against pain following chelation, similarly as in the case of the LASEK (Laser Epithelial Keratomileusis) refractive operation [6]. In advanced cases a lamellar corneal transplant is indicated [1].

At our clinic we use almost exclusively chelation with 2% EDTA for the treatment of symptomatic band keratopathy. In the majority of published studies, indication for surgery is a deterioration of visual acuity or discomfort in the eye. For our female patients an important aspect in their decision in favor of the procedure was the appearance of the affected eye, which is sometimes overlooked by doctors. Especially for women, this aspect may be a fundamental parameter in improving quality of life.

Depending on the etiology, the aim of treatment may be an improvement of visual functions. With regard to the basic diagnosis in our patients, we achieved an improvement of vision in our cohort in one patient. A large cohort of patients treated by means of chelation was described by Al-Hity et al. They performed a procedure in 108 symptomatic patients, in whom they succeeded in preserving or improving visual functions in 79.8 % of cases [13]. Najjar et al. performed surgery by this technique on 65 eyes of 54 patients. One month after surgery, corrected visual acuity had improved by two or more rows of Snellen's optotypes in 17 eyes [17]. Following combined surgery by chelation and PTK with an amniotic membrane, visual acuity was stabilised or improved in all 11 eyes [20]. In addition to visual acuity, a frequent indication is also discomfort of the eye and a painful eyeball. Spadea et al. referred to a reduction of ocular discomfort and an increase of corneal transparency in their patient's following treatment with EDTA in combination with laser therapy [21]. We also observed a positive effect in all our patients.

A no less important indicator of patient satisfaction is the cosmetic effect of the operation, which may be of fundamental significance especially for women. Only very few studies have dealt with this aspect. Im et al. published a complete disappearance of calcium plaques in all their pa-

tients, and a correlating improvement in the appearance of the afflicted eyeballs [20]. Our observation is in accordance with the results of this study, since in three patients we achieved a complete regression of the disease. In the other patients we recorded a disappearance of the majority of pathological deposits, which was also confirmed on OCT scans. It is possible to use this technique for detailed imaging of the deeper layers of the cornea, which were impossible to examine preoperatively. At the same time, displaying the depths of the hyperreflective plaques preoperatively can help us better estimate the probability of complete curing of the disease. A limitation of this examination method in our view is the absence of any possibility of precisely objectifying the extent of the surface of band keratopathy.

The literature also mentions the risk of recurrence of the pathology. Localised recurrence of calcium deposits was described by Al-Hity in 25 eyes (28%) of his cohort, but only four cases (4.5%) required repeated treatment [13]. We did not record any recurrences during the observation period in our patients.

CONCLUSION

Chelation of the cornea with the aid of EDTA is a safe and effective method of treating symptomatic band keratopathy. Based on our experiences and referred reports, this method is capable of causally resolving the pathology and improving visual functions in eyes with the potential for sight. At the same time, it suppresses discomfort and has an analgesic effect on eyes suffering from long-term irritation. The operation is also suitable for amaurotic, cosmetically unsightly eyeballs, since successful intervention preserving the eyeball and improving the appearance of such eyes brings a subject increase in patient satisfaction.

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