IRIDOCORNEAL ENDOTHELIAL SYNDROME. CASE REPORTS

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SUMMARY

Aim: Iridocorneal endothelial (ICE) syndrome is a rare disease characterized by abnormal proliferation and structural changes of the endothelium, obliteration of the iridocorneal angle, and anomalies of the iris. The consequence of these changes is secondary glaucoma and corneal decompensation. The etiology is unclear, and the syndrome more commonly affects middle-aged women.
Case reports: In this article we present two different case studies of young patients diagnosed with ICE syndrome with complications. The first case report is about a young woman in whom surgical treatment of glaucoma and corneal edema was successful. On the other hand, the second report presents a complicated case of a 29-year-old patient whose treatment was not successful despite repeated interventions.
Conclusion: This text highlights the complexity of ICE syndrome, the difficulty of its therapy and the importance of early diagnosis.
Key words: iridocorneal endothelial syndrome, secondary glaucoma, corneal diseases

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INTRODUCTION

Iridocorneal endothelial syndrome (ICE syndrome) is a rare acquired ocular pathology. It is characterized by proliferative and structural abnormalities of the corneal endothelium, progressive obstruction of the iridocorneal angle and anomalies of the iris such as atrophy, corectopia and polycoria [1]. The consequence of these changes is corneal decompensation and secondary angle-closure glaucoma [1,2]. In the case of progression of the syndrome and without necessary and timely therapy, loss of sight results in patients with ICE syndrome [3].

To date, the etiology of the syndrome is not entirely clear [4]. A whole series of hypothetical triggering factors have been described. Several authors have described the onset of uveitis or iridocyclitis preceding the onset of ICE syndrome [5–7]. Based on more recent studies, infection with the Herpes simplex virus (HSV) or Epstein-Barr virus (EBV) have been considered [4,5,8,9]. Infection leads to inflammation of the endothelium, to unusual epithelial activity and toxic affliction of the surrounding healthy tissue. The HSV may play a significant etiological role in the development of ICE syndrome. However, it may not be the sole predisposing factor. To date, there is a lack of evidence concerning the primary cause of onset of ICE syndrome. The question of the mechanism of its origin therefore still remains open [5,7].

In most cases the occurrence of the syndrome is unilateral, nevertheless bilateral or subclinical affliction of the corneal endothelium of the other eye are not exceptional [10–13]. The first manifestations of the syndrome appear in early to middle adult age, predominantly in women. However, a number of cases with an early onset have been described also in the pediatric population [1,14–16]. The syndrome covers originally separate clinical units, namely Chandler's syndrome, progressive atrophy of the iris, and Cogan Reese syndrome [10,17–19]. Figure 1.

Common to all units is the presence of abnormal endothelial cells, referred to as ICE cells. These increase in size and lose their typical hexagonal shape. On a specular microscope they appear as dark with a pale central point and a pale peripheral zone. They have a tendency to migrate to the neighboring structures and produce a pathological basal membrane, which spreads beyond the Schwalbe's line, overlaps the anterior chamber angle and the anterior surface of the iris [20–22]. Contraction of the membrane leads to changes of the iris, the onset of peripheral anterior synechiae and angle-closure glaucoma [23]. Glaucomatous pathology may also occur without manifest angle closure, because the progressing endo-

thelium may close the angle also without contraction [17]. Loss of sight in connection with ICE syndrome is usually secondary, corresponding to corneal decompensation or glaucomatous optic neuropathy [4]. Figures 2 and 3.

Patients most often report to a doctor due to a change of position of the pupil, deterioration of visual acuity or pain, photophobia and epiphora upon a background of corneal edema [24]. During a routine eye examination on a slit lamp, if the transparency of the cornea so allows, the finding on the anterior and posterior segment is evaluated. With the aid of gonioscopy, we examine the anterior chamber angle for the presence of peripheral anterior synechiae (PAS). In cases with severe corneal edema and impossibility of visualizing the anterior chamber, diagnosis may be difficult, and it is necessary to deploy further imaging methods such as ultrasound biomicroscopy (UBM) or anterior segment OCT (optical coherence tomography). It is necessary to examine the endothelium, which under microscopic enlargement has the appearance of wrought silver. Mirror microscopy is important in order to detect typical ICE cells, the presence of which confirms the diagnosis. In vivo confocal microscopy is a useful diagnostic tool, above all in patients with corneal edema. It is always necessary to conduct regular monitoring of intraocular pressure, central corneal thickness, and examination of the visual field together with evaluation of the optic nerve and the nerve fiber layers [7].

The following text presents case reports of 2 patients with ICE syndrome from our center. The aim is to highlight the complexity of the diagnosis and treatment of this nosological unit.

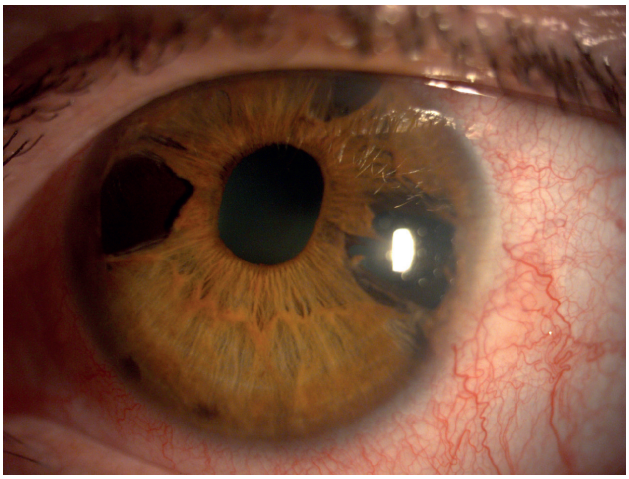

Figure 1. Anterior segment in ICE syndrome – iris atrophy with hole formation and peripheral anterior synechiae (PAS)

CASE REPORT 1

A healthy 31-year-old female patient was referred to our clinic by a local ophthalmologist with a recommendation for transplantation of the Descemet membrane with the endothelium (DMEK – Descemet membrane endothelial keratoplasty) due to corneal edema in the right eye, with an already determined diagnosis of ICE syndrome. According to the patient's anamnestic data she used low myopic co-

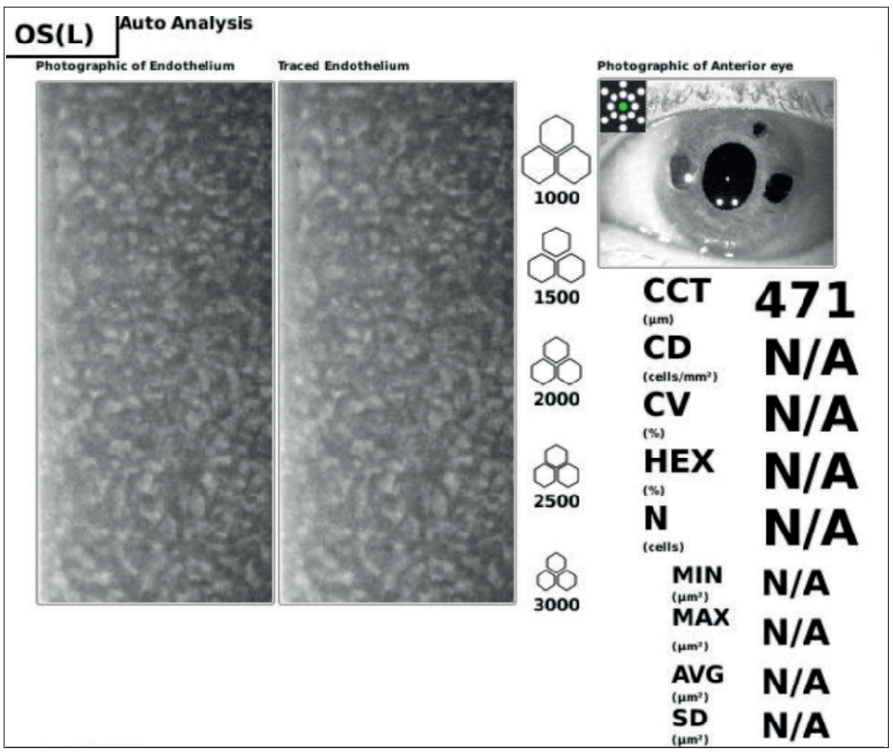

Figure 2. Specular microscopy – ICE cells
ICE – Iridocorneal endothelial

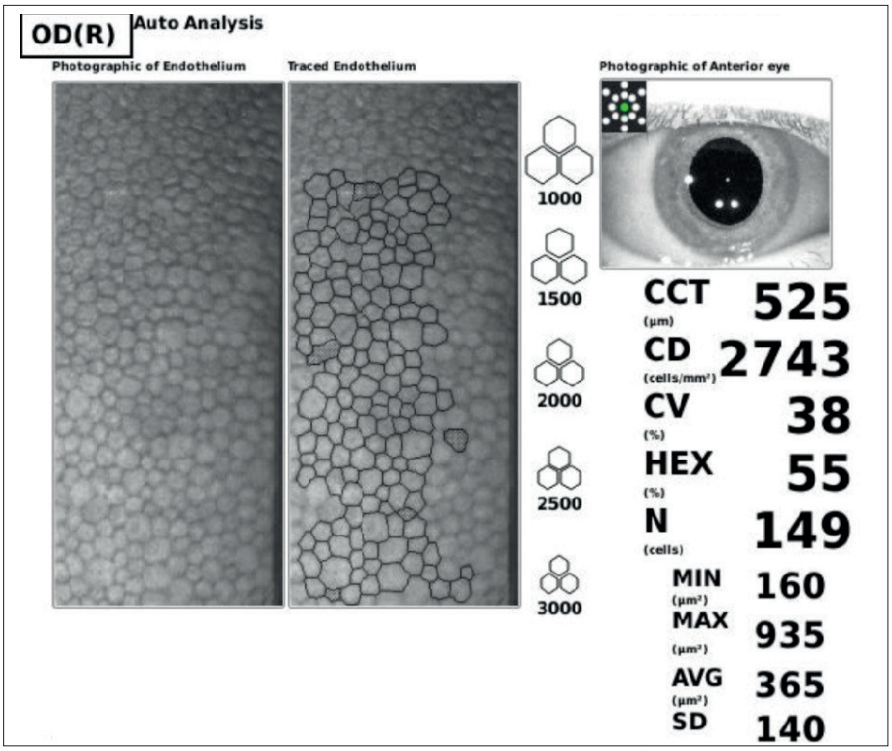

Figure 3. Specular microcopy- physiological endothelium

rrection, best corrected visual acuity (BCVA) in the right eye (RE) was 0.05 and in the left eye (LE) 1.0. For two years the patient had been receiving full local conservative anti-glaucomatous therapy for secondary glaucoma in the right eye, in which the values of intraocular pressure (IOP) at the baseline examination were 15/15 mmHg, with different central corneal thickness (CCT) in the right eye of 695 µm and in the left eye of 553 µm. For one year the patient had experienced deteriorated vision in the right eye. At an examination on a slit lamp, corneal transparency was reduced, and in the lower half we found a thickened band of bullous keratopathy. It was not possible to assess the endothelium, the anterior chamber was of an irregular depth with manifest peripheral anterior synechiae. The pupil was deformed, did not respond to illumination and was pulled in an upward nasal direction, the lens opaque. It was possible to perform only a limited examination on the posterior segment, with a finding of atrophy of the optic nerve papilla.

The patient was indicated for the performance of DMEK under general anesthesia. The procedure was conducted without complications, and one month after the procedure BCVA in RE was 0.4, IOP by palpation measurement within the norm on the existing anti-glaucomatous therapy, we locally maintained corticosteroids 1x per day. Three months after DMEK local therapy remained unchanged, visual acuity had improved to BCVA in RE of 0.7, IOP by non-contact measurement 22 mmHg, the lamella was attached, functional, cornea transparent, without edema, with CCT of 504 µm and a quantity of endothelial cells of 2203 bb/mm2. We supplemented an analysis of the retinal nerve fiber

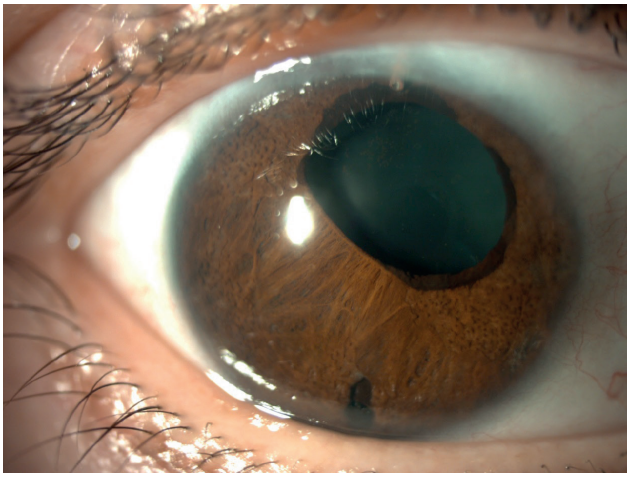

Figure 4. Anterior segment finding after DMEK surgery, ExPress implant
DMEK - Transplantation of Descemet's membrane with endothelium

layer (RNFL) and a perimetric examination, OCT demonstrated atrophy of the optic nerve with RNFL in RE of 48 µm and in LE of 100 µm. At further follow-up examinations there was a gradual elevation of IOP up to 30 mmHg. We added general anti-glaucomatous therapy, but even after this IOP was not compensated and the patient was indicated for anti-glaucoma surgery with drainage using an ExPress implant. Postoperatively we entirely discontinued anti-glaucomatous therapy, leaving only steroids in a low dose for 3 months in order to reduce the possibility of conjunctival scarring. The IOP

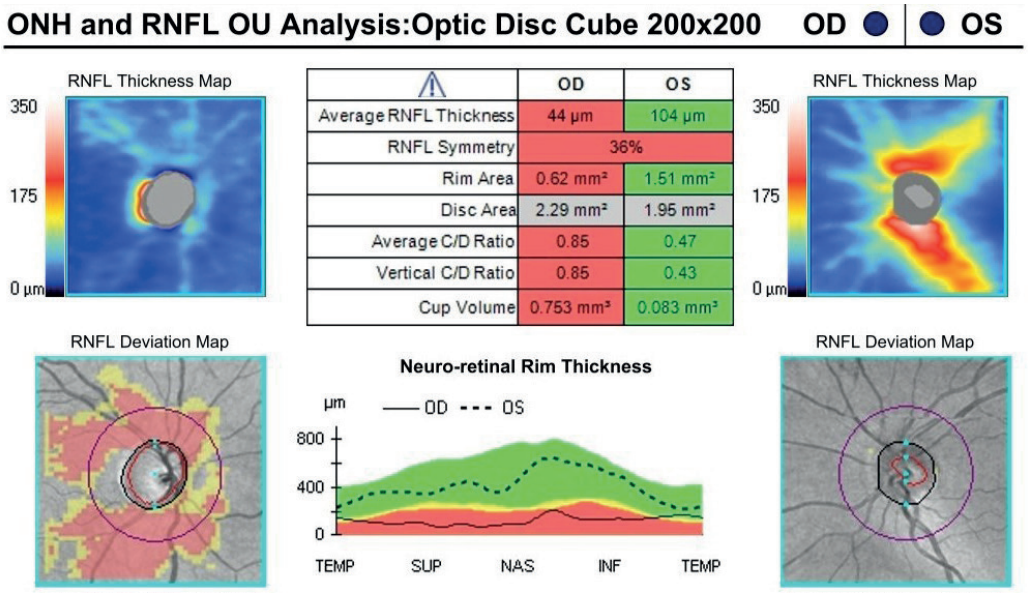

Figure 5. Optical coherence tomography – atrophy of the optic nerve in the right eye

values fluctuated within the range of 6–17 mmHg, the patient performed massage of the eyeball 3–5x per day. Due to advanced atrophy of the optic nerve we added neuroprotective supplements. The patient is under our observation to this day, at the last follow-up examination BCVA in RE was 0.9, IOP without therapy with ExPress implant ExPress 16/15 mmHg, CCT 538/549 µm, on the fundus papilla with glaucomatous excavation c/d 0.9, retinal nerve fiber layer without progression over time, and the finding remains stable. Figures 4 and 5.

CASE REPORT 2

In 2015 a 29-year-old male patient was sent for ultrasound biomicroscopy of the right eye due to a suspected finding on the iris, in order to exclude the possibility of a tumorous process. The patient's anamnestic data show low myopic correction and that for 4 years the patient had observed a change of the position of the pupil in the right eye. In the last year there has been a progressive deterioration of visual acuity, and in the last month the patient has experienced photophobia, pain and stinging. Baseline BCVA in the RE was 0.05, in the LE 1.0, IOP 20/16 mmHg with CCT of 822/613 µm. On the anterior segment, the cornea is with bullous keratopathy and edema, the pupil is ectopic, pulled towards no. 10, the lens clear. Mirror microscopy, UBM and gonioscopy were added, with a finding of PAS, but the presence of a solid lesion was not confirmed. The patient was indicated for and underwent a DMEK procedure in November 2015 under general anesthesia, with the taking of a tissue sample for histology and a sample of chamber fluid for PCR diagnosis of herpes viruses. Figures 6 and 7.

Histology confirmed a diagnosis of ICE syndrome, but PCR diagnosis excluded the presence of herpes viruses. On the first postoperative day BCVA in RE was fingers in front of the eye, IOP by palpation measurement within the norm, cornea clarified, lamella attached. Therapy was commenced of Tobramycin with Dexamethasone 5x per day for one week, then from the 2nd week only application of corticosteroids 5x per day, with decreasing frequen-

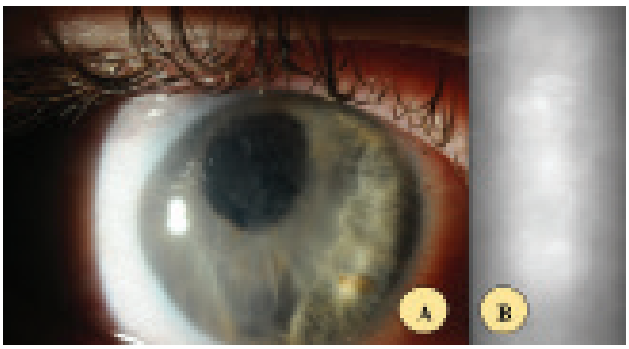

Figure 6. (A) Anterior segment changes of the right eye in ICE syndrome, **(B)** specular microscopy
ICE – Iridocorneal endothelial

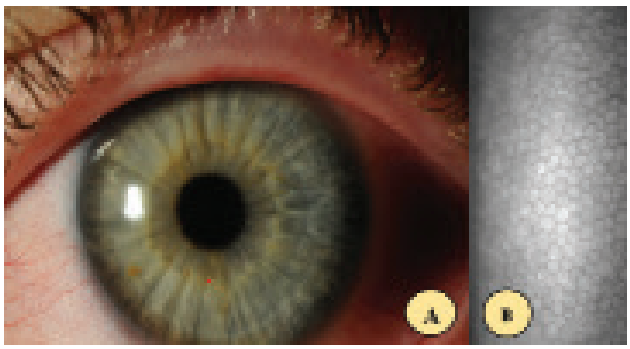

Figure 7. (A) Physiological anterior segment of the left eye, **(B)** specular microscopy from normal cornea

cy of dosing over several months. At a follow-up examination after one month, BCVA in RE was 0.9, IOP by palpation measurement within the norm, the finding on the anterior segment was pacific, excavation c/d 0.6. We supplemented examination of the visual field, OCT, and due to reduced values of RNFL in the inferior quadrant of the RE we administered a beta-blocker (BB) locally 2x per day. Figure 8.

During the course of further follow-ups, corticosteroids (CS) were progressively discontinued, and the finding remained stable up to July 2016, when BCVA in RE was 0.8, IOP 27/17 mmHg, the cornea was transparent, vision was reduced by the development of an incipient cataract. We boosted local therapy with a carbonic anhydrase inhibitor (CAI), which achieved stabilization of IOP until November 2017, when BCVA in RE deteriorated to 0.4, IOP 23/20 mmHg. The cornea was opacified. We boosted local therapy with a beta-blocker + CAI + prostaglandin (PG) and added CS 2x per day. In January 2018 the cornea was opacified throughout its entirety, IOP could not be measured by a non-contact method, by applanation it was within the norm, and BCVA in RE 0.05. Due to endothelial insufficiency and presence of cataract, a combined procedure was performed of re-DMEK with complicated cataract surgery and goniosynechialysis. After one month the patient attained BCVA in RE of 1.0, IOP within the norm on therapy of CAI + BB, lamella functional, finding on OCT and perimeter without progression. At a follow-up examination after six months, BCVA in RE was 0.2, IOP 22/18 mmHg, CCT 674/609, endothelial rejection occurred, we administered CS 5x per day, and boosted therapy with Brimonidine. In February 2019, BCVA in RE was fingers in front of the eye, IOP 25/20 mmHg, edema of the epithelium and corneal stroma, endothelium could not be measured, and an anti-glaucoma procedure was performed due to decompensated glaucoma, with drainage using an ExPress implant and an Ologen implant beneath the conjunctiva. Figure 9.

After surgery, stabilization of pressure was achieved with a functional implant, and local therapy was retained with a beta-blocker 2x per day. Due to decompensated cornea with BCVA in RE of movement in front of the eye, in November 2019 we performed a further re-DMEK procedure. Figure 10.

For the next year the finding was stable, the cornea transparent, BCVA in RE 0.7, but in December 2020 we again recorded an elevation of IOP 27/17 mmHg. We supplemented the local therapy of a beta-blocker 2x per day with PG 1x per day, at further follow-ups IOP remained

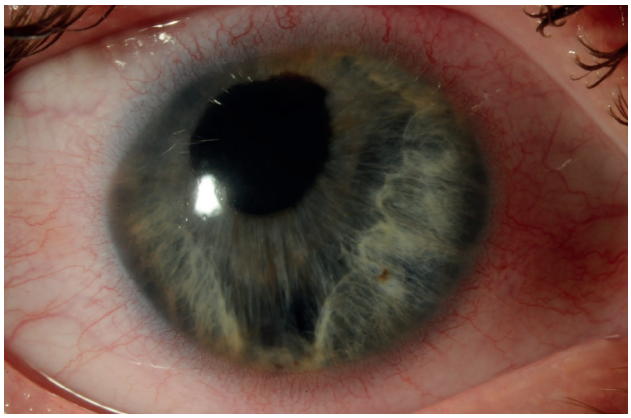

Figure 8. 1 month after DMEK surgery
DMEK – Transplantation of Descemet's membrane with endothelium

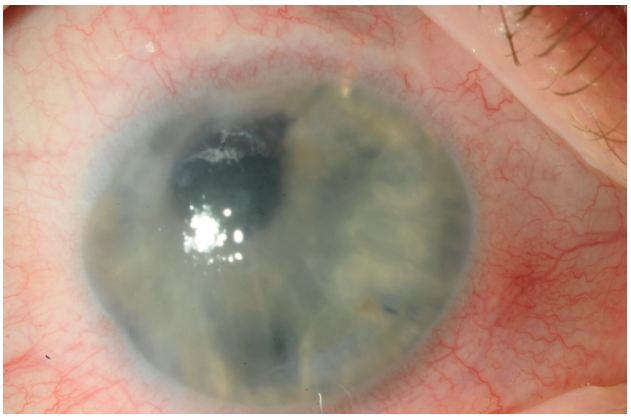

Figure 9. 1 month after glaucoma surgery- ExPress implant at 1 o'clock

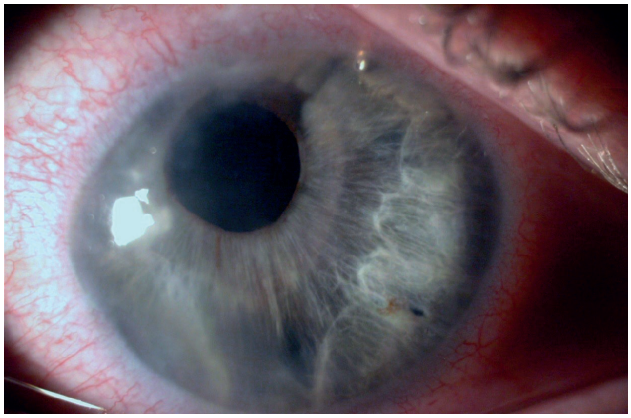

Figure 10. Transparent cornea after 2. re-DMEK, filtering ExPress implant at 1 o'clock
DMEK – Transplantation of Descemet's membrane with endothelium

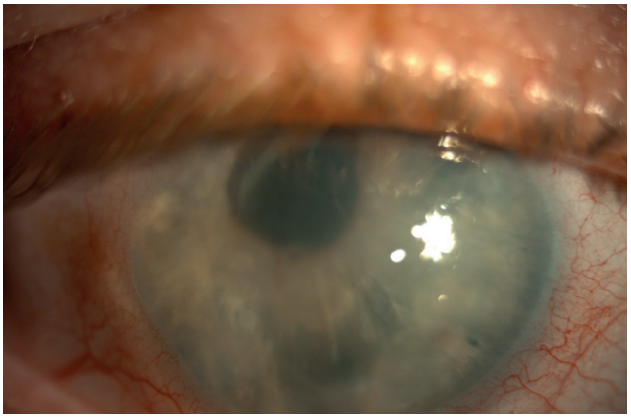

Figure 11. Picture of anterior segment finding at last checkup prior next DMEK
DMEK – Transplantation of Descemet's membrane with endothelium

unsatisfactory. We boosted therapy to a triple combination, again decompensation of the cornea occurred with deterioration of vision in RE to 0.05. Because pressure failed to respond to local therapy, in June 2021 we performed needling of the scleral flap, after which we succeeded in stabilizing IOP on the triple combination. This is a young and active patient who is motivated by improvement of visual acuity always following corneal transplantation, and so a further, fourth DMEK procedure is planned. Figure 11.

DISCUSSION

ICE syndrome is a rare disease, the diagnosis and subsequent treatment of which is difficult. In differential diagnostics it is necessary to consider endothelial corneal defects such as posterior polymorphous dystrophy and Fuchs' dystrophy, afflictions of the iris such as iris melanoma, aniridia, inflammatory nodules or Axenfeld-Rieger syndrome [25]. Timely diagnosis of ICE is essential in order to prevent the development of corneal edema and secondary glaucoma [7,25]. The development of the above complications influences the prognosis of ICE syndrome.

Therapy is targeted at addressing glaucomatous complications and corneal edema. The preservation of a transparent cornea is necessary in order to maintain good visual functions, reduce pain for the patient and also for observing changes on the optic nerve papilla and visual field in the case of associated glaucomatous pathology. The primary therapeutic target it therefore to control the development of secondary glaucoma. Conservative therapy incorporates above all substances reducing the production of chamber fluid – local beta-blockers, carbonic anhydrase inhibitors and alpha agonists. Topical prostaglandins are associated with a risk of reactivation of HSV, and as a result it is necessary to avoid their use [26,27]. In the case of insufficient compensation by means of conservative therapy, a surgical procedure is essential in order to preserve sight. A study on the Indian population from 2017 describes a cohort of 203 patients with ICE syndrome. In this analysis ICE syndrome was associated with glaucoma in more than 70% of patients, and 50% of patients required a surgical procedure in order to regulate intraocular pressure. Corneal edema was present in 56% of patients, of whom 14% underwent endothelial keratoplasty [24]. A fundamental problem of this diagnosis is that even surgical procedures do not achieve such a high success rate as in other types of glaucoma. The reason for this is the young age of the patients, due to which the process of conjunctival scarring is far more active than at a later age. A further problem is the process of endothelization of the tubes of the drainage implants or pathological growth of the basal membrane over the mouth of the implants, causing their failure. In the case of failure of classic surgical procedures, we proceed to cyclodestructive methods, especially in eyes with a poor prognosis regarding vision. Priority is given to Descemet stripping automated endothelial keratoplasty (DSAEK) and Descemet membrane endothelial keratoplasty (DMEK) instead of penetrating keratoplasty (PKP) for the treatment of corneal edema upon a background of ICE [27]. A study from 2021 evaluating the effectiveness of DMEK in patients with ICE demonstrated an 85.7% cumulative success rate of a graft after 1 year [28]. However, it is necessary to mention the problem of monitoring intraocular pressure following DMEK, in which it is impossible to measure ocular tension by non-contact method for at least 2–3 months, so as to prevent the detachment of the lamella, while IOP can be measured by applanation after one month.

CONCLUSION

Two prototype original case reports from our center are presented in the text. The first case report presents a mild form of the syndrome, in which we succeeded in compensating intraocular pressure effectively, while the second case report presents a more aggressive form in which loss of sight occurred as a consequence of glaucomatous pathology and/or corneal edema. This text highlights the complicated nature of ICE syndrome, the difficulty of its treatment and the importance of timely diagnosis.

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