EUROPEAN EYE RESEARCH

EDITORIAL

Dear Colleagues,

I would like to introduce our journal 'European Eye Research' to you. I am proud to present this first issue to ophthalmology field on the 23rd of April, National Sovereignty and Children's Day - gifted by the great leader Mustafa Kemal Atatürk.

European Eye Research is an international, scientific, open access periodical published in accordance with independent, unbiased, and double-blinded peer-review principles in English. The journal will publish original articles, reviews, case reports, and other commentary in accordance with recognized ethical guidelines. Three issues will be released every year in April, August, and December.

The primary goal of the European Eye Research journal is to contribute high-quality manuscripts from the field of ophthalmology to the international literature. The target audience includes specialists and physicians-in-training in the various branches of ophthalmology.

The editorial and publication processes of the journal were designed according to the guidelines of the International Committee of Medical Journal Editors (ICMJE), the World Association of Medical Editors (WAME), the Council of Science Editors (CSE), the Committee on Publication Ethics (COPE), the European Association of Science Editors (EASE), and the National Information Standards Organization (NISO). The journal also observes the Directory of Open Access Journals Principles of Transparency and Best Practice in Scholarly Publishing.

I would like to thank all our colleguages that took part in development, publication and reviewing of this very first issue.

As Mustafa Kemal Atatürk emphasized "If one day my words conflict with science choose science", science will always be our guiding light. With your valued contributions we will rise European Eye Research to one of the leading journals in ophthalmology area.

Filiz Afrashi, MD

Editor-In-Chief

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EUROPEAN EYE RESEARCH

ORIGINAL ARTICLE

Comparison of anterior and posterior chamber implantation of iris claw lens in corneal transplant patients

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Abstract

Purpose: This study aims to compare the surgical outcomes of anterior chamber (AC) and posterior chamber (PC) implantation of iris claw lens (ICL) combined with penetrating corneal transplantation (P-CT), in eyes with no capsular support.

Methods: The records of 20 P-CT cases who underwent ICL implantation were retrospectively evaluated. The eyes were grouped according to the location of implantation; AC ICL and PC ICL. Pre- and post-surgical best-corrected visual acuity (BCVA), post-operative complications, and graft rejection rates were compared between the two groups. Mean follow-up time was 28 (range, 12 and 76) months.

Results: ICLs were implanted during P-CT surgery in 14 (70%) eyes and as a secondary procedure after P-CT in 6 (30%) eyes. ICLs were implanted in PC in 12 (60%) and in AC in 8 (40%) eyes. Mean pre-operative BCVA was 0.064 (range, 0.001–0.02) in the PC group and 0.02 (range, 0.001–0.1) in the AC group (p=0.86). Mean post-operative BCVA was 0.17 (range, 0.0001–1.0) in the PC group and 0.14 (range, 0.0001–0.4) in the AC group (p=0.81). Glaucoma developed in 5 (41.6%) eyes with PC ICL. No eye with AC ICL developed glaucoma overtime.

Conclusion: Both AC and PC ICL implantations provide favorable visual outcomes and complication rates in CT patients. However, PC implantation of ICL seems to increase glaucoma incidence.

Keywords: Aphakia; complication; corneal transplant; glaucoma; iris claw lens; keratoplasty.

In eyes with dislocated posterior chamber (PC) intraocular lens (IOL) or aphakia, it is desirable to leave the eye pseudophakic during corneal transplant, considering the optical advantages of IOLs. However, capsular or zonular insufficiency is a frequent problem in these eyes. Therefore, PC IOL implantation during penetrating corneal transplant (P-CT) can be a challenge for the surgeon. Iris-supported (e.g., iris claw) anterior chamber (AC) or iris fixated PC IOLs are some of the various options for IOL implantation in these eyes.[1,2]

The iris claw lens (ICL) was designed by Worst, for attachment to the anterior iris in eyes without capsular support. [3] However, significant complications such as damage to corneal endothelium, particularly in patients with narrow AC and corneal grafts, were observed over time. Hence, this technique was modified by Brasse and Neuhann, by

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clipping the lens to the posterior iris, with the A-constant altered according to 117.0.[4]

The purpose of this study is to compare the outcomes of AC and PC implantation of ICL in P-CT cases.

Materials and Methods

A retrospective chart review of P-CT cases who underwent ICL implantation between 2005 and 2012 in Ege University Hospital was performed. Approval for data collection and analysis was obtained from the Institutional Review Board at Ege University and was conducted according to the principles set forth in the Declaration of Helsinki.

Patients with previous glaucoma diagnosis, posterior segment, or optic nerve diseases that may reduce visual acuity were excluded from the study. The eyes were grouped according to the location of implantation; AC ICL and PC ICL.

Best-corrected visual acuity (BCVA) was tested using the Snellen chart at a distance of 6 m. Intraocular pressure (IOP) was measured with Goldman applanation tonometer (Haag-Streit, Bern, Switzerland). Pre- and post-surgical BCVA, post-operative complications including glaucoma development, and graft rejection rates were compared between two groups.

Surgical Technique

The pupil was not dilated or constricted before the surgery. Patients received local or general anesthesia. All donor corneas were excised from the endothelial side using a Troutman corneal punch and a disposable trephine. The donor tissue ranged from 7.75 to 8.25 mm in diameter and was always 0.25 mm larger than the recipient bed. A Hessburg Barron (JedMed Instrument Co., St. Louis, Missouri, USA) suction trephine (7.50–8.0 mm) was used for full-thickness trephination of the host cornea. The excision was then completed for 360° with corneal scissors. After removing the cornea of the recipient, if the eye was pseudophakic, the IOL was carefully removed. Unless already performed in an earlier operation, anterior vitrectomy was performed. Any visible peripheral synechiae were carefully lysed. In phakic recipient eyes with insufficient capsular or zonular support, anterior vitrectomy was also combined with crystalline lens aspiration.

IOL Implantation

In all cases, non-foldable ICLs (Artisan Aphakia, Ophtec, USA) were implanted.

For AC implantation, the IOL was centered in the AC and mid-peripheral iris was grasped with a specially designed, angled forceps. The claws were depressed over the forceps so that the claws enclaved the iris. The same maneuver was repeated for the other haptic.

For PC implantation, specifically designed lens holder forceps were used to grab and guide the IOL posteriorly through the pupil in an upside down position. The IOL was centered, and the mid-peripheral iris was pushed into the claw haptics using a spatula or a Sinskey hook.

Corneal tissue was stored in minimum essential medium. The donor cornea was placed over the recipient bed and sutured into position with interrupted 10–0 monofilament sutures.

Secondary ICL implantation was performed through clear corneal incision under viscoelastic protection as was described above. A peripheral iridectomy was performed in every patient. The optic power was calculated using the SRK II formula. The manufacturer's recommendation for anterior fixation is 115.0. We assumed a surgeon's factor A constant of 118.0 for posterior fixation. IOL calculations were performed for all patients before surgery.

Postoperatively, topical 0.1% dexamethasone (Maxidex, Alcon, USA) eye drops and 0.3% tobramycin (Tobrex, Alcon, USA) eye drops were instilled at 6 h intervals. Tobramycin drops were stopped whenever the epithelization is completed. Prednisolone acetate drops were tapered slowly and stopped after 3 months of use. Topical corticosteroid treatment was continued with a safe steroid such as fluorometholone (Flarex, Alcon, USA) for at least 12 months.

Glaucoma Diagnosis

Secondary glaucoma was defined as the persistence of increased IOP (>21 mmHg) 1 month after PK, in the presence of glaucomatous optic disc changes with increased CDR (cup to disc ratio) and/or detectable glaucomatous visual field defects such as nasal step, paracentral scotoma, or arcuate defect.[5–7]

Statistical Analysis

Statistical analysis was performed with SPSS for Windows version 15.0 (SPSS Inc., Chicago, IL, USA). All data were reported as averages ± standard deviations. Statistical analysis for BCVA and IOP was performed using paired sample t-test and – to compare the two groups – independent samples t-test. For graft rejection rates, independent samples t-test was used. P=0.05 or less was considered statistically significant.

Results

Twenty eyes of 20 patients (12 males and 8 females) were included in the study. The mean age at the time of surgery was 62.8±17.6 (range, 23–89). The most common indication for P-CT was bullous keratopathy (14 [70%] eyes). Among bullous keratopathy eyes, 9 (64.3%) were pseudophakic, 4 (28.6%) were aphakic, and 1 (7.1%) was phakic. Other keratoplasty indications were keratoconus in 2 (10%) eyes, corneal opacity due to previous penetrating injury in 2 (10%) eyes, and corneal opacity due to herpetic keratitis in 2 (10%) eyes (Table 1). ICL implantation was performed as a combined procedure with PKP in 14 (70%) eyes; 7 (50%) pseudophakic eyes as IOL exchange due to pseudophakic bullous keratopathy, 3 (21.4%) phakic eyes with capsular insufficiency, and 4 (28.6%) aphakic eyes. The ICL implantation was performed as a secondary procedure in 6 (30%) eyes; 2 (33.3%) pseudophakic eyes as IOL exchange, 3 (50%) phakic eyes with capsular insufficiency, and 1 (16.7%) aphakic eye. ICLs were placed in PC in 12 (60%) and in AC in 8 (40%) eyes.

The post-operative BCVA (mean 0.16±0.07) of all eyes improved significantly ($p<0.05$), compared to the pre-operative BCVA (mean 0.01±0.06).

Mean follow-up time was 28 (range, 12 and 76) months.

Visual Recovery

No statistically significant difference in pre-operative BCVA was noted between the two groups. BCVA improved in both groups postoperatively, and there was no statistically significant difference between the two groups (Table 2).

IOP

During follow-up, glaucoma developed in 5 (41.6%) eyes with PC ICL. No eye with AC ICL developed glaucoma overtime. The prevalence of glaucoma was significantly higher in eyes with PC ICL ($p=0.02$, t-test).

Complications

Late graft rejection was observed in 1 (14.3%) eye with AC ICL and 3 (25%) eyes with PC ICL ($p=0.07$, t-test). Rhegmatogenous retinal detachment or macular edema did not take place in any of the patients. Choroidal detachment due to post-operative hypotony that occurred in an AC ICL implanted eye was successfully treated with systemic corticosteroid (methylprednisolone, 32 mg daily for 7 days and then tapered off) and resolved in a week. All other complications are listed in Table 3.

Table 1. CT indications and lens conditions of all eyes

Eye number	CT indication	Lens condition
1	BK	AC IOL
2	KK	Phakic
3	BK	Aphakic
4	KK	Phakic
5	Corneal opacity (HK)	Phakic
6	Corneal opacity (HK)	Aphakic
7	BK	PC IOL
8	BK	AC IOL
9	BK	AC IOL
10	BK	AC IOL
11	BK	Aphakic
12	Corneal opacity (PI)	Phakic
13	Corneal opacity (PI)	Phakic
14	BK	AC IOL
15	BK	Aphakic
16	BK	Phakic
17	BK	Aphakic
18	BK	AC IOL
19	BK	AC IOL
20	BK	AC IOL

AC IOL: Anterior chamber intraocular lens; BK: Bullous keratopathy; CT: Corneal transplantation; HK: Herpetic keratitis; KK: Keratoconus; PC IOL: Posterior chamber intraocular lens; PI: Penetrating injury.

Table 2. Comparison of mean BCVA between two groups preoperatively and postoperatively

Group	Pre-operative (range)	Post-operative 6th month (range)
PC ICL	0.064 (0.001–0.02)	0.17 (0.001–1)
AC ICL	0.02 (0.001–0.1)	0.14 (0.001–0.4)
P-value	0.86	0.81

PC ICL: Posterior chamber iris claw lens; AC ICL: Anterior chamber iris claw lens.

Table 3. Post-operative complications

Complication	PC ICL (%) (n=12)	AC ICL (%) (n=8)
IOL dislocation	2 (16.6)	0
Glaucoma	5 (41.6)	0
Choroidal detachment	0	1 (12.5)
Hypotony	1 (8.3)	1 (12.5)
Graft rejection	3 (25)	1 (14.3)

AC ICL: Anterior chamber iris-claw lens; IOL: Intraocular lens; PC ICL: Posterior chamber iris-claw lens.

Discussion

P-CT is a challenging surgical procedure when combined with crystalline lens extraction, or IOL explantation and secondary IOL implantation. The best option for IOL implantation at the time of P-CT in the absence of capsular support is still not clear. Scleral fixation of IOLs can be per-

formed but the procedure has its own technical difficulties and involves manipulations in the vitreous base with the risk of retinal tears and/or detachment.[8,9] Many anterior segment surgeons are not comfortable with this complicated and bothersome procedure.

The ICL was initially developed for attachment to the anterior iris. However, besides advantages of easy insertion and enclavation, AC implantation puts the corneal endothelium at risk.[10] This is particularly important in eyes with corneal transplant because the graft endothelium is already compromised and there is a risk of rejection.[11] In PC placement of ICL, the iris acts as a protective barrier for endothelium, but it requires more maneuvers and takes more time.[12,13] Moreover, PC insertion of ICL might be complicated with posterior dislocation of the IOL.[14,15]

Rijneveld et al.[16] published the first study of ICL in combination with P-CT. BCVA improved in 83% of their patients, and all eyes with BCVA ≥20/40 had an AC implantation. Complications such as glaucoma and lens dislocation were rare. Pigment dispersion – without clinical significance – was seen in 16.7% of the eyes and all of them were in the PC implantation group. Herein, BCVA improved after surgery in both groups, and there was no statistically significant difference between two groups.

Rüfer et al.[17] reported higher secondary glaucoma incidence (33%) in patients with PC ICL combined with P-CT compared to patients with PC ICL implantation alone. They concluded that P-CT could be the main risk factor for glaucoma in those patients. In the present study, secondary glaucoma incidence was significantly higher in PC ICL group (41.6%). The reason can be the pigment dispersion observed in PC ICLs in the long term. In contrast to the present study findings, Dighiero et al.[18] reported no glaucoma in a group of 5 PC ICL implanted patients. Furthermore, Gonnermann et al. did not observe any increase in IOP or worsening of glaucoma, in their study of 23 eyes with PC ICL and P-CT combination.[16]

Herein, incidence of lens dislocation was higher in PC ICL group (16.6%) when compared with AC ICL group (no eyes). Rüfer et al. observed PC ICL dislocation in 2 patients (20%) and Gonnermann et al.[11] observed the same complication in 3 (13%) eyes.[17,19] Dighiero et al.[18] and Hsing and Lee[20] did not observe ICL dislocation in any eyes with PC ICL.

Rüfer et al.[17] reported choroidal detachment in one patient with PC ICL, while Hsing et al.,[20] Rijneveld et al.,[16] and Dighiero et al.[18] reported no choroidal detachment in their studies. We observed choroidal detachment due to hypotony, which resolved in a week with treatment in one patient with AC ICL. We also observed transient hypotony in a patient with PC ICL, which did not lead to choroidal detachment. Vitreous hemorrhage did not occur in any of the patients.

The main limitation of the study is the absence of endothelial cell count after ICL implantation. However, specular microscopy is not an easy to use tool in P-CT patients. As many of them have irregular ocular surfaces, the measurement is usually not possible or not reliable.

Both AC and PC ICL implantation provide favorable visual results and complication rates in CT patients. PC ICL implantation – as shown in many previous studies – has many advantages for corneal endothelial protection, which is especially important in P-CT cases.[21–23] However, even if this technique looks safe for corneal endothelium, these patients should be carefully monitorized for IOP elevation due to increased glaucoma incidence.

Ethics Committee Approval: The study was approved by the local ethics committe at Ege University Faculty of Medicine.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Concept: M.E.B., M.P., S.E., A.Y.; Design: M.E.B., M.P., S.E., A.Y.; Supervision: M.P., S.E., A.Y.; Resource: M.P., S.E., A.Y.; Materials: M.P., S.E., A.Y.; Data Collection and/or Processing: M.E.B., M.P.; Analysis and/or Interpretation: M.E.B., M.P., S.E., A.Y.; Literature Search: M.E.B., M.P., S.E., A.Y.; Writing: M.E.B., M.P.; Critical Reviews: M.P., S.E., A.Y.

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ORIGINAL ARTICLE

The characteristics of pseudoexfoliation glaucoma in Ankara, the capital of Turkey

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Abstract

Purpose: The purpose of the study was to study the profile, clinical characteristics, and associated ocular and systemic comorbidities of pseudoexfoliation glaucoma (PEXG) in a cross-sectional multicentric study.

Methods: A total of 7500 eyes of 3750 subjects with glaucoma and suspected glaucoma underwent complete ophthalmic evaluation including history, visual acuity testing, slit-lamp examination, applanation tonometry, gonioscopy, and dilated examination of the optic disc and fundus between March 15, 2015, and May 16, 2015. Patients with PEXG were identified and their data were analyzed with respect to age, sex, intraocular pressure, ocular, and systemic diseases.

Results: A total of 1180 eyes of 666 subjects had PEXG (mean age: 72.7±9.0 years (38–97 years). The percentage of the patients with PEXG within patients with glaucoma (4604 eyes of 2541 subjects) was 26.2%. Male-to-female ratio was 402/264 (60.3%/39.6%). One hundred and three patients (15.4%) had a positive family history. Four hundred and seventy-four patients (71.17%) had an additional systemic disease and the most prevalent comorbidities were hypertension and diabetes mellitus. Five hundred and fourteen patients (77.1%) had bilateral disease. The most common surgery performed in patients with PEXG was trabeculectomy (281 eyes; 23.8%). Six hundred and thirty-six patients (95.5%) had open angle glaucoma and 30 patients had closed angle glaucoma (4.5%).

Conclusion: PEXG is common in Turkey and one-quarter of glaucoma patients were found to have PEXG in this hospital-based study. In addition, with this multicentric study, we were able to document the demographic properties of PEXG in a large study population in the Central Anatolian metropolitan area.

Keywords: Characteristic; comorbidity; glaucoma; pseudoexfoliation.

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Pseudoexfoliation (PEX) syndrome is an idiopathic, generalized disorder that is characterized by the production and accumulation of a fibrillar extracellular material in many ocular tissues.[1] Despite extensive research, the exact chemical nature of the fibrillar material is unknown. It is believed to be secreted multifocally; in the iris pigment epithelium, the ciliary epithelium, and the peripheral anterior lens epithelium.[2]

PEX has a worldwide distribution and prevalence rates vary from 10 to 20% of the general population over the age of 60 years.[3] To the best of our knowledge, there are three hospital-based epidemiologic studies on the prevalence or characteristics of PEX in Turkey. According to these studies, the prevalence of PEX in Turkey varies between 10.1% and 12.2%.[4–6] Other hospital-based studies have shown a prevalence of 9.1% in Jordanians,[7] 0.4% in Chinese,[8] 6.5% in Pakistani,[9] 7.4% in Indians,[10] and 9.6% in Iranians.[11] Kılıç et al.[12] reported a new population-based study about the prevalence of PSX in Turkey. In this study, a total of 1107 individuals were evaluated and the authors reported a prevalence of 6.5% over 40 years of age.

PEX predisposes to a number of ocular comorbidities, the most severe being glaucoma, known as PEX glaucoma (PEXG).[1,13] PEX is reported to be the most common identifiable cause of open angle glaucoma and PEXG accounts for approximately 25% of all open angle glaucomas worldwide.[14,15] PEXG has a more serious clinical course and a worse prognosis than primary open angle glaucoma.[16,17] It is believed that the fibrillary material moves into the aqueous humor and is carried to the trabecular meshwork, following the normal flow. Obstruction of the trabecular meshwork by this fibrillary material and pigment causes elevation of the intraocular pressure (IOP) leading to glaucoma.[18] PEX is now suspected to be a systemic disorder and has been associated preliminarily with stroke, systemic hypertension, and myocardial infarction in some studies,[19] whereas other studies did not report an association of PEX with cardiovascular or cerebrovascular morbidity or mortality.[20,21] In fact, pseudoexfoliative like material has been found in lungs, skin, liver, heart, kidney, gallbladder, blood vessels, extraocular muscles, and meninges by electron microscopy.[22]

This research is a part of a hospital-based cross-sectional, prospective, multicentric study designed to determine the characteristics of glaucoma in Ankara. Ankara is the capital and second largest city of Turkey, additionally, this city located in the center of country. The ophthalmology clinics that joined this study are reference centers accepting patients from different parts of the country. In this study, we aimed to include a large population with glaucoma. For this current work, we analyzed only the data of the patients with PEXG and studied the profile, clinical characteristics, and associated ocular and systemic comorbidities of these patients.

Materials and Methods

This study was conducted between March 15, 2015, and May 16, 2015. The patients who presented and/or were referred to the glaucoma units of nine tertiary ophthalmology centers in Ankara and were diagnosed with glaucoma in either one eye or both eyes were included in the study. In brief, of the 3750 individuals with glaucoma and suspected glaucoma who underwent clinical examination, 2541 fulfilled the inclusion criteria of glaucoma and were eligible for the study. The study was carried out after approval by the Institutional Research and Ethics Board of the Gülhane Military Medical Academy (2015–27). Adherence to the Declaration of Helsinki for research involving human subjects was confirmed. Written informed consent was taken before proceeding for the recording of information and confidentiality was ensured.

Data were entered into a standardized form that had been constructed before the commencement of the study. All data collections were performed under the supervision of a glaucoma specialist. In this current study, patients with PEXG were identified and their data were analyzed with respect to age, sex, ocular parameters, and systemic diseases. We have to underline that the patients with only PEX (without glaucoma) were excluded from the study.

Examination Procedures

The examination included detailed medical and ophthalmic history; visual acuity testing using Snellen chart; slit-lamp examination; Goldmann applanation tonometry; gonioscopy using Goldmann three-mirror system; visual field examination (24–2 full-threshold test (stimulus size III) on a Humphrey automated perimeter (Humphrey Instruments, Inc., Dublin, California, USA); and dilated fundus examination. Visual field evaluation was performed to all patients except patients in category 3. Subjects with open angles had dilated their pupils with 5% phenylephrine and 1% tropicamide eye drops. Patients with typical pseudoexfoliative material on the anterior lens surface in either or both eyes were labeled as having PEX. Only eyes where the diagnosis was absolutely certain were included in the study. The aphakic and pseudophakic patients who were undoubtedly diagnosed as "PEXG" according to the reliable file data were included in this study. Stereoscopic evalua-

tion of the fundus and the optic disc with the +90 D lens was performed.

The patients who were found to have narrow or occludable angles on gonioscopy were first offered laser iridotomy treatment. The rest of the evaluation was then deferred to a later date. An angle was considered occludable if the pigmented trabecular meshwork was not visible in 180° or more of the angle.

The presence of glaucoma was defined under the guidelines according to the International Society for Geographical and Epidemiological Ophthalmology (ISGEO) Classification.[23,24] Eyes with an ophthalmoscopic vertical cupping to disc ratio (C/D ratio) or C/D ratio asymmetry >97.5th percentile for the normal population, or a neuroretinal rim width reduced to <0.1 C/D ratio (between 11 and 1 o'clock or 5 and 7 o'clock) that also showed a definite visual field defect consistent with glaucoma was then assessed under category 1 criteria (structural and functional evidence). When perimetry was not possible, glaucoma was considered to be present if category 2 (advanced structural damage with unproven field loss) criteria were fulfilled (C/D ratio 99.5th percentile in the absence of any other explanation), or if category 3 (optic disc not seen, field test impossible) criteria were fulfilled when disc assessment was not possible (visual acuity <3/60 and IOP >99.5th percentile, or visual acuity <3/60 and the eye shows evidence of glaucoma filtering surgery, or medical records confirm glaucoma).

Cutoff points for 97.5th and 99.5th percentile for ophthalmoscopic C/D ratio were accepted as 0.7 and 0.9, respectively. Cutoff points for 97.5th and 99.5th percentile of ophthalmoscopic C/D ratio asymmetry were accepted as 0.2 and 0.3. Cutoff point for 97.5th percentile of IOP was accepted as 22 mmHg.[24,25]

Criteria for blindness were defined as best-corrected visual acuity less than 3/60 in the worse eye for monocular blindness and less than 3/60 in the better eye for binocular blindness.[26,27]

For calculation of values such as mean IOP, C/D ratio, and index of visual field test, only one eye of each patient with bilateral disease was considered. In those with bilateral PEXG, only the worse eye was included. Worse eye was selected depending on the amount of visual field damage and C/D ratio. In patients with unilateral PEXG, the eye with PEXG was included.

Best-corrected visual acuity was measured with a decimal visual acuity chart and converted into logMAR units for analysis. Number of current glaucoma medications and previous glaucoma surgeries were recorded.

Data were entered and analyzed using the Statistical Program for Social Sciences (SPSS version 21.0 for Windows software). Chi-square test was used to compare discrete variables and Mann–Whitney U-test was used to compare ordinal data. P<0.05 was considered to indicate statistical significance.

Results

A total of 1180 eyes of 666 subjects had PEXG. Thus, the prevalence of PEXG in the patients with glaucoma (4604 eyes of 2541 subjects) was 26.2%.

Men outnumbered women in the PEXG patients. Four hundred and two cases (60.4%) were male and 264 cases (39.6%) female with a male-to-female ratio of 1.52/1.

Fifty-one patients (7.6%) were diagnosed with PEXG during this study period. The remaining 615 patients (97.5%) had the disease for more than 1 year. One hundred and three patients (15.4%) had a positive family history.

Mean age of the patients with PEXG was 72.7±9.0 years (38–97 years). Table 1 shows age distribution of the patients. Prevalence of PEXG increased with age and was highest among subjects aged between 70 and 80 years. Large proportion of all PEXG patients (92.1%) was over 60 years old.

The big amount (71.2%) of the patients had additional systemic disease and the most prevalent comorbidities were hypertension (53.0%) and diabetes mellitus (18.4%). Table 2 shows the systemic diseases of the patients with PEXG.

Table 1. Age distribution in the study population

Age range (years)	No. of subjects	Percentage (%)
49>	7	1.1
50–59	45	6.8
60–69	184	27.6
70–79	259	38.9
80<	171	25.7

Table 2. The systemic diseases of the patients with pseudoexfoliation glaucoma

Age range (years)	No. of patients	Percentage (%)
Hypertension	353	53.0
Diabetes mellitus	123	18.4
Heart disease	104	15.6
Lung disease	45	6.7
Thyroid disease	29	4.3
Vasospastic disorder	8	1.2
Migraine	5	0.7
Anemia	3	0.4
Neurologic disorder	2	0.3

Table 3. The characteristics of patients with pseudoexfoliation glaucoma

	Mean	Median	Range
BCVA (LogMAR)	0.5±0.6	0.2	0-2
C/D	0.8±0.2	0.7	0.5–1.0
MD	−13.4±9.2	−8.3	−32.1–1.8
PSD	6.6±3.4	5.6	1.1–22.1
Number of drugs	1.7±1.6	2	0–5

BCVA: Best-corrected visual acuity; C/D: Cupping to disc ratio; MD: Mean deviation; PSD: Pattern standard deviation.

Table 4. The comparison of IOP, C/D ratio, and visual field test index between patients with unilateral and bilateral disease

	Bilateral	Unilateral	p-value*
IOP			
Mean	17.3±7.2	15.1±5.5	0.051
Median	16	15	
Minimum-maximum	3–47	6–50	
C/D			
Mean	0.7±0.3	0.7±0.4	0.67
Median	0.7	0.7	
Minimum-maximum	0.5–1.0	0.5–1.0	
MD			
Mean	−12.7±9.3	−10.7±8.5	0.022
Median	−10.2	−7.8	
Minimum-maximum	−31.8–1.4	−32.1–1.8	
PSD			
Mean	6.4±3.3	5.8±3.4	0.032
Median	6.6	5.1	
Minimum-maximum	1.4–14.6	1.1–16.2	

*Mann–Whitney U-test. IOP: Intraocular pressure; C/D: Cupping to disc ratio; MD: Mean deviation; PSD: Pattern standard deviation.

Six hundred and thirty-six patients (95.5%) had open angle glaucoma and 30 patients had closed angle glaucoma (4.5%). The gender distribution in patients with closed angle glaucoma (11 men and 19 women) was different from the patients with open angle glaucoma (393 men and 243 women) ($p=0.018$; $\chi^2=5.59$). The age, IOP, C/D ratio, and visual field test index were similar between open angle and closed angle glaucoma groups ($p>0.05$).

The mean IOP was 16.7±6.5 mmHg, ranging from 3 to 56 mmHg (median: 16 mmHg). The IOP obtained from the medical history as the highest IOP was named as "maximum IOP." Maximum IOP was 30.96±8.66 mmHg, ranging from 25 to 66 mmHg (median: 29.00 mmHg). Table 3 shows the overall characteristics of our patients.

Five hundred and fourteen patients (77.1%) (298 men and 216 women) had bilateral disease and 152 patients (22.9%) (100 men and 52 women) had unilateral disease. The men-women ratio in patients with unilateral PEXG (1.92/1) was significantly higher than the patients with bilateral disease (1.37/1) ($p=0.034$; $\chi^2=4.518$). The mean ages of patients with uni- and bilateral PEX were 69.6±9.7 (range: 38–97 years; median: 69 years) and 74.2±8.3 years (range: 38–92 years; median: 75 years), respectively, the difference being significant (Mann–Whitney U-test, $p\leq0.001$). Table 4 shows the comparison of IOP, C/D ratio, and visual field test index between patients with unilateral and bilateral disease. IOP and C/D ratio were found to be similar between patients with unilateral and bilateral disease, however, visual field test index of patients with unilateral disease was better than bilateral disease.

Table 5. The most common surgery types performed in patients with pseudoexfoliation glaucoma

	No. of eyes	Percentage (%)
Argon/selective laser trabeculoplasty	18	1.5
Trabeculectomy	308	26.1
Once only	281	
Twice or more	27	
Seton surgery	8	0.6
Cyclodestruction	5	0.4
Non-penetrative glaucoma surgery	8	0.6

The most common glaucoma surgery performed was trabeculectomy (281 eyes; 23.8%). Table 5 shows the most common surgery types performed in patients. Four hundred and fourteen eyes (35.1%) were pseudophakic and 9 eyes (0.8%) aphakic.

On the basis of ISGEO criteria, 431 (64.7%) of the patients were in category 1, 208 (31.2%) were in category 2, and 27 (4.0%) were in category 3. Monocular blindness was present in 168 (25.2%) patients, while binocular blindness was present in 17 (2.6%) patients.

Discussion

There are extensive variations in design or sampling methods of studies about PEX and PEXG. In addition, there are genetic, geographical, or racial variations in these study groups. Because of that, comparisons between studies on prevalence and characteristics of PEX are difficult. We want to emphasize that only the patients (1180 eyes of 666 patients) with PEXG were included in this study. We also determined a PEXG prevalence of 26.2% among patients with glaucoma, similar to other studies.[14,15]

Conflicting reports exist regarding the association between gender predilection and prevalence of PEX. There are stud-

ies reporting a higher PEX frequency in females.[28,29] Other studies reported that there was no sex predilection.[7,30,31] In our study, men outnumbered women and the male-to-female ratio was 1.52/1. Similar to our study, some authors reported that[32,33] PEX was more common among males than in females in their countries. In two studies from Turkey, Yalaz et al.[4] and Kılıç et al.[6] found PEX to be more common in males, but Cumurcu et al.[5] found that women were more frequently affected than men.

PEX has a greater prevalence in the older population,[3,9,32,34] and increasing age has been universally accepted as a significant risk factor for the development of PEX.[32,35] In our study, we found that the mean age of the patients with PEXG was 72.7±9.0 years. Prevalence of PEXG increased with age and was highest among subjects aged between 70 and 80 years. About 92.1% of all PEXG patients were over 60 years old which is comparable to the previously published reports.[5,30,36]

Open angle glaucoma is more prevalent in patients with PEX compared to angle closure glaucoma.[37,38] Various studies reported that the prevalence of occludable angle was between 4% and 23% in patients with PEX.[30,37,39] In our study, 95.67% of the patients had open angle glaucoma and 4.32% had closed angle glaucoma. The gender distribution in patients with closed angle glaucoma was different from the patients with open angle glaucoma. We observed that closed angle glaucoma was more common in women and open angle glaucoma was more common in men.

In this study, 77.1% of patients had bilateral disease and the remaining 22.9% had unilateral disease which is comparable to the previously published reports.[7,31,38,40] The men-women ratio in patients with unilateral PEX (1.92/1) was found to be significantly higher than the patients with bilateral disease (1.37/1). The mean ages of people with uni- and bilateral PEXG were 69.6±9.66 and 74.17±8.26 years, respectively, the difference being significant ($p \leq 0.001$). These findings are similar to those of other studies.[30,41] It has been known that unilateral PEX converts to bilateral disease in up to 50% of patients within 5–10 years.[10,38] The patients with unilateral disease were found to be approximately 5 years younger than the cases with bilateral disease in our study. This may be related to the conversion to bilateral disease within 5–10 years.

There is a well-known association between PEX and cataract.[5,7,9,42] We did not directly record cataract as a finding or investigate the frequency of cataract among the patients with PEXG, however, we detected that 35.08% of eyes were pseudophakic and 0.76% aphakic. Because of that, it seems that the cataract frequency in PEXG patients in our study was lower than the previous studies.[4–6,8] Regarding the cataract frequency in PEX cases in studies conducted in Turkey, the authors found a frequency of between 44% and 85%.[4–6]

Recent studies have highlighted the association between PEX and visual morbidity rates.[30,42] Similarly, in the current study, blindness was strongly associated with the presence of PEXG. Monocular blindness due to glaucoma was present in 25.2% of patients, while binocular blindness due to glaucoma was present in 2.6% of patients. Thomas et al.[42] found that 4.1% of patients with PEX were blind due to glaucoma and it was comparable with our study.

The relationship between PEX and cardiovascular diseases still remains controversial. Many studies have shown a positive relationship between cardiovascular diseases and PEX.[19,43–45] The Blue Mountains Eye Study reported a significant relationship between PEX and a history of hypertension, a history of angina or combined angina or myocardial infarction, and a history of stroke.[19] Of the studies from Turkey, Citirik et al.[20] showed a significant relationship between coronary arterial disease and PEX, but Emiroglu et al.[21] found no relationship. Kılıç et al.[6] found no relationship between PEX and hypertension or diabetes mellitus in their study, but a significant relationship was found to be with coronary arterial disease. However, there are a lot of studies which have found no relationship between PEX and cardiovascular disease.[46–48] In our study, we detected that 53% of patients had hypertension, 18.46% of patients diabetes mellitus, and 16.81% of patients cardiovascular disease.

As a result, this work was conducted in Ankara as a cross-sectional multicentric study. Our study had some limitations. This study was hospital based rather than population based. However, only the PEXG patients who were defined with strict criteria by nine different ophthalmology clinics were included in this study. In addition, with this multicentric study, we were able to document the demographic properties of PEXG in a large study population in the Central Anatolian metropolitan area. We think that the data of this study would contribute to the literature and will be a base for the future population-based studies in Turkey.

Ethics Committee Approval: This study was approved by Gülhane Military Medical Academy Ethics Committee (2015–27).

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Authorship Contributions: Concept: S.G.G., A.A., A.B.; Design: A.A., A.B.; Supervision: A.A., A.B.; Resource: S.G.G., A.A., A.B., U.E., O.T., T.T., U.E., A.Y., T.M., Z.A., A.K., O.E.K.; Materials: S.G.G., A.A., A.B.,

U.E., O.T., T.T., U.E., A.Y., T.M., Z.A., A.K., O.E.K.; Data Collection and/or Processing: S.G.G., A.A., A.B., UE, O.T., T.T., U.E., A.Y., T.M., Z.A., A.K., OEK; Analysis and/or Interpretation: S.G.G., A.A., A.B., UE, O.T., T.T., U.E., A.Y., T.M., Z.A., A.K., O.E.K.; Literature Search: S.G.G.; Writing: S.G.G.; Critical Reviews: A.A., A.B.

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ORIGINAL ARTICLE

The influence of light condition on anterior segment parameters with Pentacam in healthy subjects

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Abstract

Purpose: The objectives of the study were to determine whether different light conditions influence anterior segment parameters of healthy subjects as measured with Pentacam.

Methods: Anterior segment parameters of 50 healthy subjects were measured with Pentacam under dim light condition and room light condition. Paired t test was used to compare measurements under different light conditions.

Results: Mean age in the study group was 31.7±8.5 (range; 22–43) years. Measurements between 2 sessions were significantly different for the parameters of anterior chamber depth, anterior chamber volume (ACV), and pupilla diameter ($p<0.05$).

Conclusion: Taking Pentacam Scheimpflug measurements in room light causes a significant increase in anterior chamber angle and decrease in ACV as well as pupilla diameter in healthy subjects. When using Pentacam, the effect of light condition on these parameters should be considered and all measurements should be obtained under standard dim light conditions as suggested by the manufacturer.

Keywords: Anterior chamber angle; anterior chamber depth; anterior chamber volume; anterior segment; Pentacam.

The assessment of anterior segment parameters is an important issue when planning ocular refractive and cataract surgery, diagnosing and treating glaucoma, and assessing corneal health.[1–3] Anterior segment imaging technologies, including Pentacam rotating Scheimpflug camera (Oculus Optikgeräte GmbH, Wetzlar, Germany), promise quantitative and qualitative imaging of cornea, anterior chamber, and iridocorneal angle for clinical practice and research settings.[1,4,5]

Reliable anterior segment measurements are important for screening and follow-up of the subjects. Obtaining accurate measurements with Pentacam depends on many properties, including the compliance of the subject, experience of the examiner, and environmental conditions such as room light. Although the manufacturer's guideline suggests taking measurements in a dim light condition, in some clinics, this issue might be underestimated. For reliable and consistent clinical results, it is important to de-

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termine how the room light condition influences anterior segment parameters. To the best of our knowledge, alterations in anterior segment parameters, as measured with the Pentacam device under different light conditions, have not been reported previously in the literature. For this reason, we aimed to explore the importance of the room light condition when taking Pentacam measurements in healthy individuals.

Materials and Methods

This prospective study involved randomized 50 healthy adult subjects and was conducted in accordance with the tenets of Declaration of Helsinki. The study was approved by a local ethical committee (02-2019/07). All subjects signed informed consent before they were enrolled in the study.

The inclusion criteria were: A best-corrected visual acuity of 10/10 (on the Snellen scale) for both eyes; a refractive error (in spherical equivalent) within ± 2.00 diopters. The exclusion criteria were: Diseases that could affect measurements in either eye, such as corneal diseases, pterygium, and cataracts; a history of contact lens use or prior ocular surgery.

The Pentacam device is based on a single rotating Scheimpflug camera (180°) that provides a 3-dimensional scan of the anterior segment of the eye. The Scheimpflug camera rotates around the optical axis of the eye and captures 25 slit images of the anterior segment within 2 s. In this study, all measurements were obtained by the same observer who was skilled at using the Pentacam. All subjects were positioned using a headrest and instructed to fixate on an internal target on the center of the camera without blinking during the scans. When using the Pentacam providing automatic measurements, only the scans with an examination quality specification of "OK" were retained for analysis; data from substandard scans were discarded, and the scans were repeated. Subjects were asked to blink once completely just before the scan was initiated to allow an optically smooth tear film to spread over the cornea. After each measurement, the subject was asked to sit back and the system was realigned for the next measurement. The first group measurements were taken under a dim light condition. The second group measurements were taken after the room light was turned on. Flat radius and steep radius (in mm) of anterior and posterior cornea, mean astigmatism, corneal volume (CV), anterior chamber volume (ACV), anterior chamber depth (ACD), anterior chamber angle (ACA), and pupilla diameter measurements that were provided by Pentacam system automatically were recorded. Measurements were taken from both eyes; however, only the right eye of each subject was included for statistical analysis.

The paired t-test was used for data analysis after the Kolmogorov–Smirnov test confirmed the normality of assumption. $P<0.05$ was considered as statistically significant. A post-hoc power analysis was conducted to assess sufficiency of the sample size.

Results

This study included 28 female and 22 male subjects with a mean age of 31.7±8.5 (range; 22–43) years. Table 1 shows data of analyzed parameters under dim light and room light conditions.

The mean ACA was 34.0±5.6° (range; 22.7°–49.0°) under dim light condition and 36.55±6.07° (range; 23.1°–53.6°) under room light condition (p=0.02). Mean ACV measurement was 163.5±38.6 (range; 95–248) mm^3 under dim light condition and 153.6±37.3 (range; 94–246) mm^3 under room light condition (p<0.0001). The change in mean pupilla diameter was also statistically significant with a mean

Table 1. The measurements under dim light and room light conditions

	Dim light Mean±SD (95% CI)	Room light Mean±SD (95% CI)	p-value*
Rf-ant	7.94±0.27 (7.86–8.01)	7.93±0.27 (7.85–8.01)	0.20
Rs-ant	7.77±0.26 (7.70–7.85)	7.77±0.27 (7.70–7.85)	0.86
Rf-post	6.61±0.26 (6.54–6.69)	6.61±0.25 (6.54–6.68)	0.74
Rs-post	6.19±0.26 (6.11–6.27)	6.21±0.26 (6.13–6.28)	0.14
Mean astigmatism	0.42±0.14 (0.37–0.46)	0.39±0.14 (0.35–0.43)	0.16
Mean CV	60.0±3.94 (58.9–61.1)	60.2±3.83 (59.1–61.3)	0.22
Mean ACA	34.0±5.6 (32.4–35.6)	36.55±6.07 (35.8–37.3)	0.02
Mean ACD	2.93±0.37 (2.82–3.04)	2.93±0.37 (2.82–3.03)	0.76
Mean ACV	163.5±38.6 (160.3–166.7)	153.6±37.3 (148.1–159.1)	<0.0001
Mean PD	3.46±0.66 (3.28–3.64)	3.10±0.58 (2.94–3.26)	<0.0001

*Paired t-test. Rf-ant: Flat radius of anterior cornea; Rs-ant: Steep radius of anterior cornea; Rf-post: Flat radius of posterior cornea; Rs-post: Steep radius of posterior cornea; CV: Corneal volume; ACA: Anterior chamber volume; ACD: Anterior chamber depth; ACV: Anterior chamber volume; PD: Pupil diameter; SD: Standard deviation.

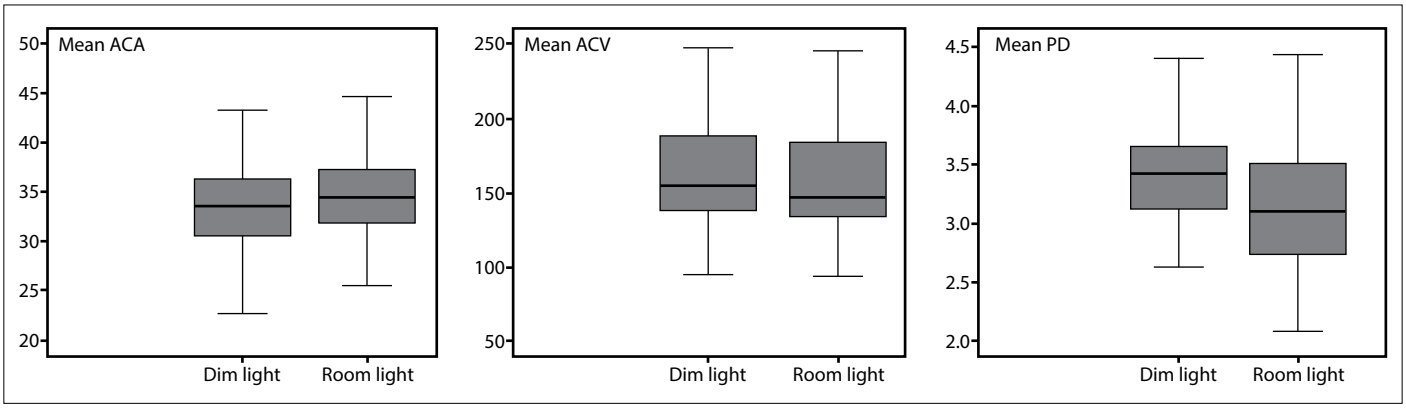

Fig. 1. The changes in statistically significant parameters as box - plots under dim light and room light conditions.

of 3.46±0.66 (range; 2.17–5.01) and 3.10±0.58 mm (range; 2.08–4.44) under dim light and room light conditions, respectively (p<0.0001). Figure 1 demonstrates the changes in statistically significant parameters as box-plots under dim light and room light conditions.

No significant difference in flat or steep radius of anterior and posterior cornea, mean astigmatism, mean CV, and mean ACD measurements was found between dim light and room light conditions. The mean radius value of anterior cornea was 7.94±0.27 (range; 7.31–8.42) mm under dim light condition and 7.93±0.27 (range; 7.29–8.43) mm under room light condition for flat radius (p=0.20) and 7.77±0.26 (range; 7.21–8.24) mm under dim light condition and 7.77±0.27 (range; 7.21–8.24) mm under room light condition for steep radius (p=0.86). The mean flat radius value of posterior cornea for dim light and room light conditions was 6.61±0.26 (range; 5.90–7.11) mm and 6.61±0.25 (range; 5.97–7.09) mm, respectively (p=0.74). The mean steep radius value of posterior cornea was 6.19±0.26 (range; 5.40–6.65) mm under dim light condition and 6.21±0.26 (range; 5.40–6.70) mm under room light condition (p=0.14).

Mean astigmatism was 0.42±0.14 (range; 0.1–0.8) D under dim light condition and 0.39±0.14 (range; 0.1–0.7) D under room light condition (p=0.16). Mean CV was 60.0±3.94 (range; 54.1–73.3) mm^3 under dim light condition and 60.21±3.83 (range; 54.2–73.4) mm3 under room light condition (p=0.22). Mean ACD was 2.93±0.37 (range; 2.25–3.80) mm under dim light condition and 2.93±0.37 (range; 2.17–3.79) mm under room light condition (p=0.76).

Considering the mean ACV in post-hoc analysis, the power for the sample size used was found to be 90%.

Discussion

Developments in imaging techniques allow the clinician to quantitatively calculate the anterior segment parameters.[5,6] Among these devices, the Pentacam is a rotating Scheimpflug system that allows noninvasive assessment of the anterior chamber structures. In various studies, it has been reported that Pentacam provides repeatable and reliable measurements.[1,7] To take accurate measurements, the compliance of the subject, the experience of the examiner, and environmental properties, including the room light condition, are important. In different light conditions, the pupil reacts to the light that enters through pupilla. Therefore, in increased light conditions, the pupillary light reflex is activated. The pupillary light reflex is a reflex that controls the diameter of the pupil in response to the intensity of light that falls on the retina, thereby assisting in adaptation of vision to various levels of lightness/darkness. The control of the diameter of the pupil is also under parasympathetic and sympathetic axons. In the current study, we sought to determine whether the different light conditions modify anterior segment parameters of healthy subjects.

The ACA, ACV, and ACD are important anterior segment parameters in ocular pharmacokinetics and primary angle-closure glaucoma development.[8,9] In our study, the mean ACA, ACV, and pupilla diameter were significantly different between dim light and room light conditions; however, the ACD was not. It has been reported that the iris bowing is an important biometric parameter that determines the ACA from dark to room light conditions.[10] The decrease in iris bowing from dim light to room light condition could contribute to the decreased narrowing of the angle due to the pupillary miosis in the room light. The probability of primary angle-closure glaucoma formation increases with smaller iridocorneal angle width values. For this reason, it is important to examine the angle under dim light, especially for evaluation of angle closure. The increasing pupil diameter leads to higher ACV measurements.[11] When the pupil is dilated, iris volume also reduces, thus

creating space in the anterior chamber. Thus, decreased iris volume and increased pupilla diameter could influence the higher ACV measurements under dim light condition. Obtaining a correct ACD measurement is very important for precise biometric evaluation and phakic anterior chamber intraocular lens implantation. We did not observe an effect of light condition on ACD measurements different from other studies that focused on influences of pharmacological dilatation on anterior segment parameters. With these agents, the increase in ACD is associated with the lens thickness decrease and the backward moving of the lens.[12–14]

In summary, to take Pentacam measurements under room light causes a significant increase in ACA and decrease in the ACV readings in healthy subjects. For this reason, to obtain reliable and consistent results with Pentacam all measurements should be obtained under standard dim light conditions as suggested by the manufacturer.

Ethics Committee Approval: This study was approved by SANKO University Faculty of Medicine Ethics Committee (02-2019/07).

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ORIGINAL ARTICLE

Correlation of corpus callosum index and optic coherence tomography findings in multiple sclerosis with or without optic nerve involvement

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Abstract

Purpose: To evaluate the correlation of spectral domain optical coherence tomography (SD-OCT) parameters including peripapiller retinal nerve fiber length (RNFL) and ganglion cell layer (GCL) analysis with corpus callosum volumes, which were determined by corpus callosum index (CCI) radiologically in multiple sclerosis (MS) patients.

Methods: Forty MS patients, with or without optic neuritis in history, were involved in the study on which RNFL and GCL analysis by SD-OCT were performed. Anterior, middle, posterior, and overall CCI were calculated for all subjects on 1.5 T magnetic resonance imaging scans, on conventional best mid-sagittal T1W image.

Results: Seventeen patients had unilateral optic neuritis in history (42.5%) and had significantly lower CCIs compared to cases without optic nerve involvement ($p<0.05$ for each); lower RNFL measurements and lower GCL values in involved eyes compared to uninvolved side ($p=0.03$ and $p<0.001$, respectively). Overall CCI was lower in patients with more attacks in history and in elder MS patients ($p=0.011$ and $p=0.06$, respectively). Overall CCI was also lower in cases with lower mean RNFL and mean GCL measurements possessing a high positive correlation coefficient ($p=0.047$, $p=0.002$; $r=0.316$, $p=0.478$, respectively).

Conclusion: This study demonstrated that involvement of optic nerve in MS patients is with lower anterior, middle, posterior, and overall CCI values in addition to lower mean RNFL and GCL values of OCT. The positive correlation of CCIs with OCT parameters shows that the neuroaxonal degeneration in MS simultaneously affects the retina and the brain.

Keywords: Corpus callosum index; ganglion cell layer analysis; multiple sclerosis; optic coherence tomography; retinal nerve fiber length.

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Multiple sclerosis (MS) is a chronic inflammatory disorder of the central nervous system which is known to affect young population with 20–40 years of age. It's main etiopathology is based on demyelination and neuronal degeneration leading to axonal loss.[1] It has been reported that postmortem analysis of MS patients indicated 94–99% optic nerve lesions in these subjects, even though no evident optic neuritis in history.[2,3]

Unmyelinated axons of retinal ganglion cells (GC) constitute retinal nerve fiber layer (RNFL), which can be objectively measured by spectral domain optical coherence tomography (SD-OCT) – a high-resolution, non-X-ray retinal imaging technology.[4] OCT gained its popularity in neuro-ophthalmology for its effective use in neurodegenerative diseases. This non-invasive technique yields high-resolution images of retinal morphology.[5] It uses near-infrared light and can analyze the integrity of GC and their axons, which are myelinated after they leave the eye at the level of lamina cribrosa.[6]

It has been known that acute stage of optic neuritis is with a manifest increase in RNFL thickness in up to 82% of cases, measured by OCT due to the axonal stasis and secondary edema of the optic nerve head.[7,8] RNFL values are decreased at the chronic stages of optic nerve involvement, indicating atrophy of the optic nerve axons.[7,8]

RNFL is reported to be thinner in MS patients, which shows a correlation with disease activity and white matter lesion volume in magnetic resonance imaging (MRI).[4] Recent studies concluded that the decrease in RNFL thickness is regarded to be correlated to neurodegeneration, cerebral atrophy, and progressive disease in MS patients.[5,9]

Improved image resolution in SD-OCT also enables to measure the GC-inner plexiform layer (IPL) (GC layer [GCL]) in the macular area which is another recently popular OCT marker for detecting and monitoring the neuronal degeneration.[10] GCL analysis together with the IPL is called GCIPL complex and is analyzed by different segmentation algorithms in different OCT devices of variable manufacturers.[11] GCL thickness measurements are important in acute stages for the evaluation of the disease prognosis since RNFL is evidently increased by optic nerve head edema in acute phase but GCL analysis is not altered by axonal stasis and could potentially provide prognostic evaluation in neurodegeneration during the follow-up.[11]

MRI is the gold standard in MS which absolutely has the main role for the diagnosis and monitoring of treatment response. The whole brain, the white and gray matter volumes – together with the volume of brain lesions are some of the traditional quantitative MRI parameters used in MS patients.[12] However, the need of specially designed post-processing methods and dependence on three-dimensional MRI sequences for their application limits their use in common practice.[13]

Corpus callosum is the connective bundle formed by white matter fibers crossing across the cerebral hemispheres. It is the favorite topic of recent studies since it is proposed to have a role in reflecting the level of brain atrophy in demyelinating diseases – due to its sensitivity in focal loss of white matter.[14] Assessment of CC quantitatively is based on two methods; manually as two-dimensional measurements of the CCI and CC area or with the use of some software programs for volumetric analysis such as the CC volume.[9,15] Calculating the CCI is regarded by far the most practical method in current literature.[13] The corpus callosum index (CCI) regarded as a new radiological marker in neurodegenerative disorders and is thought to correlate to the level of brain atrophy in MS.[13] It even shows a high correlation with the lesion load and cognitive dysfunction in these patients.[13]

Our study was designed to evaluate the correlation of SD-OCT parameters including RNFL and GCL in MS patients with corpus callosum volumes, which were determined by CCI radiologically, and mainly aiming to investigate the effect of optic nerve involvement on this correlation.

Materials and Methods

The study was approved by the local ethics committe at Ufuk University Faculty of Medicine on May 16, 2018 (no: 20180516/7) and was in accordance with the ethical standards stated in the 1964 Declaration of Helsinki. Informed consent was obtained from all participants.

Forty MS patients having at least 5 years of disease duration were enrolled in the study. MS diagnosis was made according to the 2010 revised McDonald criteria,[16] and all patients were recruited from the outpatient clinics of our neurology and ophthalmology departments. Patients aged between 18 and 50 years and Expanded Disability Status Scale (EDSS) score between 0 and 5.5 were included in the study. Patients who had an MS attack in the past 30 days and patients who were uncooperative to ophthalmological evaluation were excluded from the study. Data including the duration of follow-up (follow-up time since diagnosis) and number of attacks during follow-up were detected from patient records.

Ophthalmological evaluation included detection of best-corrected visual acuity, slit lamp biomicroscopy, intra-

ocular pressure measurement, fundus examination, examination of refractive errors, and visual field examination by Humphrey perimeter.

OCT scan was performed using a Cirrus HD 400 spectral OCT platform (Carl Zeiss Meditec, Model 400, Dublin, USA, Version 8.1.0.117). Only high-quality images (signal strength ≥7) were selected for the study. The peripapillary retinal nerve fiber length (RNFL) thickness was measured by an optic disc cube scan protocol (200 × 200 pixels) in a 6×6 mm^2 area centered on the optic disc. The macular cube scan 512 × 128 protocol was used to evaluate 6×6 mm^2 area centered on the fovea in terms of GC complex layer (GCL) analysis. The algorithm of the GCL analysis protocol is based on the identification of the macular GC-IPL, from the outer boundary of the RNFL to the outer limit of the IPL.

The average RNFL thickness (and those of the four quadrants; superior, nasal, inferior, and temporal), the thicknesses of the six wedge-shaped sectors of the GCL were automatically calculated and reported. Scans with misalignment, segmentation failure or decentration of the measurement circle, artifacts induced by eye movement during scan, and dropout or missing parts on deviation maps were excluded from the analysis. OCT scans with signal strength equal to or more than 7 (out of 10) were included in the study.

The brain MRI studies were performed on the same week with clinical examinations and OCT scans, using a 1.5 Tesla GE Signa HD×T scanner with a 16-channel head coil. Anatomical images were acquired with the following parameters: T1-weighted sagittal sequence; TE/TR = 23.74/2889.4 ms; flip angle = 90; matrix size = 288×192; FOV = 256 mm; slice thickness = 5 mm; slice gap = 0 mm; and 46 slices. For lesion assessment, T2-weighted images were acquired with the following parameters: FLAIR sequence; TE/TR = 144.3/8800 ms; flip angle = 90; matrix size = 320×224; FOV = 240 mm; slice thickness = 5 mm; slice gap = 0 mm; and 30 slices. Other T1- and T2-weighted images also obtained in axial and coronal planes. Intravenous gadolinium was used when it was necessary. When contrast media were injected, three-dimensional BRAVO sequences with TE/TR = 450/8.95 ms; flip angle = 12; matrix size = 256×256; FOV = 240 mm; slice thickness = 1 mm; slice gap = 0 mm; and 320 slices were created.

The CCIs for all patients were calculated independently by two radiologists (GKA and BS). Mid-sagittal T1-weighted magnetic resonance images were used for the method. The greatest anteroposterior axis of the CC was marked with a straight line and its craniocaudal axis at its midpoint was also marked with another straight line perpendicular to the first. Points named as a, a', b, b', and c, c' were noted. The anterior (aa'), medium (cc'), and posterior (bb') segments of the CC were measured and their proportion to the greatest anteroposterior diameter of the CC (ab) was calculated according to the pre-described formula by Figueira et al., determining the overall CCI in our study. [13] We also calculated three additional CCI types (anterior CCI, middle CCI, and posterior CCI) in addition to the pre-described CCI to check out which segment of CCI is effected more in neurodegenerative process of MS. Figure 1 describes calculation of CCI types calculated in our study. Correlation analysis was performed between OCT and CCI values.

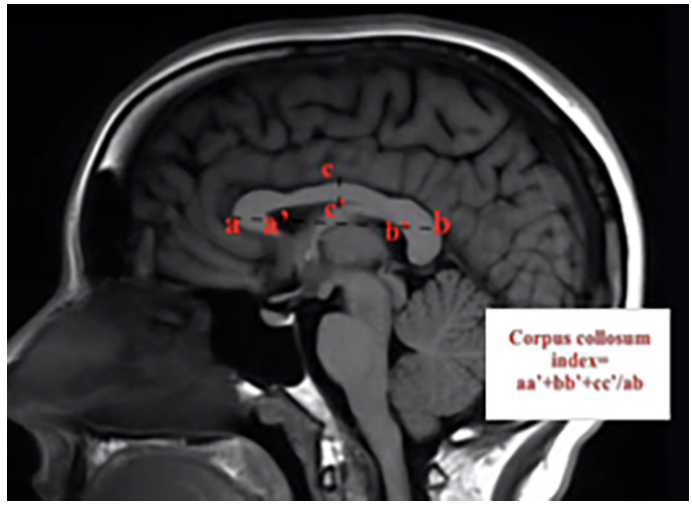

Fig. 1. Calculation of corpus callosum index types used in our study.
aa': Anterior CC, bb': Posterior CC, cc': Middle CC, ab: Total CC
aa'+bb'+cc'/ ab =Corpus callosum index (Overall)
aa'/ab= Anterior corpus callosum index
bb'/ab= Posterior corpus callosum index
cc'/ab= Middle corpus callosum index.

Statistical Analysis

Data analyses were performed using SPSS for Windows, version 22.0 (SPSS Inc., Chicago, IL, United States). The normality of distribution of continuous variables was determined by Kolmogorov–Smirnov test. Levene test was used for the evaluation of homogeneity of variances. Unless specified otherwise, continuous data were described as mean±SD for normal distributions and median (minimum-maximum value) for skewed distributions.

Differences of statistical analysis among normally distributed variables between two independent groups were compared by Student's t-test. Mann–Whitney U-test was applied for comparisons of the not normally distributed data.

Univariate linear regression, univariate logistic regression, and multivariate linear regression were performed to analyze the association of risk factors thought to be related with disease groups. The degrees of relation between variables were analyzed with Pearson correlation or Spearman correlation analysis. P<0.05 was accepted as level of significance in all statistical analysis tests.

Results

Forty MS patients (28 females-12 males) were included in the study. Mean age of the patients was 39±10.81 (22–67) years. Mean follow-up time was 5.05±2.93 (2–14) years and mean number of attacks was 3 (minimum 1-maximum 6).

Overall CCI was lower in patients with more attacks in history and in elder MS patients (p=0.011 and p=0.06, respectively). Duration of the disease was not found to have a significant correlation with CCIs in MS patients (p>0.01) (Table 1 and Fig. 2).

Increase in age and number of attacks were significantly correlated to lower average RNLF in OCT of all MS patients (p=0.002 and p=0.034, respectively), and elder age of the patients was significantly associated with lower average GCL values (p<0.001) (Table 2). Female or male gender did not have any significant difference on OCT measures or CCIs of MS patients (p>0.05).

Overall CCI was lower in cases with lower average RNFL and average GCL measurements among all eyes of MS patients with high correlation coefficients (p=0.047, p=0.002; r=0.316, p=0.478, respectively) (Table 3, Figs. 3 and 4).

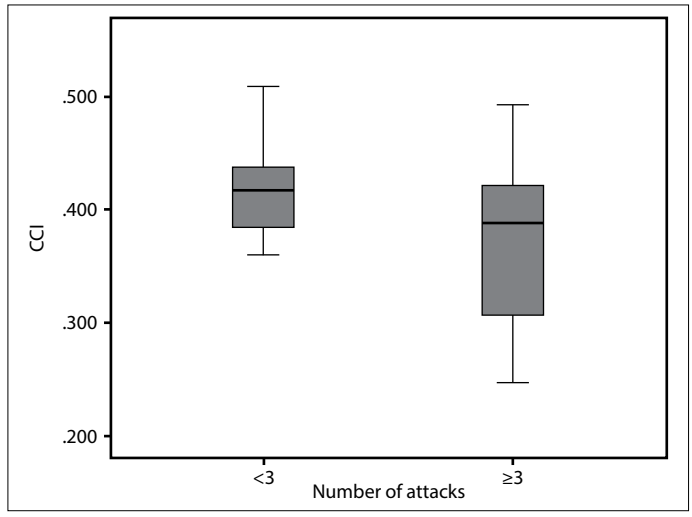

Fig. 2. Effect of number of attacks on overall CCI measures (p=0.011). CCI: Corpus callosum index.

Seventeen patients had optic neuritis in history (42.5%), and all were unilaterally affected. They had significantly lower overall CCI than MS patients without optic neuritis in history (p=0.004). Anterior, middle, and posterior CCI values are also found to be significantly lower in MS cases with optic nerve involvement compared to cases without optic nerve involvement (p<0.05 for each) (Table 4).

Cases with optic neuritis in history had lower RNFL measurements and lower GCL values in involved eyes compared to uninvolved side (p=0.03 and p<0.001, respectively) (Table 5).

The interobserver reliability of this method is found to be high since no significant variations were found between

Table 1. Effects of clinical and demographical properties of MS patients on measures of CC

Measures of corpus callosum		Age of patient (years)	Number of attacks	Duration of disease (years)
Anterior CC	r	–0.457	–0.350	–0.159
	p	0.003	0.027	0.326
Middle CC	r	–0.467	–0.283	–0.224
	p	0.002	0.077	0.164
Posterior CC	r	–0.259	–0.189	–0.260
	p	0.107	0.243	0.106
Total CC	r	–0.045	0.187	–0.122
	p	0.784	0.249	0.454
CCI	r	–0.424	–0.400	–0.208
	p	0.006	0.011	0.198
Anterior CCI	r	–0.407	–0.424	–0.113
	p	0.009	0.006	0.489
Middle CCI	r	–0.455	–0.295	–0.195
	p	0.003	0.064	0.227
Posterior CCI	r	–0.254	–0.332	–0.225
	p	0.113	0.037	0.162

r: Pearson's correlation coefficient. Statistically significant p and r values are in bold. CC: Corpus callosum; CCI: Corpus callosum index.

Table 2. Effects of demographical and clinical properties of multiple sclerosis patients on measures of OCT

Measures of OCT*		Age	Number of attacks	Duration of disease
A-RNFL	r	–0.481	–0.336	–0.101
	p	0.002	0.034	0.534
T-RNFL	r	–0.270	–0.050	0.162
	p	0.092	0.762	0.319
N-RNFL	r	–0.382	–0.169	–0.017
	p	0.015	0.296	0.915
S-RNFL	r	–0.471	–0.402	–0.359
	p	0.002	0.010	0.023
I-RNFL	r	–0.375	–0.249	–0.098
	p	0.017	0.121	0.547
A-GCL	r	–0.880	–0.285	–0.069
	p	<0.001	0.074	0.674

*OCT values for each patient are detected by the mean of OCT measures from both eyes. r: Pearson's correlation coefficient, statistically significant p and r values are in bold. OCT: Optic coherence tomography; RNFL: Retinal nerve fiber length; GCL: Ganglion cell layer. A: Average; T: Temporal; N: Nasal; I: Inferior; S: Superior.

Table 3. Correlation of OCT measures with CCI values in multiple sclerosis patients

Measures of CC (mm)		Average RNFL*	Average GCL*
Anterior CC	r	0.235	0.390
	p	0.145	0.013
Middle CC	r	0.273	0.529
	p	0.088	<0.001
Posterior CC	r	0.332	0.309
	p	0.036	0.052
Total	r	0.042	-0.022
	p	0.796	0.893
CCI	r	0.316	0.478
	p	0.047	0.002
Anterior CCI	r	0.206	0.372
	p	0.202	0.018
Middle CCI	r	0.261	0.515
	p	0.103	0.001
Posterior CCI	r	0.333	0.324
	p	0.036	0.041

*OCT values for each patient are detected by the mean of OCT measures from both eyes. r: Pearson's correlation coefficient. Statistically significant p and r values are in bold. OCT: Optic coherence tomography; RNFL: Retinal nerve fiber length; GCL: Ganglion cell layer; CC: Corpus callosum; CCI: Corpus callosum index.

the CCI calculations of the two radiologists involved in our study ($p<0.05$).

Discussion

GCL and retinal nerve fiber analysis by OCT are recently used parameters to detect the level of neurodegeneration in many neurological disorders such as MS, Alzheimer's disease, or Parkinson's disease based on degenerative background.[17]

In our study, increase in age and number of attacks were found to be significantly correlated to lower average RNLF in OCT of all MS patients. In addition, elder age of the patients was significantly found to be associated with lower average GCL values. MS cases with optic neuritis in history revealed lower RNFL measurements and lower GCL values in involved eyes compared to uninvolved side. Decrease in RNFL and GC complex analysis values in MS patients even without any optic nerve involvement during the disease was subject of many previous studies and was thought to

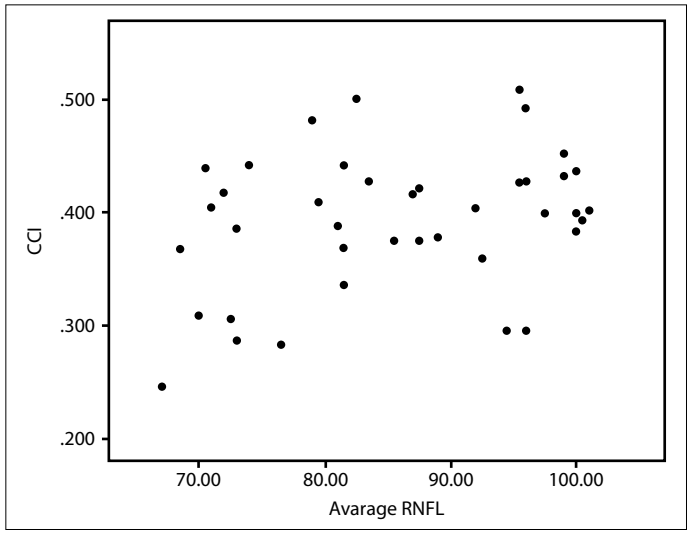

Fig. 3. Correlation analysis of overall CCI and average RNFL values in all MS cases (Scatter plot analysis) (r=0.316, p=0.047). CCI: Corpus callosum ındex; RNFL: Retinal nerve fiber length; MS: Multiple sclerosis.

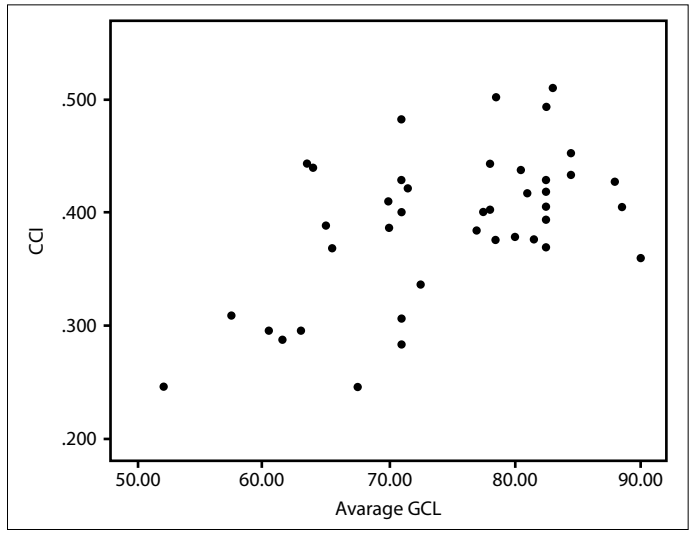

Fig. 4. Correlation analysis of overall CCI and average GCL values in all MS cases (Scatter plot analysis) (r=0.478, p=0.002). CCI: Corpus callosum index; GCL: Ganglion cell layer; MS: Multiple sclerosis.

Table 4. Corpus callosum measures in study groups

Corpus callosum measures	Optic neuritis (+) MS patients (n=17)	Optic neuritis (–) MS patients (n=23)	p-value
Anterior CC (mm)	0.98±0.18	1.14±0.16	0.005
Middle CC (mm)	0.48 (0.46)	0.65 (0.46)	0.154
Posterior CC (mm)	1.01±0.20	1.14±0.13	0.034
Total CC (mm)	6.89±0.41	6.93±0.43	0.779
CCI	0.36±0.07	0.42±0.04	0.004
Anterior CCI	0.14±0.03	0.17±0.03	0.013
Middle CCI	0.07±0.02	0.09±0.02	0.003
Posterior CCI	0.15±0.03	0.16±0.02	0.035

Continuous variables are expressed as either * the mean±standard deviation or βthe median (range). Continuous variables were compared with a Student's t-test or the Mann–Whitney U-test. Statistically significant P-values are in bold. CC: Corpus callosum; CCI: Corpus callosum index; MS: Multiple sclerosis.

Table 5. OCT measures in multiple sclerosis cases with optic neuritis in history

OCT measures	Group 1 Optic neuritis +		p-value
	Involved eyes (n=17)	Uninvolved eyes (n=17)	
Mean RNFL	75.88±12.54	81.76±9.40	0.030
T-RNFL	51.88±11.13	52.65±13.80	0.770
N-RNFL	62.53±6.62	63.41±9.19	0.751
S-RNFL	101.59±21.53	105.00 (50)	0.134
I-RNFL	98.00 (60)	97.00 (49)	0.753
Mean GCL	63.00±6.51	70.59±4.64	<0.001

Continuous variables are expressed as either *the mean±standard deviation or βthe median (range). Continuous variables were compared with a Student's t-test or the Mann–Whitney U-test. Statistically significant P-values are in bold. OCT: Optic coherence tomography; RNFL: Retinal nerve fiber length; GCL: Ganglion cell layer; T: Temporal; N: Nasal; I: Inferior; S: Superior.

reflect the subclinical disease activity, concurrent demyelination of optic nerve axons, and/or retrograde degeneration of the optic nerve in MS patients.[18] In the meta-analysis by Britze et al., the thickness of GCL was found to be significantly reduced in MS subjects both with and without previous ON compared to healthy controls.[19] This thinning was reported to be associated with visual function and EDSS score of the patients. Reductions in GCL measurements appear before RNFL thinning and are a strong predictor of visual dysfunction over 6 months.[9,19] Since GCL and RNFL analyses were reported in many studies to highly correlate with visual functions and disability in MS, the importance of diagnostic use of OCT is better understood.[19]

Measurement of CCI is a two-dimensional calculation method for brain atrophy and does not require a special computer program – easily applied in a few seconds on the scans.[15] Recent studies are focused on its clinical effectivity and its correlation with brain volumetric measurements. It is highly used nowadays as a clinical marker of atrophy and lesion load in MS.[13,15]

Overall CCI was found to be lower in patients with more attacks in history and in elder MS patients. Duration of the disease was not found to have a significant correlation with CCIs in MS patients. Among our study subjects, 42.5% had optic neuritis in history and all were unilaterally affected. They had significantly lower overall CCI than MS patients without optic neuritis in history. Anterior, middle, and posterior CCI values are also found to be significantly lower in MS cases with optic nerve involvement compared to cases without optic nerve involvement. The literature contains limited data about the effect of age, duration of the disease, number of attacks, and involvement of optic nerve on CC volumes and CCI values. CC is normally resistant to age-related changes in healthy individuals, but it has been shown that CC atrophy emerges in MS patients overtime.[20] CC volume, CCI values, and regional changes correlate well with disability in MS patients.[21,22] Simon et al. reported that patients with relapsing remitting MS and moderate disability have measurable amounts of cerebral atrophy that progresses yearly and that the course of cerebral atrophy was influenced by prior inflammatory activity of MS evaluated by the presence of gadolinium-enhancing brain lesions as seen on MRI, but the study does not yield exact correlations of disease duration and CC volumes.[23] In a recent study by Cilingir et al., lower CCI values were found in MS cases with longer disease duration.[4]

Overall CCI was calculated to be lower in our study, in cases with lower average RNFL and average GCL measurements among all eyes of MS patients with high correlation coefficients. In fact, there are limited studies in the literature about the association between RNFL and CC measures. The thinning of RNFL in MS is shown to be associated with the atrophy of whole-brain white matter and total deep gray

matter.[24,25] According to a study by Scheel et al., a positive correlation between the volume of the central part of the CC and RNFL thickness was found and reported.[26] Cilingir et al. reported that lower RNFL values in MS patients were associated with lower CCI values. They reported no association between CCI and RNFL measurements in the control group. They also noted that they found this correlation in patients with no history of ON.[4] However, the association between CCI and GCL analysis measurements during the follow-up of MS cases is still a mystery and has no reported data in former studies.

The calculations of CCI measurements in our study were performed by two radiologists, which were detected to have statistically insignificant variations among their measurements. Hence, the described method used to analyze CCIs on MR scans is thought to be reliable. The interobserver and intraobserver reliability of this method is reported to be high in previous studies, too.[4,27]

Our study additionally calculated and used new measures of CCI (anterior, middle, and posterior) which have not been used previously in any other study. Our aim was to investigate if there was a predilection for atrophy in any part of CC during the process of neurodegeneration. No specific type of CCI was found to be selectively effected, pointing out homogeneous degeneration of the area.

Main limitations of our study are the small sample size, it's cross-sectional design, and lack of the long-term follow-up results. The main strength of our study is its novel research of the correlation between already known OCT measures of neurodegeneration and different types of CCIs which have not been used previously in the literature for MS cases.

In the light of our study, we report that involvement of optic nerve in MS patients is with lower anterior, middle, posterior, and overall CCI values. It's high correlation with RNFL and GCL measures of OCT supports its parallel effectivity in the use of monitoring neuroaxonal degeneration in MS. New randomized and larger sized controlled trials on the topic should be carried on in the future.

Ethics Committee Approval: The study was approved by the local ethics committe at Ufuk University Faculty of Medicine on May 16, 2018 (no: 20180516/7).

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ORIGINAL ARTICLE

Biometric features and amblyopia risk factors in children with congenital nasolacrimal duct obstruction that underwent probing after 1-year-old

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Abstract

Purpose: The purpose of the study was to evaluate the biometric values of children with congenital nasolacrimal duct obstruction (CNLDO) who underwent nasolacrimal probing after 1-year-old and to determine the effect of probing success and laterality on these values.

Methods: The medical records of children with CNLDO who underwent probing were retrospectively reviewed. Biometric measures (cycloplegic refraction, keratometric data, and axial length measurements), presence of anisometropia, and other amblyopia risk factors were analyzed according to both probing success and laterality. In unilateral cases, the affected eyes were compared with contralateral eyes.

Results: A total of 49 eyes of 39 patients were examined. One or more amblyopia risk factors were detected in 13 (33.3%) patients. Clinically significant anisometropia was detected in six (20.7%) of 29 unilateral cases and two (20%) of 10 bilateral cases. Six eyes of 6 patients (18.8%) among the 32 eyes for which probing was successful and six eyes of 5 patients (35.3%) among the 17 eyes for which probing failed had at least one risk factor with no statistically significant difference between the groups. In unilateral CNLDO cases, the spherical equivalent refraction of the eyes with CNLDO was significantly higher than that of contralateral eyes (p=0.03). However, no significant differences in terms of keratometric or axial length measurements were detected.

Conclusion: The data yielded by this study show amblyopia risk factors in patients with CNLDO regardless of probing results and significantly higher refraction in unilateral CNLDO eyes compared to contralateral eyes.

Keywords: Amblyopia risk factors; biometric features; congenital nasolacrimal duct obstruction; ocular biometric features.

Congenital nasolacrimal duct obstruction (CNLDO), which is characterized by epiphora and discharge, affects 20–30% of all newborns and, in 96% of cases, resolves spontaneously by 1 year of age.[1–3] However, lacrimal system probing, the first surgical procedure used to correct CNLDO, might still be needed in cases with persistent symptoms (approximately 4% of these children).[3] Although this condition is widely considered to be benign, several

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studies have evaluated the relationship between CNLDO and amblyopia risk factors, including anisometropia.[4–12] According to some authors, visual development and emmetropization might be disturbed in children with CNLDO due to persistent epiphora.[4,5] It was also suggested that children with CNLDO and no amblyopia risk factors have an exceedingly small chance of later developing amblyopia or strabismus.[13] However, some researchers reported no significant difference compared to normal population in the prevalence of amblyopia in children with CNLDO.[6] The probability of structural abnormalities, especially in cases in which probing failed and their possible effects on anisometropia, was also reported.[7]

It is possible that biometric values such as keratometric data and axial length measurements which play an important role in emmetropization could be also affected in these children due to some anatomic abnormalities. However, to the best of our knowledge, no studies have evaluated these values in literature. In this study, we aimed to evaluate the biometric values of children with CNLDO who underwent nasolacrimal probing. Moreover, we determined whether refractory obstruction and laterality affected these values.

Materials and Methods

The files of the children with CNLDO who underwent nasolacrimal probing after 1-year-old by the same surgeon were retrospectively evaluated from the medical records. All patients had a positive lacrimal sac regurgitation test before probing. Children with additional ocular or systemic problems that may interfere with normal visual development, ptosis, manifest strabismus, and children with a family history of amblyopia or anisometropia were excluded from the study. Data regarding the patients' age, gender, and course of the treatment were reviewed. Ocular alignment, motility, and anterior and posterior segment findings were recorded. Cyloplegic refractions were measured by applying cyclopentolate 1% eye drops 3 times in each eye within 5-min intervals and examining the results using an auto kerato refractometer (Topcon KR-7000P; Topcon Europe BV, Capelle a/d IJssel, The Netherlands). Corneal power (in diopters [D]) was also measured by the same device, and the mean keratometric values at two principle meridians were noted. Axial length measurements were performed by the same individual using A-scan biometry (Eye Scan; Sonogage, Cleveland, OH, USA; OTI-Scan 1000-B/A/3D; OTI Ophthalmic Technologies, Inc., Toronto, Canada). All measurements were performed by the same author, at the 1st-month control visit following probing.

Amblyopia risk factors, except anisometropia, were accepted based on the American Association for Pediatric Ophthalmology and Strabismus referral criteria guidelines published in 2013 (Table 1).[14] An interocular difference in spherical equivalent cycloplegic refractions of ≥1.5 D indicated anisometropia, in line with previous studies.[4,15,16]

The patients were classified into two groups: Bilateral cases and unilateral eyes. These groups were subdivided into successful probing and failed probing groups for further evaluation of the biometric values and probable increased risk of amblyopia based on initial probing results. The successful probing group included cases with no tearing or

Table 1. American Association for Pediatric Ophthalmology and Strabismus referral criteria guidelines (2013) for amblyopia risk factors[14]

	Refractive risk factors	Refractive risk factors
Age of children	Amblyopia risk factors	All ages
12–30 months	Astigmatism >2.0 D	Media opacity >1 mm
	Manifest strabismus >8 PD in PP	
	Hyperopia >4.5 D	
	Anisometropia >2.5 D	
	Myopia >−3.5 D	
31–48 months	Astigmatism >2.0 D	
	Hyperopia >4.0 D	
	Anisometropia >2.0 D	
	Myopia >−3.0 D	
>48 months	Astigmatism >1.5 D	
	Hyperopia >3.5 D	
	Anisometropia >1.5 D	
	Myopia >−1.5 D	

D: Diopters; PD: Prism diopters; PP: Primary position.

discharge after simple probing, whereas the failed probing group included cases with persistent tearing or discharge after initial probing, requiring other interventions such as nasal endoscopic probing with or without bicanalicular silicone tube intubation and dacryocystorhinostomy. Further, in unilateral group, biometric values of affected eyes were compared with the normal fellow eyes.

Pearson's Chi-square, t-test, paired t-test, Shapiro-Wilk test, and Fisher's exact test were used for statistical analysis. All parents or guardians of the infants studied provided written informed consent to the screening and all assessments. Informed consent forms were obtained from the legal guardians of all patients. The study was approved by a local ethics committee and the research protocol adhered to the Declaration of Helsinki for research involving human subjects.

Results

Forty-nine eyes of 39 consecutive patients who underwent nasolacrimal probing were examined. Of the 39 patients, 17 (43.6%) were male and 22 (56.4%) were female. Ten patients had bilateral CNLDO, 19 patients had unilateral CNLDO in the right eye, and 10 had unilateral CNLDO in the left eye. The mean age at the time of probing was 25.2±14.9 (range: 12–90) months. The mean spherical equivalent refraction (SER) was 1.2±1.4 (range: −1.9–5) D, the mean keratometric value was 43.6±1.5 (range: 40.5–48) D, and the mean axial length measurement was 21.2±0.7 (range: 19.6–22.7) mm in all affected eyes. Overall out of 39 patients, one or more amblyopia risk factors were detected in 13 (33.3%) patients. No patients had myopia or media opacity. Of the children with any amblyopia risk factor, 10 had unilateral, whereas three had bilateral CNLDO.

Clinically significant anisometropia (≥1.5 D) was detected in six (20.7%) unilateral cases and two (20%) bilateral cases. In unilateral anisometrope cases, severe hyperopia or astigmatism was found mostly in the affected eyes (85.7%), suggesting an increased likelihood of ipsilateral amblyopia. Bilateral high refractive error could also be a problem even in unilateral ones, as we detected in 3 children out of 29 unilateral cases.

When amblyopia risk factors were evaluated according to probing success, six eyes of six patients (18.8%) (of the 32 eyes that underwent successful probing) and six eyes of five patients (35.3%) (of the 17 eyes that underwent failed probing) displayed at least one amblyopia risk factor. No statistically significant difference was found between the successful and failed probing groups regarding amblyopia risk factors (Pearson's Chi-square; p=0.45). When patients were evaluated according to the success of probing regarding biometric data, no differences in terms of SER, keratometric data, and axial length measurements were detected (Table 2).

In the 29 cases of unilateral CNLDO, there was no statistically significant difference between biometric values in terms of probing success (p=0.19 for SER; p=0.28 for keratometric values; p=0.79 for axial length measurements; independent t-test). Six of the 23 eyes that underwent successful probing and three of the eight eyes that underwent failed probing displayed at least one amblyopia risk factor. However, no statistically significant difference was found between the successful and failed probing groups in terms of amblyopia risk factors (Pearson's Chi-square; p=0.54).

Table 2. Mean SER, keratometric data, and axial length measurements in successful and failed probing groups

	Probing success		p-value*
	Successful probing (n=32 eyes)	Failed probing (n=17 eyes)	
Mean SER (D)	1.3±1.3 ([−1.87]–5)	1.1±1.5 ([−1.12]–4.25)	0.67
Mean keratometric measurements (D)	43.6±1.5 (40.5–48)	43.6±1.4 (40.8–46)	0.87
Mean axial length measurements (mm)	21.2±0.8 (19.6–20.7)	21.4±0.7 (19.9–22.6)	0.43

*t-test; D: Diopters; mm: Millimeters; SER: Spherical equivalent refractions.

Table 3. Mean SER, keratometric data, and axial length measurements in unilateral CNLDO eyes compared with normal fellow eyes

	Unilateral CNLDO		p-value*
	Eyes with CNLDO	Normal fellow eyes	
Mean SER (D)	1.1±1.3 ([−1.12]–5)	0.9±1.2 ([−1.25]–4.25)	0.030
Mean keratometric measurements (D)	43.6±1.6 (40.5–48)	43.7±1.5 (40.75–47.5)	0.203
Mean axial length measurements (mm)	21.2±0.7 (19.6–22.5)	21.2±0.7 (19.8–22.7)	0.577

*t-test; D: Diopters; mm: Millimeters; SER: Spherical equivalent refractions; CNLDO: Congenital nasolacrimal duct obstruction.

When eyes with unilateral CNLDO were compared to normal eyes, the mean SER was significantly higher in eyes with CNLDO (p=0.03; paired t-test). However, no differences in terms of keratometric data and mean axial length measurements were detected (Table 3).

Discussion

Amblyopia affects approximately 1.6–3.6% of the normal population.[17] Although several population studies have been conducted, the exact prevalence of anisometropia in this age group is unknown. Donahue[16] reported the prevalence of anisometropia in the general pediatric population to be approximately 2%, based on his review of several studies on refractive errors in children at various ages. Giordano et al.[18] reported that the Baltimore Pediatric Eye Disease Study revealed the prevalence of anisometropia (≥1 D) was 2.4% among African-American children and 3.9% among white children aged between 6 and 72 months. The Multi-Ethnic Pediatric Eye Disease Study found that the prevalence of anisometropia was 4.3% among Hispanic subjects and 4.2% among African-American subjects.[19]

CNLDO is generally considered to be a relatively benign condition that does not affect visual maturation. Ellis et al.[6] found no evidence suggesting that visual maturation is adversely affected by allowing spontaneous resolution of CNLDO. They reported no correlation between refractive errors and CNLDO and no significantly increased incidence of anisometropia, amblyopia (1.6%), or strabismus (4.2%) in a large series of 2249 patients with CNLDO, compared with control patients.[6] Similarly, in a recent study, it was reported that there was no evidence to suggest that the prevalence of amblyopia risk factors is higher in CNLDO patients compared with normal controls. The authors also found no difference in the rate of anisometropia between patients with unilateral and bilateral CNLDO.[20] However, some other studies reported that children with CNLDO display amblyopia risk factors, especially anisometropia, more frequently than the general population.[4,7–10,13]

In a recent study of more than 1,200 patients with CNLDO, Kipp et al.[10] stated that there is an association between unilateral CNLDO and the development of anisometropia. They found that anisometropia is twice as likely to occur in unilateral patients (3.6%) and showed a significant relationship between same-sided CNLDO and higher hyperopia. In another study, Piotrowsky et al.[4] described a 9.8% prevalence of anisometropia higher than that of the general population with or without amblyopia in a series of 305 CNLDO patients, with 26 of 30 patients developing hyperopic anisometropia and almost 90% presenting with same-sided CNLDO in the more hyperopic eye. Amblyopia risk factors were present in 13.1% of the patients. Matta et al.[8] identified amblyopia risk factors in 22% of CNLDO patients, whereas Badakere et al.[21] found the same ratio as 14% in unilateral cases. Moreover, Ozgur et al.[22] reported that 27.5% of children undergoing nasolacrimal duct irrigation and probing had amblyopia risk factors, which is consistent with the present study.

Of the 39 patients in our study with CNLDO who required nasal probing, 13 (33.3%) had one or more amblyopia risk factors. The prevalence of anisometropia was 20.5% in our study group. Despite the slightly increased frequency of high astigmatism, hyperopia was not found to be the major causative factor of amblyopia, as reported in earlier studies. However, we observed higher refractive errors, most of which occurred in the affected eye, in concordance with the literature on the relationship between anisometropia and CNLDO. In our study, the presence of both amblyopia risk factors and anisometropia were found to be higher than in the literature. This discrepancy might be due to our study group, which consisted of cases that underwent nasolacrimal probing rather than cases that were spontaneously resolved.

When we compared the successful and failed probing groups, we found the rate of patients with amblyopia risk factors to be 25% and 29%, respectively. Interestingly, all three patients with bilateral CNLDO in the failed probing group had amblyopia risk factors. Although small sample size, bilaterality, and failure in probing together could be effective in a further increase in amblyopia risk.

Researchers have different opinions about the mechanism of anisometropia in children with CNLDO. Chalmers and Griffiths[5] reported 5 cases of anisometropic amblyopia among 130 cases of CNLDO, with more severe hyperopia occurring in eyes with epiphora, suggesting that persistent epiphora may disrupt emmetropization. They stated that accumulation of mucopurulent discharge, excessive tear film, and antibiotic ointments may lead to a lack of proper emmetropization, resulting in greater hyperopia in the affected eye. Improper emmetropization may also occur as a result of associated structural abnormalities, such as maldevelopment on one side of the face that could lead to both an abnormal nasolacrimal duct system and a smaller eye.[5] Piotrowsky et al.[4] hypothesized that distortion of retinal images due to persistent tearing in patients with CNLDO may result in ametropia and that the partial disruption of emmetropization may lead to increased prevalence

of hyperopic anisometropia. Eshraghi et al.[7] stated that the higher prevalence of anisometropia (>1.5 D) (compared to the prevalence in the general population) and the significantly higher spherical equivalents in eyes with CNLDO (compared with contralateral eye) in unilateral cases with CNLDO, especially those that failed probing, may support structural abnormality as an explanation for the possible relationship between CNLDO and anisometropia. Interestingly, it was also reported that patients with early spontaneous resolution of dacryostenosis were more likely to have a higher, not lower, rate of anisometropia than those with late spontaneous or surgical resolution.[23]

In this study, we evaluated biometric data such as corneal power and axial length measurements, which, to the best of our knowledge, had not been considered in earlier literature. We observed that the absolute differences between eyes in terms of keratometric values and axial lengths were more prominent in anisoastigmatic patients. These findings seem to corroborate the theory of partial disruption of emmetropization. It is well known from the literature that CNLDO has a possible relationship with amblyopia. Besides, we also investigated the possible relationship of amblyopia risk factors and biometric measurements with the success of treatment, classifying the patients as successful or failed probing ones. However, prospective studies with long follow-up periods are necessary for further analysis.

The potential limitations of our study include its retrospective study design and small sample size. However, the inclusion of only treated patients older than 1-year-old could be a limiting factor in number cases.

Conclusion

The data gathered in this study suggest a high rate of amblyopia risk factors in patients with CNLDO undergoing nasolacrimal duct irrigation and probing compared to the normal population. This risk as well as the biometric measurements seems to be similar in both successful and failed probing groups. Monitorization of all patients with CNLDO for amblyopia is essential. Amblyopia risk factors might be detected in both eyes, despite the fact that only one eye is probed, or in ipsilateral or contralateral eyes, despite the fact that unilateral probing was performed. A structural abnormality can be possible as an explanation for the possible relationship between CNLDO and anisometropia regardless of probing. However, more research needs to be done to confirm this observation.

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EUROPEAN EYE RESEARCH

ORIGINAL ARTICLE

Simple limbal epithelial transplantation method in the treatment of unilateral limbal stem cell deficiency due to chemical burn

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Abstract

Purpose: The objectives of the study were to evaluate the success of the simple limbal epithelial transplantation (SLET) method in the treatment of unilateral limbal stem cell deficiency (LSCD) due to chemical burn.

Methods: Seventeen patients with unilateral LSCD due to chemical burn were included in this retrospective study. Mean age of patients was 50.3±20.8 (28–75) years. Mean duration of follow was 18.9±6.9 (12–24) months. In the recipient eye following peritomy, pannus tissue was cleared and covered with amniotic membrane with fibrin glue. Limbal stem cell received from the fellow eye was implanted cornea surface 2–3 mm inside limbus with fibrin glue on the amniotic membrane and placed contact lens. In control examination of all patients who completed minimum 12 months postoperatively, regression in corneal vascularization, duration of epithelial healing, visual acuity, need for keratoplasty, and complications (dropping of contact lenses, separation of amniotic membrane, and graft failure) were evaluated.

Results: Corneal epithelization was completed between 4 and 6 weeks in all patients. Total and partial separations in the amniotic membrane occurred in two patients. Marked regression in corneal vascularization and increase in visual acuity was observed in all patients. Five patients (29.4%) underwent keratoplasty in the follow-up period. Limbal failure did not occur in healthy eyes. In two patients (11.7%), corneal vascularization recurred after 6 months.

Conclusion: SLET technique is an efficient method in unilateral LSCD in that it requires a lesser amount of donor tissue than keratolimbal autograft transplantation. Moreover, regress vascularization before keratoplasty in LSCD eyes may decrease graft rejection rates.

Keywords: Chemical burn; fibrin glue; limbal stem cell deficiency; Limbal stem cell transplantation.

Corneal blindness continues to be the second most common cause of blindness in the developing world.[1] Out of all the causes for corneal blindness, ocular burns carry a poor prognosis as they may result in damage to the limbal stem cells and cause limbal stem cell deficiency (LSCD).[2] Chemical eye injuries can affect patient's visual acuity and quality of life. There are various treatment approaches in acute and chronic period. Accomplished management of each stage of the disease results in the improved visual outcome and reduced complication rates.[3,4] LSCD is char-

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acterized by chronic epithelial defects, neovascularization, conjunctivalization, and stromal inflammation, leading to corneal opacification and loss of vision.[5,6] Since penetrating keratoplasty (PK) carries a poor prognosis in these patients, various other treatment modalities have been described over the past few decades.[7]

Stem cells located in limbal region are required for regular regeneration of epithelial layer and protection of avascular structure of cornea. Thus, transparency of cornea is maintained. Damage in limbal stem cells with various causes results in corneal vascularization and impairment of corneal epithelization.[1] Ocular surface burn is a common reason for LSCD.[8] In LSCD, treatment is adjusted according to the severity of disease. Lubrication of ocular surface, suppression of ocular surface inflammation, surface reconstruction with amniotic membrane, scleral lens employment, and transplantation of limbal tissue are among treatment options. In patients with unilateral LSCD, keratolimbal autograft (KLAL), cultured limbal epithelial transplantation (CLET), and simple limbal epithelial transplantation (SLET) are recommended, while in bilateral LSCD KLAL, allogenic CLET is preferred.[9–11]

SLET method was developed by Sangwan et al.[12] in 2012. In patients with unilateral LSCD, minimal donor tissue was transplanted from health eye. Transplanted tissue covered with amniotic membrane was placed over cornea, making in vivo spread of limbal stem cells possible. SLET technique eliminated the need for the excessive amount of limbal tissue which may lead to iatrogenic LSCD in the healthy eye and also in case of failure, tissue cannot be obtained again. Opposite to allograft transplantations which have a high risk of tissue rejection and require immunosuppressive treatment, SLET seems to be an advantageous method.

The aim of the current study was to evaluate the success of SLET method in unilateral LSCD eyes.

Materials and Methods

The patients who had SLET surgery due to LSCD secondary to chemical burns were involved in this study. The records of the patients were documented retrospectively. The study was performed in adherence to the tenets of the declaration of Helsinki and approved by Ankara City Hospital local ethics committee. The patients who had at least 12 months regular follow-up period were included in the study. Exclusion criteria were history of any other ocular disease, atopy, systemic disease (diabetes, hypertension, renal, or hepatic dysfunction), other LSCD causes and incomplete ophthalmology visits.

The diagnosis of LSCD was made with slit-lamp biomicroscopic examination based upon the absence of pigmented Vogt palisades, irregularity in cornea when stained with fluorescein, persistent epithelial defect, fibrovascular pannus, and conjunctivalization of corneal surface. LSCD in at least 2 quadrants underwent SLET. Total LSCD was seen in 3 eyes (17.6%) and 14 eyes (82.3%) had partial LSCD ranging from 6 to 9 clock hours of limbal involvement.

LSCD was described in 3 stages based on the amount of corneal and limbal involvement in biomicroscopic examination. Staging was defined depending central corneal involvement, such as normal corneal epithelium in central 5 mm (Stage I), affected central 5 mm of cornea (Stage II), and affected entire corneal surface (Stage III). In addition, limbal involvement was defined as substages (A, B, C) whether 0–100% of limbal cells are affected.[13] During visits, regression in corneal vascularization, duration of epithelial healing, visual acuity, need for keratoplasty, and complications (dropping of contact lenses, separation of amniotic membrane, and graft failure) were evaluated.

Visual acuity values were measured Snellen chart then convert to their logMAR results. Mean visual acuity was calculated by adding up all patients visual acuity according to logMAR then divided patients number.

Surgical Procedure

Two-hour quadrants of limbal tissue were removed from healthy eye using crescent knife and vannas scissors. In the recipient eye, after 360° peritomy was carried out, pannus tissue was cleared. Epithelium was completely removed. Amniotic membrane which was prepared previously and kept at –80° was placed to the extent of the peritomy with fibrin glue. Limbus tissue obtained from a healthy eye was divided into 8–10 pieces and distributed to all cornea surfaces 2–3 mm inside limbus on the amniotic membrane with fibrin glue and operation was completed by placing therapeutic contact lens. In post-operative treatment, topical moxifloxacin 0.1% drop (Vigamox®, Alcon) was used for 1 week and topical dexamethasone 0.1% drop (Maxidex®, Alcon) was performed 8 times a day for 1 week and dose was tapered during first 6 weeks.

Statistical Analysis

Data were analyzed using SPSS version 15.0. Descriptive statistics were expressed with mean±standard deviation and minimum-maximum. Changes in visual acuity were evaluated Wilcoxon signed-rank test and $p<0.05$ was considered statistically significant.

Results

A total of 17 eyes of 17 patients (1 female, 16 male) were enrolled. The mean age of the patients was 50.3±20.8 (28–75) years. The mean follow-up was 18.9±6.9 (12–24) months. Causes of chemical burn were alkali 11 eyes (64.7%), acid 5 eyes (29.4%), and unknown 1 eye (5.8%). The demographic characteristics of the patients and causes of LCHD were presented in Table 1. The median duration after injury to SLET procedure was 12 months (range: 6–45 months). The median duration of follow-up time was 15 months. Mean corneal epithelialization time was 5.14±1.02 (4–6 weeks) in patients. One patient (5.8%) had a total separation of the amniotic membrane and one patient (5.8%) had partial amniotic separation of the amniotic membrane. In these patients, the amniotic membrane was sutured to the surface and contact lenses were placed again. The other amniotic membranes were removed when contracted and separated from the corneal surface. Fibrovascular pannus and conjunctivalization of corneal surface regressed in all patients. LSCD was not observed in eyes with limbal stem cells. Table 2 shows the success and failure rates across different parameters. When a complete healing of epithelial defect and avascular corneal surface was evaluated as success criteria, our success rate was 88.23% (15 of 17 patients) (Stage I). Two male patients with alkali injury (11.7%) had revascularization after 6 months, but it did not reach to central 5 mm cornea (Stage II). These patients were treated with conjunctival recession and weekly subconjunctival bevacizumab for 3 months, but no regression was shown in two cases. Post-operative mean visual acuity (according to logMAR) was increased compared to pre-operative period after SLET (1.98±0.07, 0.66±0.05, respectively, p=0.001).

While pre-operative period visual acuity was <20/200 in 7 (41.1%) eyes, between 20/40 and 20/200 in 10 eyes (58.8%), after 6 month SLET period, visual acuity was <20/200 in 3 eyes (17.6%), between 20/40 and 20/200 in 13 eyes (76.4%) and >20/40 in 1 eye (5.8%). Five patients (29.4%) underwent keratoplasty at least 6 months after SLET. The images of eye who underwent SLET after chemical injury are shown in Figure 1a-c.

Table 1. Severity and cause of LSCD

	Total (n=17) (%)
Limbal stem cell deficiency stages	
Stage I	(3 eyes, 17.6)
Stage II	(11 eyes, 64.8)
Stage III	(3 eyes, 17.6)
Cause of chemical burn	
Alkali	11 (64.7)
Acid	5 (29.4)
Unknown	1 (5.8)

LSCD: Limbal stem cell deficiency.

Table 2. Primary outcome in subgroups

Characteristics	Total numbers	Success (%)
Gender		
Male	16	14 (87.5)
Female	1	1 (100)
Age		
<40	11	11 (100)
>40	6	4 (66.6)
Agents		
Alkali	11	9 (81.8)
Acid	5	5 (100)
Unknown	1	1 (100)
Time interval to SLET		
<12 months	10	9 (90)
>12 months	7	6 (85.7)

SLET: Simple limbal epithelial transplantation.

Discussion

In the treatment of LSCD depending on chemical burns, new methods have recently been developed. As classical

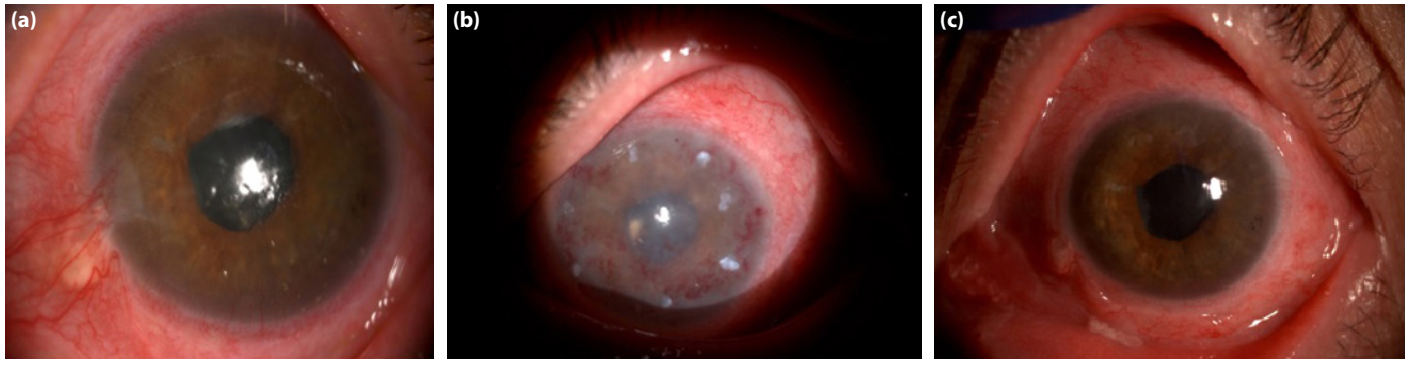

Fig. 1. **(a)** Partial limbal stem cell deficiency after chemical burn, **(b)** left eye ocular surface cover with amniotic membrane and after 1 week simple limbal epithelial transplantation (SLET), **(c)** left eye corneal vascularization regression after 2-month SLET

techniques used in the management of LSCD cause some complications and success rates are low, techniques using a lower amount of autograft have become more popular.[14,15] Among these techniques, SLET is one of the most popular. The aim of the present study is to evaluate the outcome of SLET procedure for the treatment of unilateral LSCD.

Chemical burn leads to high ocular inflammation, and the time between surgical intervention and chemical burn is very critical. Despite all of the interventions and anti-inflammatory treatment, further damage may continue and lead to severe vision loss.[16] Since ocular chemical burn is an emergency, treatment is prompt and should be begun with immediate continued irrigation. The purpose is supporting epithelialization, suppression of inflammation, and prevention of complications.[17] The milestones of treatment include lubrication, topical corticosteroid therapy, ascorbate, and biological medications. Amniotic membrane transplantation is a quick early-stage method for these patients. As it decreases inflammation and support epithelial healing. However, when corneal conjunctivalization is extensive, limbal stem cell transplantation is required, and final keratoplasty may be needed to improve visual acuity.[16] Inflammation should be controlled before limbal stem cell transplantation. In our study, we gave in an interval of at least 6 months for surgery after chemical burn.

Autologous limbal stem cell transplantation has been used successfully for about three decades and developed from conventional conjunctival limbal autografting to the more sophisticated methods such as SLET and CLET.[9,10] However, in CLET, 1×1 mm size tissue is obtained from limbal region and cultured in vitro to increase the number of cells and transplant again to the impaired eye. Success rate of this method has been established to vary between 73% and 100%.[18,19] There is no precise protocol for cell culture for CLET and it includes different substrates in culture media. Thus, success rates are variable.[20,21] Limbal cells are harvested from a healthy autologous or allogeneic donor limbus. Because of allogeneic cases, including the risk of immunoreactivity, autologous CLET grafts tend to show better outcomes compared with allogeneic in LSCD eyes.[22,23] Although it has advantages use of very little limbal tissue, possibility of repetition, and not needing for immunosuppressive treatment, cost is high because cell cultures are used.[24] Unlike CLET, SLET success is not affected by age and chemical cause. In our study, patients were predominantly male. Because male subjects work with chemicals much more than females, their ratio in these injuries is higher. Since we have only one female subject, we could not compare SLET success according to gender. When we looked at chemical cause 2 patients whose success was lower than others had alkali injury; however, the chemical cause did not affect the success rate.

Age-matched comparison studies show that SLET was more effective than repeat CLET in children. The author interpreted that though the size of the biopsy is the same as that in SLET, the biopsy is divided into two pieces, but only one is used for transplantation. Thus, the number of transplanted cells is higher in SLET than CLET.[24] The success of SLET in this study was 88.23% at a median follow-up of 15 months. This is more or less comparable to the recent data about SLET. Some major SLET studies done in recent years have described their success as 76% (Basu et al.),[26] 66% (Jain et al.),[25] and 83% (Vazirani et al.),[27] with a mean follow-up period of 35.5 months, 6.2 months, and 12 months, respectively. In addition, SLET may be a reasonable alternative in unsuccessful CLET cases.[28,29] For example, in the study of Basu et al.,[29] when CLET surgery failed in 30 cases of unilateral chemical burn, SLET was shown to be successful, with an increase of visual acuity, regression in conjunctivalization, and vascularization in 80% of patients. They stated that SLET is a good alternative method in LSCD after CLET failure. Moreover, they claimed that the number of effective cells may be higher in SLET as fresh limbal stem cell is transplanted without undergoing any laboratory procedure.

The advantages of SLET have been reported to be its low cost, no need for laboratory infrastructure and no requirement for immunosuppressive treatments. In the multicentric study, 68 autologous SLET operations have been carried out in eyes with LSCD. When a complete healing of epithelial defect and avascular corneal surface is considered as success criterion, 57 cases (83.8%) success was reported to be obtained. After 12 months of follow-up, the presence of symblepharon and keratoplasty procedures in the same session was found to be associated with clinical failures.[29] Many studies were shown that the simultaneous performance of PK with SLET correlates the graft rejection. In addition, SLET evolves the corneal environment, which may promote self-clearing of the stroma. Thus, PK is recommended for at least a year after SLET.[30–32] In our cases, the success rate was 88.23%. The high success rate can be explained by the fact that we performed keratoplasty after waiting for at least 6 months, although the recommendation time 1 year, not in the same session, and the low prevalence of symblepharon in patients.

Singh et al.[31] described performance of deep anterior lamellar keratoplasty in pediatric patients 9–15 months post-SLET giving visual improvement of 64%. Lower suc-

cess rate in children can be explained by more inflammation and undergo surgery earlier (before inflammation is fully controlled) in children.[32,33] Because of not including the pediatric case in the current study, our outcomes may have been more successful.

Although SLET has been described as a method of unilateral LSCD, in some studies, SLET was taken from the cadaver in patients with bilateral LSCD despite the risk of immune rejection. Although these studies have shown that SLET surgery from relatives or cadavers is beneficial in bilateral LSCD cases, the risk of rejection should always be kept in mind.[34,35] Therefore, transplantation of limbal stem cells to be obtained by stimulating pluripotent stem cells with developing technology will be beneficial for patients with bilateral LSCD.[36]

Our findings have to be considered in the context of the limitations of this study, which include its retrospective nature, the small number of eyes studied. The limited patient numbers did not allow the formation of subgroups and because of this small sample size. Furthermore, the absence of a control group who received solely medical therapy or limbal cell transplantation without amniotic membrane was another limitation of the study. Since there were not groups without using amniotic membrane, we could not comment on whether amnion has additional benefits.

Conclusion

SLET is a promising surgical method, especially in unilateral LSCD. The main advantage is the low cost due to the lack of laboratory dependence and no need for immunosuppression. To see long-term results, studies in larger series are needed about SLET.

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EUROPEAN EYE RESEARCH

REVIEW

Stem cells in degenerative retinal diseases

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Abstract

Degenerative retinal diseases are very common and can be encountered in all age groups. They are a major cause of blindness and result in significant morbidity. Treatment options are either very limited or not available. Therefore, it raises the need for regenerative treatments. Clinical studies have been conducted with different stem cell types and different application methods. Especially in retinal pigment epithelium replacement and studies utilizing neurotrophic effects of stem cells, significant evidence has been obtained in efficacy and safety. In this review, clinical trials were evaluated and case reports in the literature were investigated to collect clues about current knowledge, possible complications and issues that may cause concern.

Keywords: Age-related macular degeneration; bone marrow stem cell; embryonic stem cell; hematopoietic stem cell; induced pluripotent stem cell; mesenchymal stem cell; retina; retinal degeneration; retinitis pigmentosa; stem cell transplantation; stem cell.

The function of the retina is to receive light and converts it into a neural signal.[1] It performs this function by photoreceptor cells in the outer retinal layer. While the photoreceptor layer performs this function, its relationship with the surrounding structures, particularly the retinal pigment epithelium (RPE), is crucial.[1] It has been demonstrated by basic and clinical studies that dysfunction in the RPE results in photoreceptor cell apoptosis and consequent vision loss.[2]

Degenerative retinal diseases are important causes of blindness.[3] Retinal degeneration occurs in various forms such as age-related macular degeneration (AMD), Stargardt's macular dystrophy (SMD), and retinitis pigmentosa (RP). AMD is the fourth most common cause of blindness.[4] AMD has a multifactorial pathophysiology that results in photoreceptor degeneration in the macula.[5] SMD and RP are primarily genetic disorders of the RPE, followed by photoreceptor degeneration.[6,7] In these diseases, it is observed that the outer layers of the retina and RPE are affected, and the relationship between these two tissues is disrupted.[7] Since the inner retinal layers are not affected; it is thought possible to restore vision by RPE and photoreceptor replacement. Therefore, these diseases are the focus of regenerative treatment studies in the retina. The first animal studies on this subject are decades ago. RPE cell transplantation was performed in a retinal dystrophy rat model.[8] Substantial evidence has been reached regarding survival and function of transplanted RPE cells.

Stem cells are distinguished by their ability to regenerate themselves and differentiate into other type of cells.[9] They

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differ from progenitor cells that can only differentiate into one cell type and have limited division ability.[10] They can be found in both adult and embryonic tissues. Differentiation abilities vary depending on which tissue they are derived from.[9] The cells obtained from the inner cell mass at the blastocyst stage of embryonic development have the potential to differentiate into all cell types in the human, so they are pluripotent. When isolated and cultured in vitro, they are capable of indefinitely division. These cells are known as human embryonic stem cells (hESCs).[11]

There are also stem cells in selected locations on adult tissues, called niches, such as muscle, liver, bone marrow, and corneal limbus.[12] They can differentiate into one type or a few types of cells, which makes them unipotent or multipotent.[13]

In addition, a pluripotent stem cell was derived from the mature cell with a method described in 2006.[14] It has been shown that mature human fibroblasts can be reprogrammed with transcription factors and gain pluripotency. These cells are known as induced pluripotent stem cells (iPSC). Studies about iPSCs are the most recent part of pluripotent stem cell studies in retina.

Retina, A Favorable Tissue for Stem Cell Studies

Stem cell research in the eye has primarily focused on the cornea.[15] However, cornea is not the only available tissue for stem cell researches in the eye. There are features that make the retina eligible in this regard. Thanks to the transparent structure of the eye, it can be evaluated directly. Thus, it is possible to follow the treatment success in vivo. It is immune-privileged with the contribution of the blood-retina barrier.[16] This feature may positively affects the survival of transplanted stem cells. In the early stages of degenerative retinal diseases, inner retinal layers are not affected yet. At the last stages, photoreceptor cell loss occurs as result of dysfunction in the RPE.[7] This suggests that a RPE replacement performed in the early stages of diseases may prevent vision loss. RPE is a single layer of uniform pigmented cells.[17] Therefore, it is relatively easy to differentiate from stem cells and produces in vitro. As a result, RPE is the focus of retinal stem cell studies. At present, it is the only retinal cell group that has reached the clinical trial stage in cell replacement studies.

In addition, the functions of stem cells other than regeneration are also targeted in studies. It has not been demonstrated that mesenchymal stem cells (MSCs) differentiate into RPE. However, preservation of retinal function has been observed after subretinal transplantation of MSCs in rat model of retinal degeneration.[18] It is thought that neurotrophic factors secreted by MSCs such as brain-derived neurotrophic factor (BDNF) and ciliary neurotrophic factor (CNTF) may protect degenerated cells. The eye is very convenient to investigate such an effect because it is easy to deliver the treatment to the tissue. It can be performed in many ways such as intravitreal, subconjunctival, or subretinal.

Stem Cells in Preclinical Studies

Non-pluripotent Stem Cells

Transplantation studies have been carried out with stem cells obtained from other stem cell sources such as hematopoietic system, bone marrow, and umbilical cord.[12] Bone marrow stem cells consist of MSCs and hematopoietic stem cells (HSCs). MSCs can be obtained from both embryonic tissues and adult tissues. From embryonic tissues, they can be found in the umbilical cord blood and Wharton's jelly.[11] They can be obtained from adult tissues from different places such as bone marrow and adipose tissue. The mainstay of the studies of MSCs is their trophic effects rather than cell replacement. These cells exhibit immunomodulatory effects in the microenvironment and secrete trophic mediators such as BDNF and CNTF.[19] It has been demonstrated that retinal microcirculation increases after MSC injections.[19] HSCs may also be effective in degenerative retinopathies where vascular pathogenesis is important, such as DR, with their trophic effects on vascular tissue. It has been demonstrated in DR rat models that after intravitreal HSC transplantation, stem cells can be integrated into damaged tissue and vascular pathogenesis is slowed compared to the control group.[20]

hESCs

hESCs are obtained from the inner cell mass at the blastocyst stage of embryological development.[11] hESCs have self-renewal capability. Different types of adult human cells including RPE cells can be derived from hESCs.[21] Since they are obtained from embryo, it brings along ethical concerns. In addition, hESC transplants are allogeneic transplants so may cause an immunogenic reaction. Another concern with hESCs is that these cells have the unlimited ability to divide, so there is a risk of adverse proliferation. Therefore, before clinical studies with hESCs, cell lines that have been observed to not cause adverse proliferation in animal studies should be studied.

iPSCs

In 2006, a study was published for the first time describ-

ing the method of generating iPSCs. Dermal fibroblasts were transduced by viral vectors expressing four transcription factors (optical coherence tomography [OCT] 4, SOX2, Krüppel-like factor 4 [KLF4], and C-MYC).[14] It has been observed that mature fibroblasts reach pluripotency similar to hESCs. Subsequently, it has been observed that retinal cells can be derived from iPSCs. Subretinal injection of iPSCs derived retinal progenitor cells performed in rat models with retinal degeneration. Improvements in electroretinography findings and visual function-related behaviors were observed after treatment.[22]

Another good aspect of autologous iPSCs is that it eliminates ethical concerns as they are not embryo-sourced. Autologous transplantation is possible as they are derived from mature fibroblasts; however, it is quite costly and genetic diseases are expected to persist. To prevent these issues, it was planned to create human leukocyte antigen homozygous iPSCs culture banks.[23] Thus, cell lines derived from healthy donors can be produced and stored. It can be used in daily clinical applications at low cost in the future.

Clinical Trials About Stem Cells in Retina

Bone Marrow Derived Stem Cells (BM-SCs)

An early report of a clinical study conducted in 20 patients with RP in Brazil in 2012 was published.[24] It was reported that cystoid macular edema regressed on the 7th day after intravitreal autologous BM-HSCs injection in a patient with RP-associated macular edema. It was observed that this result persists for 1 month. It was considered highly promising. Later, in the statistical evaluations made in the 3rd month in the long-term results of the same study, a significant increase was found in the quality of life in the study group compared to the control group. However, it did not last long. There was no difference between the two groups in the 12 months quality of life assessment.[25] In another study in which BM-SC intravitreal injections were performed in six patients, it was reported that intraocular inflammation or hyperproliferation was not observed during the 6-month follow-up.[26] They did not report improvement in visual functions, but reported that they observed findings suggestive of incorporation of new cells in OCT.

Following the publication of these clinical studies, BM-SC injections in retinal diseases have been turned on. Apart from clinical study protocols, patient-funded practices have been performed in different centers. Subsequently, reports of worrying cases of the negative consequences of these practices were published.[27–30] These complications were retinal detachment and proliferative vitreoretinopathy following subretinal autologous BMSC injection,[28] epiretinal membrane (ERM) formation after intravitreal injection,[29] and central retinal artery occlusion after peribulbar injection.[27] After the development of ERM, vitrectomy was applied to the patient and CD34 + cells were found in the pathological evaluation of the membrane.[29,30] This suggests that stem cells may be directly responsible for membrane formation or indirectly by transforming into myofibroblasts.

These results show that more studies are needed for injection of BMSCs in the retina to be considered treatment option. Patients should be warned that BMSC injections carry various risks regardless of the injection site. Administration of these injections outside of clinical study protocols is currently not acceptable.

MSCs

The results of a clinical study which targeted the potential effects of MSCs on the microenvironment have been published. Wharton jelly derived MSCs are allogeneically isolated from a single donor. Stem cells were injected into the sub-tenon space in 34 eyes with diagnosis of RP. After 1-year of follow-up, no immunogenic reaction or adverse proliferation was observed. Best corrected visual acuity (BCVA) and multifocal electroretinogram (ERG) amplitude improved significantly.[31]

MSCs are relatively easy to obtain from adipose tissue. This method is less invasive and low budget. Autologous transplantation is also advantageous as it is possible. A study was published evaluating the results of total vitrectomy, followed by subretinal adipose tissue derived stem cell (ATSC) injection in 11 patients with diagnosis of RP.[32] Stem cells were isolated from subcutaneous adipose tissue from a single donor. Ocular complications were reported in six patients. It was reported that choroidal neovascular membrane (CNVM) developed in one patient at the injection site and ERM developed in five patients. It was stated that objective improvement could be observed in visual acuity, visual field, and ERG in one of the patients. There was minimal improvement in visual acuity in three patients. These patients stated that they began to see colors brighter subjectively. However, subretinal ATSC application has various complications. There is insufficient evidence for its effectiveness. More studies are needed to obtain reliable data.

In another clinical study on ATSCs, the efficacy and safety of suprachoroidal application were investigated.[33] In 11 eyes with dry AMD, the ATSC graft was implanted in the suprachoroidal area and the BCVA and microperimetry re-

sults were evaluated. To increase the amount of growth factor in the microenvironment, platelet-rich plasma has also been added to the autograft. It was reported that there was an increase in the mean BCVA (0.58 logMAR–0.38 logMAR) and the microperimetry test (11.44 dB–12.59 dB) compared to the control group at 6 months. They did not report macular edema, sub-retinal neovascular membrane, retinal detachment, or similar retinal complications. There is a potential risk of choroidal rupture and subsequent bleeding due to the surgical technique applied, but they also stated that they did not encounter such a complication. As a result, promising results have been achieved. It was thought that GFs secreted from suprachoroidal autograft were transmitted to RPE, photoreceptors, Müller cells and caused improvements by neurotrophic and angiogenic effects.

On the other hand, worrying case reports of ATSC injection associated complications have been published. Severe vision loss developed following intravitreal ATSC injection in three patients with AMD whose last recorded BCVA values before injection were in the range of 20/30–20/200.[34] Tractional retinal detachment, vitreous hemorrhage, retinal hemorrhages, lens dislocation, and intraocular hypertension have been reported in patients.[34] Subsequently, it was reported that bilateral retinal detachment occurred in one of the patients.[35] In another case report, a 44-year-old patient with RP was reported to have tractional retinal detachment and PVR after intravitreal autologous ATSC injection.[36] Chronic retinal detachment and neovascular glaucoma have been reported in a 42-year-old patient diagnosed with Usher syndrome following ATSC intravitreal injection.[37]

As a result, more evidence is needed of efficacy after ATSC injections. There are serious risks especially regarding intravitreal injections. Larger case series are needed to determine the optimal delivering method and effectiveness of ATSCs. During this period, it is important to inform patients in detail about the limited efficacy and complications of these injections.

hESCs

Since hESCs are pluripotent, they have been studied for replacement, unlike multipotent BMSCs and ATSCs. It has been shown that pigmented uniform cells displaying the characteristics of RPE cells can be differentiated from hESCs.[21] Results of a clinical study conducted with subretinal transplantation of hESC-derived RPE cells in 18 patients (9 AMD, 9 SMD) have been published.[38] No signs of adverse proliferation were found during the 36-month follow-up period. No systemic or ocular side effects related to the transplanted tissue were reported. No evidence was found in favor of immunological rejection. Side effects were reported to be related to surgery or immunosuppression. In 13 of the 18 patients, it was observed that subretinal pigment increased in the grafted areas. It was reported that BCVA was increased in ten eyes and this improvement was not observed in untreated eyes. There was an increase in quality of life in both SMD and AMD patients at three and 12 months. In yet another study, subretinal transplantation of hESC-derived RPE cells was performed in four Asian patients and the results were published.[39] In this study group consisting of 2 AMD and 2 SMD patients, ectopic tissue formation, adverse proliferation, and immunological rejection were not observed. At the end of 1 year follow-up, 9–19 letter BCVA increase was observed in three patients. There was no change in BCVA in one patient. With these studies, important evidence has been obtained regarding the long-term survival, safety, and even efficacy of pluripotent stem cells in the human retina.

On the other hand; following these studies, another clinical study in which hESC-RPE cells were implanted subretinally was published.[40] In this study of 12 patients with SMD, patients were followed for 12 months. At the end of the follow-up, no significant increase in visual acuity was achieved in any eye. There was no significant improvement in microperimetry. Hyperpigmentation was detected in the area compatible with the injection area of the patients. However, this hyperpigmentation has not been shown to have a positive effect on photoreceptor function. In one patient, localized thinning of the retina and a decrease in photosensitivity in the area where hyperpigmentation developed were reported and potential damage was thought to be possible.

In conclusion, when the current clinical trial results are evaluated, there is no consensus regarding the safety and efficacy of subretinal implantation of hESC-RPE cells, although they are promising.

hESC Derived RPE Monolayer

Subretinal injection of hESCs suspensions is not the only method for delivering. There are clinical studies involving the hESC derived RPE monolayer into the subretinal space. A single layer of hESC-RPE cells was formed on a synthetic basement membrane coated with human vitronectin.[41] This patch was implanted subretinally using a surgical device of their own design. In the 12-month follow-up of these two patients with AMD, an improvement of 29 and 21 letters in BCVA was reported. In another clinical study, a hESC-RPE mono-layer was created using a very thin Pa-

rylene material.[42] This patch was implanted subretinally in five patients with AMD. In 1 eye, BCVA improved by 17 letters and improvement in fixation were reported in two patients. There was no patient with a decrease in visual acuity. Findings indicating the integration between host photoreceptors and the transplanted RPE monolayer were observed in OCT.

As a result, regenerative treatment studies with hESC derived RPE patches are promising. As stronger evidence on its safety and efficacy is needed, studies in larger case series are required.

iPSCs

iPSC derived RPE is one of the newest options for regenerative retinal therapy research. Therefore, data from clinical studies are very limited. The most promising publication is the study of autologous iPSC derived RPE transplantation in a patient with exudative AMD.[43] CNVM was removed from the subretinal area and iPSC derived RPE was implanted. Results regarding the 4-year follow-up of the patient have been published. The organization of the outer nuclear layer remained stable in the patient 4 years after transplantation. Although the vascular structure-like remnants of CNVM removed from the patient were observed in fluorescein angiography, there was no exudative change. Anti-VEGF injection was not required. There was no significant change in visual acuity, no graft-related ocular complications or adverse proliferation observed.

More clinical research is needed on this subject to make conclusions about iPSC derived RPE transplantations. These results show promise in terms of survival and safety.

Conclusion

Degenerative retinal diseases are significantly common diseases that can affect different age groups. In advanced stages, they can cause serious vision loss. As with the exudative variant of age-related macular disease, treatment options are available to slow the progression of these diseases. However, the capabilities of these treatment options are limited and they are not effective in advanced stages. Therefore, it raises the need for regenerative treatments. Promising evidence has been obtained in clinical studies on RPE replacements and neurotrophic effects of stem cells. However, when the literature is reviewed, there are also case reports that may cause concern, especially those related to intravitreal stem cell injections. As of today, we are unfortunately far from being accepted as a treatment option. Thanks to the developing technology and studies focusing on this subject, more steps will be taken in this regard.

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EUROPEAN EYE RESEARCH

CASE REPORT

Accidentally detected unilateral peripapillary retinoschisis: A case presentation

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Abstract

This study aims to describe an atypical presentation of peripapillary retinoschisis (PPRS) in a young myopic patient. A 14-year-old female with high myopia −10.50 diopters in the right and −12.0 diopters in the left eye and good visual acuity (20/20) in both eyes. She presented with splitting of the inner retinal layers in the superior peripapillary quadrant as an incidental finding on spectral-domain optical coherence tomography (SD-OCT) on her left eye. The macula and outer retinal layers were unaffected and it was not associated with any other ocular pathology except myopia in both eyes. Our patient represents an atypical form of PPRS determined incidentally on SD-OCT with schisis of inner retinal layers without macular involvement.

Keywords: Myopia; optical coherence tomography; peripapillary retinoschisis; young patient.

Peripapillary retinoschisis (PPRS) is characterized by the abnormal splitting of the peripapillary retinal nerve fiber layer and frequently tends to be bilateral with asymmetrical involvement. Macular retinoschisis is mostly found together with PPRS and associated with X-linked retinoschisis,[1] stellate nonhereditary idiopathic foveomacular retinoschisis (SNIFR),[2,3] high myopia,[4] glaucoma,[5] vitreomacular traction syndrome,[6] and congenital optic disc abnormalities such as optic pit[7] and optic disc coloboma.[8] The underlying pathophysiology and the factors associated with PPRS have not been completely understood yet.

In this case report, multimodal imaging in a case with atypical presentation of unilateral PPRS without any sign of macular involvement was presented.

Case Report

A 14-year-old female admitted to our clinic for a routine eye examination without any complaint. Her medical history was unremarkable. She had bilateral high myopia (−10.50 D in OD and −12.0 D in OS). Her best-corrected visual acuities were 20/20 in both eyes. The axial lengths were 27.0 mm OD and 28.0 mm OS. Applanation tonometry revealed intraocular pressures of 13 mmHg OD and 14 mmHg OS. Her anterior segment examination was unremarkable in both eyes. There was no evidence of afferent pupillary defect. The color vision was normal in both eyes. Family history was negative for hereditary eye diseases. In dilated fundus examination, there was a slight elevation of the superotemporal peripapillary retina in the left eye

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(Fig. 1a) and myopic fundus appearance in the right eye. Fundus fluorescein angiography (Heidelberg retinal angiography 2, Spectralis®, Heidelberg Engineering, Heidelberg 2, Germany) did not reveal any sign of leakage in both eyes. In the fundus autofluorescence (Spectralis®, Heidelberg Engineering, Heidelberg 2, Germany), there was a slight hypofluorescence in the superotemporal area adjacent to the left optic disc (Fig.1b and c). The spectral-domain optical coherence tomography (SD-OCT; Spectralis Heidelberg Engineering, Heidelberg 2, Germany) scans demonstrated splitting of various layers of the inner retina in the superotemporal peripapillary region, primarily at the level of the nerve fiber layer, ganglion cell layer, and inner plexiform layer. There was no foveal involvement in the left eye, and the right eye was normal (Fig. 1d and e). The splitting in the left eye corresponded to the area of retinal thickening noted topographically on SD-OCT (Fig. 1f). The swept-source OCT angiography (SS-OCTA; DRI OCT Triton Plus®; Topcon Corporation, Tokyo, Japan) images (12×12 mm) revealed no prominent changes in the superficial capillary plexus. The reflectivity of splitting in superficial retinal layers partially causes dark back shadowing in DCP. En face SS-OCTA images highlighted the areas of retinoschisis as areas of increased reflectivity of the retinal nerve fiber layer (Fig. 2a-d). There was no evidence of vitreoretinal traction and SS-OCT did not reveal any pathology in the optic disc and the fovea. Structural SS-OCT determined normal choroidal thickness and no lamina cribrosa alterations. There was no defect in the visual field testing (Humphrey®, Visual Field Analyzer-3, Zeiss, Germany) of both eyes. During 24 months of follow-up, no changes have been detected in the inner retinoschisis pathology and the patient was scheduled for 6 monthly follow-up visits.

Discussion

PPRS frequently occurs bilaterally with macular involvement. Most of the reported cases are asymptomatic and incidentally detected on OCT. Data on PPRS are limited, but several retrospective studies reported its association with

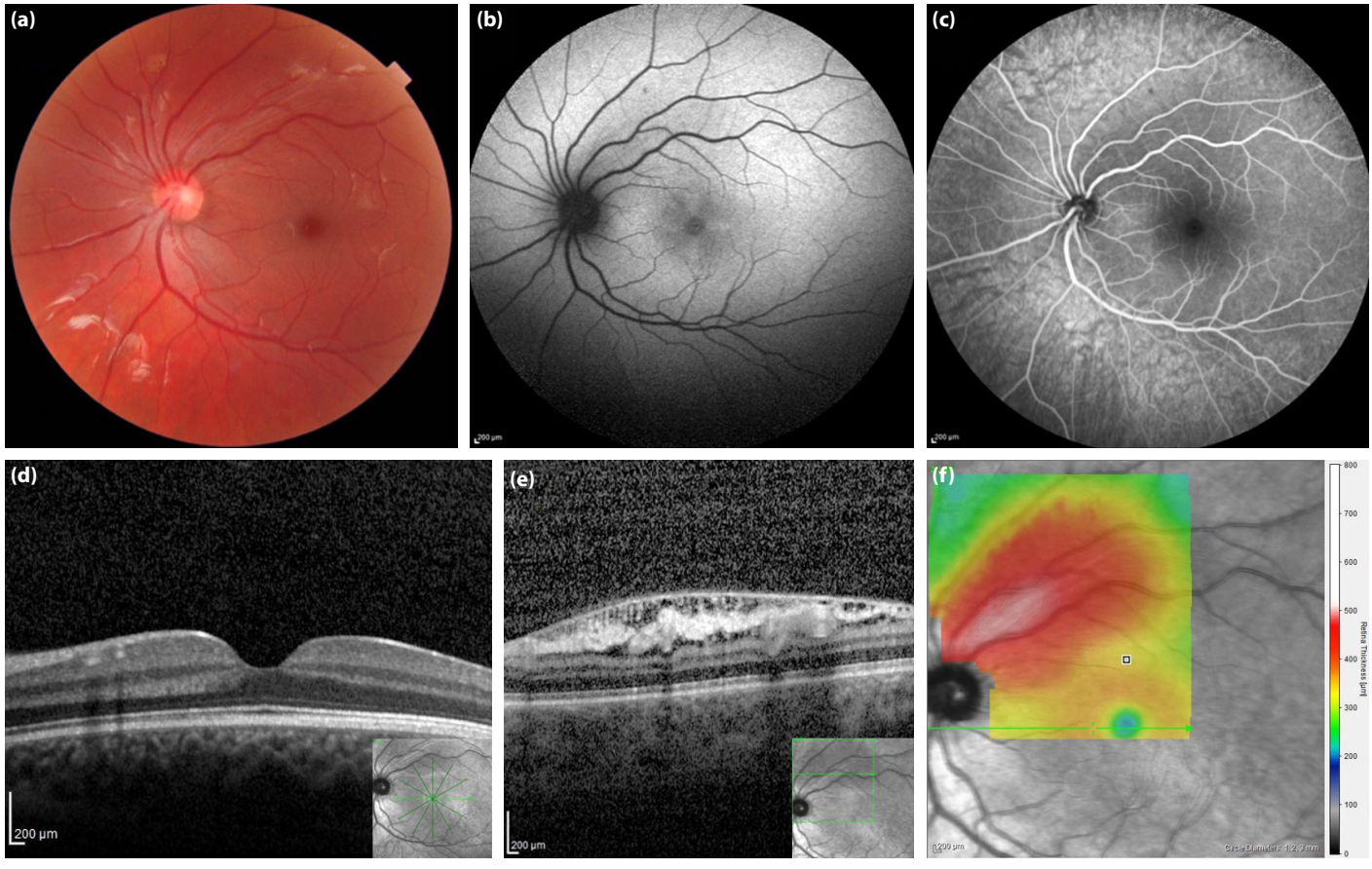

Fig. 1. Peripapillary retinoschisis is typically difficult to discriminate in color fundus photography **(a)**. A slight hypofluorescence in the superotemporal quadrant adjacent to the left optic disc (fundus autofluorescence) **(b)**. Normal fluorescein angiographic appearance in retinoschisis area **(c)**. Spectral-domain optical coherence tomography (SD-OCT) demonstrated a normal foveal contour in the left eye **(d)**. SD-OCT B-scan revealed splitting of various layers of the inner retina in the left eye **(e)**. Retinal thickness map showed significant thickening at the superotemporal peripapillary retina.

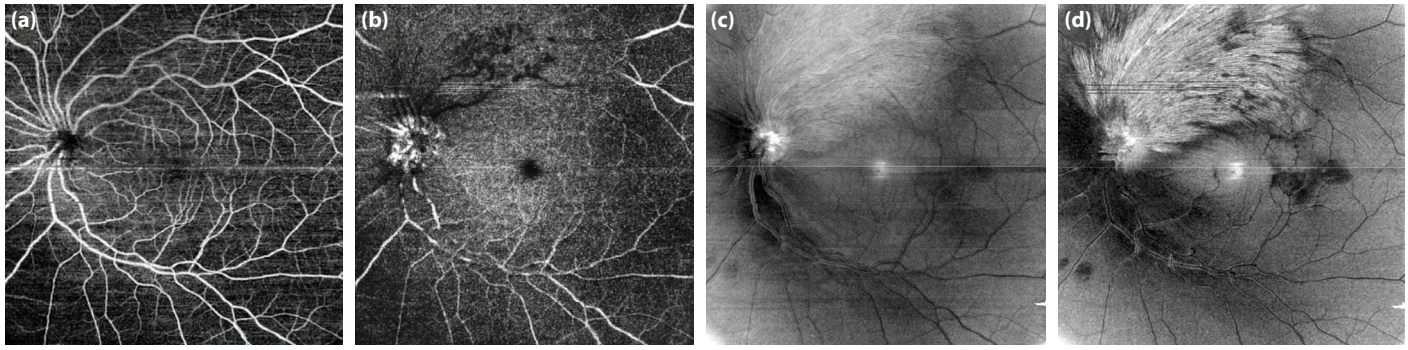

Fig. 2. In swept-source optical coherence tomography angiography (SS-OCTA) images; superficial capillary plexus revealed no prominent changes **(a)**. Splitting in superficial retinal layers partially causes dark back shadowing in DCP **(b)**. En face SS-OCTA images revealed a markedly increased reflectivity in the areas of retinoschisis **(c** and **d)**.

X-linked retinoschisis, primary acquired retinoschisis, SINFR, degenerative myopia, glaucoma, and congenital optic disc abnormalities.[1–8]

Congenital juvenile X-linked retinoschisis is a rare disorder and all affected individuals have typical foveal schisis with approximately half also exhibiting some degree of peripheral schisis. It almost exclusively occurs in males because of the X-linked inheritance pattern and is mostly seen bilaterally.[1,9] Primary acquired retinoschisis has been reported in patients within the third decade of life (20–30 years), commonly involves the inferior temporal retina bilaterally with minimal pigment alterations. It is characterized by splitting of the neurosensory retina at the outer plexiform layer and foveal affection is hardly present, even though rare cases of progression with retinal detachment including the macula were reported.

Our case had no associated ocular conditions such as X-linked retinoschisis, primary acquired retinoschisis, glaucoma, and congenital optic disc abnormalities. We speculated two theories regarding the development of PPRS in our case. One hypothesis is that high myopia is responsible for the peripapillary inner retinoschisis. High myopia is characterized by abnormal axial elongation with retinal microstructural degenerative changes such as retinoschisis, especially at the posterior pole. Sherman et al.[10] described that PPRS seems to be a clinical entity more prevalent in high myopia. In their study including 600 eyes, 19 exhibited retinoschisis around the optic disc. The splits were usually bilateral, variable in location and often appeared to exist in several layers, most often found in the inner and outer plexiform layers. Sixteen of them had normal or near-normal visual acuity and none had a macular involvement. However, most eyes demonstrated visual field defects as the enlargement of the blind spot. Eight eyes had one or more zones of vitreoretinal traction that might be the etiology of the schisis. They concluded that PPRS without macula schisis appears to be a new entity not previously reported but easily documented with SD-OCT images around the optic disc. Scans through the macula will miss the PPRS unless the peripapillary area is included in the OCT scan.[10]

Pathologic myopia with staphyloma is another cause of foveomacular retinoschisis due to a tractional maculopathy most likely arising from residual cortical vitreous after posterior vitreous detachment.[4] In their study, Shimada et al.[4] also reported that nearly in 48% of high myopic eyes with myopic conus, the peripapillary retinal vessels with tractional microfolds on OCT scans are associated with retinoschisis mostly showing an extension toward the macular area. Although our patient is bilaterally high myopic with long axial lengths, she did not exhibit any signs of degenerative myopia with myopic conus, staphyloma, or traction maculopathy on radial SD-OCT scans. The retinoschisis was unilateral and only involving the inner retinal layers rather than outer plexiform layer.

Second hypothesis is associated with PPRS, is SNIFR. SNIFR is an uncommon cause of foveomacular retinoschisis. Most cases are unilateral and highly myopic women with good visual acuity.[2,3] Recent evidence suggests that apart from foveomacular retinoschisis, peripheral imaging is key in identifying the other findings of SINFR, including mid-peripheral peripapillary inner retinoschisis. Although the clinical manifestation of SNIFR is based on OCT examination and defined as a stellate foveal splitting of the outer plexiform layer, the latest reports revealed coexisting peripapillary inner retinal changes on OCT.[2,3]

Our case is very similar to patients reported in the SNIFR series of Ober et al.[2] in which most of them were female with relatively good visual acuity, myopia, and unilateral involvement. Javaheri and Sadda[9] reported a 36-year-old woman with the diagnosis of SNIFR. She had mild myopia with good visual acuity (20/20) and exhibited macular split-

ting of the outer plexiform layer with peripapillary inner retinoschisis, involving the outer plexiform layer and inner retina in her left eye. Ahmed et al.[3] described an atypical case of bilateral SNIFR with a petaloid foveomacular splitting of the outer plexiform layer extending to the temporal periphery on the right eye on OCT, whereas on the left eye, there was only the cleavage of the outer retina started at the peripheral posterior pole, approximately 3.5 mm temporal to the umbo of the fovea. No pathology could be detected in FA and OCTA. They also claimed that there might be an early stage of SNIFR without foveal involvement. A possible expansion of the mid-peripheral splitting of the outer plexiform layer toward the center could lead to a secondary affection of the foveomacular zone which develops over a certain time and manifests as slight visual symptoms, once the fovea is chronically damaged.

Our case differs from these case series because she had only unilateral peripapillary inner retinoschisis instead of OPL and macular involvement. Our patient may also represent an early stage of SNIFR without foveal involvement as Ahmed et al.[3] described in their case report. With the standard use of SD-OCT in routine cases, PPRS will likely be diagnosed more frequently in the future as it can easily be recognized with its characteristic pattern. Longer follow-up and larger case series should be maintained to clarify this entity.

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Informed Consent: Written informed consents were obtained from the parents for publication of this case report and accompanying images.

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Authorship Contributions: Concept: M.K.; Design: M.K.; Supervision: M.K.; Resource: M.K.; Materials: M.K.; Data Collection and/or Processing: M.K.; Analysis and/or Interpretation: M.K.; Literature Search: M.K.; Writing: F.A.; Critical Reviews: M.K.

Conflict of Interest: None declared.

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Eur Eye Res 2021;1(1):47–52

EUROPEAN EYE RESEARCH

CASE REPORT

Simple limbal epithelial transplantation in limbal stem cell deficiency after chemical eye injury

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Abstract

To present a pediatric patient with unilateral limbal stem cell deficiency (LSCD) after acetone burn, managed by simple stem cell transplantation simple limbal epithelial transplantation (SLET) surgery and to review the literature on limbal stem cell transplantation techniques. A 12-year-old boy was admitted to the emergency department for acetone burn on his left eye. Following acute management of the chemical injury and amniotic membrane transplantation, the cornea healed with extensive conjunctivalization. He suffered severe photophobia and visual acuity (VA) loss up to 0.16 Snellen lines. Because of severe clinical findings of LSCD, SLET surgery was performed. He had dramatic improvement in corneal epithelialization, stromal transparency, and disappearance of photophobia 2 weeks after the surgery. At 1 year postoperatively, his VA was 0.7 with a stable epithelial surface and minimal corneal haze and he had returned to normal life. SLET is a viable alternative technique in the management of unilateral LSCD and should be present in the armamentarium of all corneal surgeons.

Keywords: Chemical eye injury; limbal stem cell deficiency; simple limbal epithelial transplantation.

Chemical burn is a leading cause of corneal blindness. Ocular surface injuries lead to 19 million unilateral and 1.6 million bilateral visual losses annually.[1] Incidence of blindness due to trauma and corneal ulceration is approximately 2 million cases per year.[2] Among all ocular injuries, the rate of chemical burn is 1.5–22.1%.[3,4] Inadequate management of the acute burn or late sequela may lead to severe dry eye syndrome, limbal stem cell deficiency (LSCD), corneal neovascularization, and corneal opacities. Eyelid disorders, trichiasis, symblepharon, ankyloblepharon, corneal keratinization, subsequent corneal infections, or glaucoma require life-long follow-up of the patients, probable additional interventions, and eventually loss of labor of the patient and may cause great economic impact.

Chemical eye burn is a major cause of LSCD. Corneal scraping, amniotic membrane transplantation, conjunctival limbal autograft (CLAU) or allograft, keratolimbal allograft, and *ex vivo* cultivated limbal stem cell transplantation have been used for the treatment of LSCD. Simple limbal epithelial transplantation (SLET) is a recently introduced technique for LSCD. Its advantages include need for a small limbal biopsy, being repeatable due to low risk of iatrogenic damage at the healthy fellow eye and being applicable at low-budget facilities. Immunosuppressive

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treatment is not required as there is essentially no risk of immune rejection.

Herein, we present a pediatric case whose unilateral LSCD due to acetone burn was successfully treated by SLET; as well as a review of the literature on the treatment of LSCD. Consent and permission upon publication of the medical data was obtained from the patient and his parents.

Case Report

A 12-year-old male patient was admitted to Dokuz Eylul University, Department of Ophthalmology, after blasting eye injury with an acetone bottle. His eye was rinsed with saline solution at the emergency department, before referring to our clinic. At the initial admission, his visual acuities were 1.0 at the right eye and 0.5 at the left eye, in Snellen lines. Slit-lamp examination revealed wide corneal epithelial defect, 360° limbal ischemia, and chemosis on the left eye (Fig. 1). Right eye examination revealed normal findings.

In our clinic, his injured eye was rinsed deliberetely again with ringer lactate solution. A silicone hydrogel bandage contact lens (balafilcon A, PureVision®, Bausch & Lomb, USA) was fitted and topical preservative-free dexamethasone qid, moxifloxacin tid, trehalose - sodium hyaluronate qid, cyclopentolate tid, polivinil alcohol/povidone tears, and (PO) 500 mg vitamin C were prescribed. On the 3rd day of the injury, slit-lamp examination revealed initiation of corneal epithelization. However at the 4th week, only less than a quarter of corneal epithelium has healed and amniotic membrane transplantation was performed to decrease ocular inflammation and improve epithelialization (Fig. 2a and b). At the 2nd week of surgery, the amniotic membrane has dissolved and the epithelium has completely healed leaving stromal haze, vascularization, and conjunctivalization implying LSCD (Fig. 3a and b). His visual acuity (VA) initially improved to 0.4 with +0.25(−1.25 at 140), but severe photophobia was restricting his life and he quitted attending his school. The healed epithelium itself was loose, displaying recurrent erosions with associated pain and discomfort. At the postoperatively 3rd month, VA worsened to 0.16 levels and stayed stabile in the following visits.

Confirming the diagnosis of LSCD by clinical findings, SLET surgery was performed at the 10th month following chemical burn, by taking the limbal donor tissue taken from the fellow eye (İD, CAU) (Fig. 4a and b). Initially, 2 mm×2 mm area on the donor eye limbus was marked and a conjunctival fleb was dissected toward limbus to prepare the graft tissue. Conjuctival graft was cut into 14 small pieces. The conjunctiva that has grown onto the cornea with LSCD was gently dissected and the corneal surface was covered with

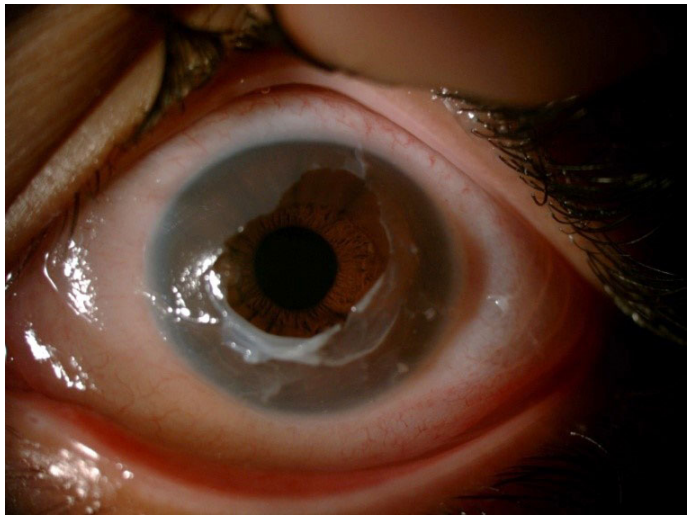


Fig. 1. Large corneal epithelial defect, chemozis, and limbal ischemia immediately after ocular acetone burn.

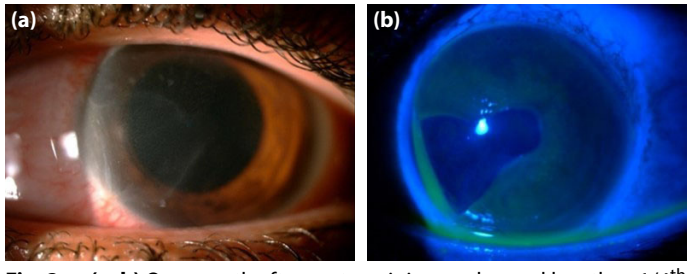


Fig. 2. **(a, b)** One month after acetone injury, only nasal less than 1/4th cornea has re-epithelialized.

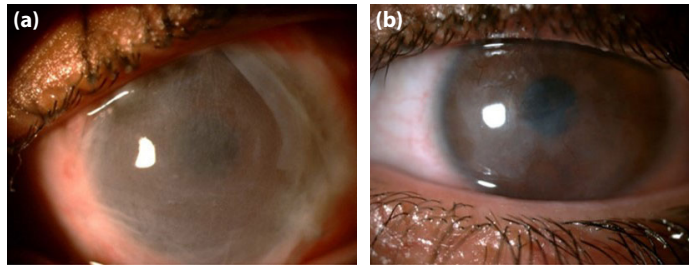


Fig. 3. **(a, b)** Following amniotic membrane transplantation, corneal epithelium healed with corneal haze, vascularization, conjunctivalization, and scarring.

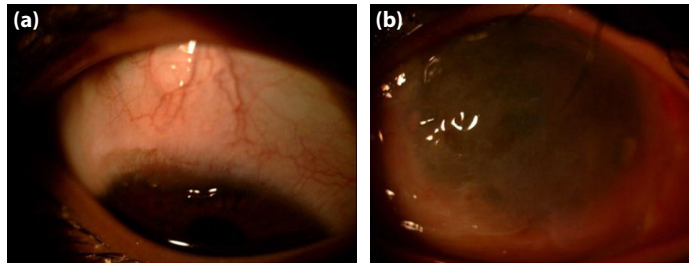


Fig. 4. **(a, b)** Simple limbal epithelial transplantation surgery in conjunction with amniotic membrane transplantation was performed with superior limbal biopsy from the healthy fellow eye.

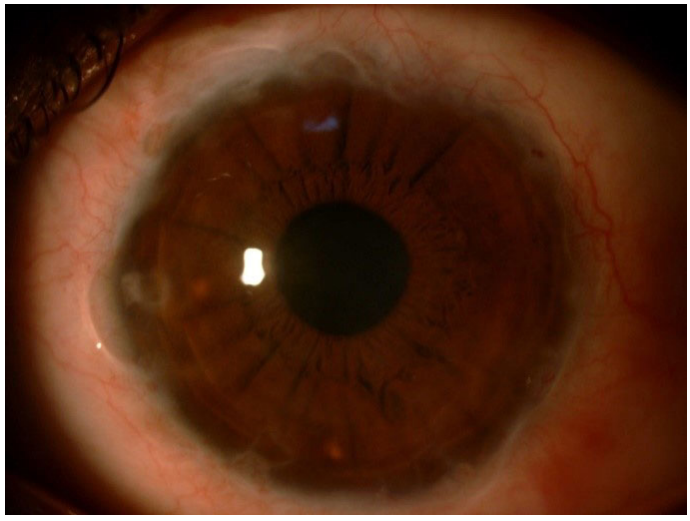


Fig. 5. Postoperatively, the corneal stroma was transparent. There was no epithelial defect, neovascularization, and limbal deficiency. Limbal stem cell grafts can be seen circumferentially.

amniotic membrane using tissue fibrin sealant (Tisseel, Baxter Healthcare, US). Small limbal stem cell grafts were placed circumferentially for 360° on the limbus intermittently, over amniotic membrane with fibrin sealant. A 14.0 mm diameter silicone hydrogel contact lens (balafilcon A, PureVision®, Bausch & Lomb, USA) was placed at the end of the surgery.

Postoperatively, topical treatment of moxifloxacin qid, preservative-free dexamethasone qid, and 0.15% sodium hyaluronate artificial tears frequently was commenced. On the post-operative 2nd week, upon melting and dissolving of the amniotic membrane, clear stroma has appeared. His VA improved to 0.3 uncorrected and 0.5 with −0.50 (−1.50@100) D. Photophobia improved dramatically, and the patient could return his normal life and school. At the slit-lamp examination, minimal cornea haze was present with no epithelial defect or neovascularization (Fig. 5). Topical treatment was switched to cyclosporine 0.05% qid and preservative-free 0.15% sodium hyaluronate qid.

At the 1st year follow-up, his corneal stroma had only minimal haze with regular epithelial surface. The uncorrected and corrected VAs were 0.6 and 0.7 with −0.50 (−1.50 at 100), respectively. The patient is still under medical treatment with cyclosporine 0.05% bid and preservative-free artificial tears, as needed.

Discussion

Chemical burn is one of the leading causes of permanent visual loss in the opthalmic emergencies.[5] Treatment and prognosis vary according to severity of the chemical damage, depth and extend of area affected at the central cornea and limbal stem cell area. The exposure time and area of the ocular surface and type, concentration, temperature, and pH of the chemical also affect the prognosis.[6,7] Irreversible chemical damage of limbal basal epithelial cells that are known to have vital roles for epithelialization,[8–15] may cause LSCD. The clinical picture of LSCD may present in a broad spectrum, from undulating finger-shaped epithelial irregularities with stippled corneal fluorescein staining in vortex pattern and late fluorescein staining that extend from the limbus to the center, up to severe and total conjunctivalization of the corneal surface. Eventually, LSCD may cause serious corneal problems such as permanent conjunctivalization, basal membrane destruction, and fibrous tissue growth over cornea.[16,17]

Biomicroscopic findings of LSCD include irregular corneal surface varying in terms of depth and transparency. Severe LSCD results in fibrovascular pannus, chronic keratitis, cicatrization, and calcification.[18] Since the conjunctivalized corneal epithelium is more permeable, it stains with fluorescein irregularly, as compared to normal corneal epithelium.[19] Conjunctivalized corneal epithelium is thinner, disorganized, and stains in a punctate pattern.[20,21] In partial LSCD, a demarcation line between damaged and normal corneal area can be seen. Fluorescein stain tends to pool on the conjunctivalized area, where the epithelium is thinner.[22,23] In severe cases, persistant epithelial defects, corneal melting, and even perforation can be seen.[18] LSCD can be diagnosed histologically by showing goblet cells in the conjunctivalized corneal epithelium with impression cytology.[24] This diagnosis has vital importance to exclude conventional corneal transplantation as a treatment option.[18]

In case of a chemical injury of the eye, main goal of acute management is to suppress the inflammation, prevent progression of epithelial and stromal defects and induce epithelialization.[25] Partial LSCD that does not affect the corneal center could be managed by topical medications to improve lubrication by artifical tears, suppress inflammation by steroid and non-steroid eye-drops, and support epithelialization by autologous serum eye drops.[26–29] Autologous serum eye drops aim at providing healthy epithelial proliferation and migration and preventing corneal adhesion to tarsal conjunctiva leading to symblephora.[30–32] Therapeutic contact lenses and scleral lenses may prevent formation of new corneal epithelial defects, aid in healing persistant epithelial defects, decreasing pain, and photophobia. Lubrication prevents epithelial adhesion to tarsal conjunctiva but unlike autologous serum eye drops, artificial eye drops do not induce limbal stem cell prolifera-

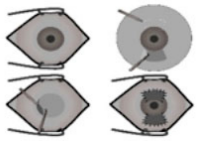
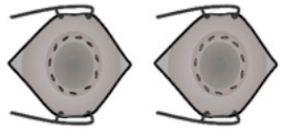
tion.[33,34] In the presence of severe LSCD, (i.e., 360° corneal vascularization, conjunctivalization, and severe visual loss) limbal stem cell transplantation surgery is the only treatment approach. SLET is a new generation technique in this context.[35]

Surgical treatment options for LSCD aim at restoring the healthy corneal epithelial surface and transparent stroma (Table 1). Corneal scraping procedure aims at removing conjunctival tissue over the cornea to help re-epithelization of corneal surface.[36] Amniotic membrane transplantation is frequently performed to induce residual limbal stem cell islands' proliferation and migration, at the early phase of chemical injury. It helps healing corneal surface, improves VA, reduces pain, and particularly photophobia. Amniotic membrane has low immunogenic, high anti-inflammatory, anti-angiogenic, antifibrinogenic, antimicrobial, and anti-apoptotic properties. After removing conjunctival overgrowth on the cornea, amniotic membrane is fixed using tissue fibrin sealants and/or sutures.[32–34,36,37] However, in terms of severe LSCD, it does not allow transparent epithelialization of the cornea. CLAU is another technique, where limbal graft from the healthy fellow eye is taken using conjunctiva as a carrier tissue. However, due to the size of the harvested graft, the technique carries inherent LSCD risk for the donor healthy eye. Conjunctival limbal allograft can be excised from alive relative or cadaver using conjunctiva as a carrier tissue. In this case, systemic immunosuppression is mandatory and risks of infection and neoplasia, as well LSCD risk as in CLAU technique, are present. Keratolimbal allograft is another technique of limbal stem cell transplant from cadavers, using cornea as carrier tissue. Larger tissue is transplanted comparing to other transplants. Its risks also include risks of systemic immunosuppression including infection.[33,38–40] *Ex vivo* cultivated stem cell transplantation (CLET) is a technique, where autologous or allogenic limbal stem cells are grown in the culture media over amniotic membrane or various carriers, and then transplanted. Main advantages include low risk of LSCD in the donor eye and low immunologic rejection risk as Langerhans cells do not reside in the composite graft.[39,41,42] Finally, simple oral mucosal epithelial transplantation (SOMET) can be used when no limbal stem cells are available in bilateral LSCD cases, to decrease ocular surface inflammation and corneal neovascularization. SOMET has particular advantage in improving photophobia and preparing ocular surface for future CLET.

SLET technique is one of the recent advances for monocular LSCD cases. In 2012, Sangwan et al.[43] presented autologous SLET surgery as a new technique combined with amniotic membrane transplantation. Basu et al.[44] analyzed long-term consequences of SLET, and reported successful results in 125 eyes of 95 patients with ocular chemical burn, at post-operative 1.5 years follow-up. Vazirani et al.[45] analyzed outcomes of SLET in 68 eyes at eight centers in three countries; and reported successful results in 57 eyes at the end of 1 year follow-up.

For successful SLET, limbal biopsy should be excised from a healthy limbal area. The biopsy size 2 mm×2 mm is adequate. A larger limbal biopsy may create a risk of LSCD in the healthy eye. Advantages of SLET include being repeatable due to low risk of iatrogenic damage at healthy fellow eye with a small biopsy requirement. In repeated SLET surgeries, biopsy might be harvested close to former biopsy area but they should not overlap. Of note, SLET is

Table 1. Comparison of limbal stem cell transplantation techniques

	CLAU	CLET	SOMET	SLET
				
Donor tissue size	10–20 mm	2×2 mm	3×4 mm	2×2 mm
Laboratory need	No	Yes	No	No
Amnion use	No	Yes	Yes	Yes
Repeatability	No	Yes	Yes	Yes
Donor eye LSCD risk	Yes	No	No	Yes
Cost	Low	High	Low	Low
Preference in unilateral LSCD	Rare	Yes	No	Yes
Preference in bilateral LSCD	Yes	No	Yes	No

CLAU: Conjunctival limbal autograft; CLET: Ex vivo cultivated stem cell transplantation; SOMET: Simple oral mucosal epithelial transplantation; SLET: Simple limbal epithelial transplantation; LSCD: Limbal stem cell deficiency.

applicable at low-budget facilities, as no laboratories for cultivating limbal stem cells are needed. SLET does not require immunosuppressive medication, as risk of immune rejection essentially does not exist.[46] Unfortunately, the autologous SLET is not applicable for bilateral LSCD cases. Allograft SLET can be an option for bilateral LSCD cases, but the rate of surgical success may be lower with this technique. The presence of symblephora might also decrease the rate of surgical success. Per-operative symblephora excision and use of amniotic membrane can be a solution.[47] To transplant the stem cell niches onto a quiet ocular surface with minimal to no inflammation, at least 4–6 months medical treatment after the chemical burn would improve the rate of post-operative success.[43]

To sum up, SLET technique is a viable and minimally invasive alternative in monocular LSCD to improve corneal epithelialization and final VA, as well as to resolve photophobia.

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EUROPEAN EYE RESEARCH

CASE REPORT

Torpedo maculopathy: A single entity with three different presentations

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Abstract

Torpedo maculopathy (TM) is a benign and non-progressive congenital lesion of the retina pigment epithelium in association with the disruption of outer retinal layers. In this case series, three patients with unilateral torpedo lesions who displayed different clinical features were reported. In all cases, there was somewhat distortion of the outer retinal layers with a corresponding increase in the choroidal reflectance under the lesion in optical coherence tomography (OCT). Fluorescein angiography and OCT angiography were performed in the only adult case. As TM is mostly a benign entity without causing any visual disturbance, its differential diagnosis carries paramount importance.

Keywords: Hypopigmented lesion; multimodal imaging; optical coherence tomography; retina pigment epithelium; torpedo maculopathy.

Torpedo maculopathy (TM) is a rare, solitary hypopigmented lesion of the retina pigment epithelium (RPE) located in the vicinity of the macula mostly without causing any significant visual deficit. The condition was described as albinotic nevi of RPE, congenital hypomelanotic freckle, and solitary amelanotic spot by several authors but a unilateral "torpedo-shaped" hypopigmented lesion, typically located temporal to the macula with a nonprogressive course is the common presentation.[1,2] Although it is well-recognized by its characteristic shape, the underlying pathophysiological process is not clearly known yet. Several theories have been proposed as of the etiology, including a dysgenetic RPE, a developmental defect in the "fetal temporal bulge", abnormalities of underlying choroid vasculature, or failure of the RPE to close the overlying the region near the emissary canal of ciliary vessels.[3,4] Visual acuity (VA) is typically not affected. Although progression is not expected, these lesions are fraught with macular neovascularization (MNV) occurrence due to RPE and outer retinal damage and should be regularly monitored.[5] In our case series, we report three patients with TM presented with different clinical features.

Case Report

Case 1– A 2-year-old Caucasian girl was referred to our clinic for suspicion of squint presence. Her VA was recorded

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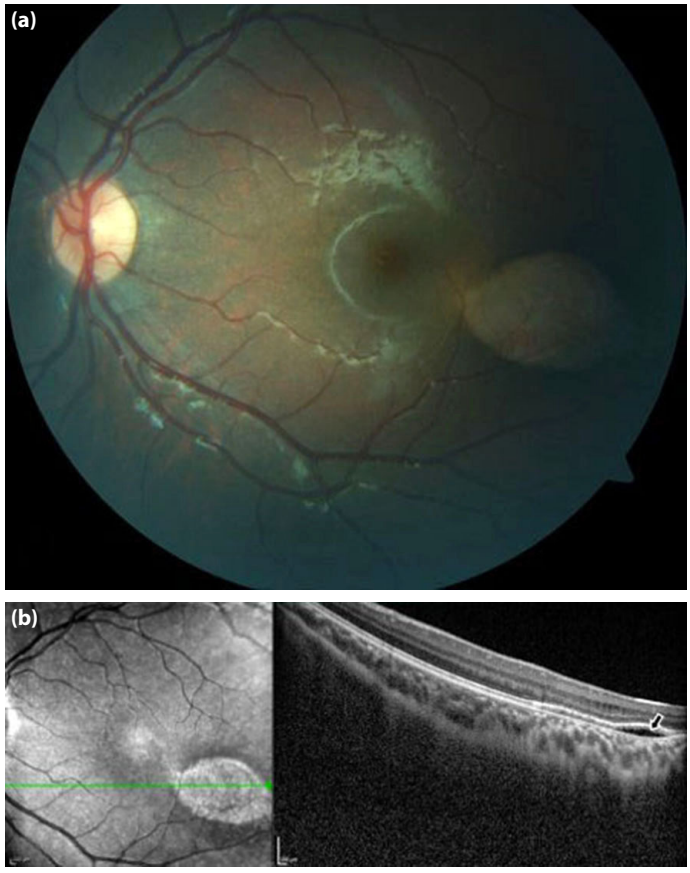

Fig. 1. **(a)** Color fundus photo of left eye demonstrates a flat, torpedo-shaped hypopigmented lesion with a tail pointed toward the fovea. **(b)** Enhanced depth imaging optical coherence tomography scan shows outer retinal layer disorganization accompanied by a subretinal cleft (arrow) and increased reflectivity of the choroid underneath.

as fix and follow and central, steady, maintained bilaterally. Her anterior segment evaluation and ocular alignment were unremarkable, and her cycloplegic refraction was within normal limits for her age group. Fundus examination revealed a torpedo-shaped hypopigmented lesion with a well-defined margin temporal to the left macula (Fig. 1a). Enhanced depth imaging optical coherence tomography (EDI-OCT) scan through the lesion showed distortion of the outer retina with increased reflectivity of the choroid together with a subretinal cleft (Fig. 1b). She was diagnosed with TM and scheduled for follow-up examinations. At age 4, her VA was 20/25 in both eyes and there was no progression of the lesion.

Case 2– A 8-year-old Caucasian girl was referred to our retina clinic for a macular lesion detected in her left eye. Her VA was 20/20 bilaterally. Her right fundus was unremarkable; however, there was a well-circumscribed, hypopigmented, and torpedo-shaped lesion in the left temporal macula, whose tip was pointing towards the fovea (Fig. 2a). Optical

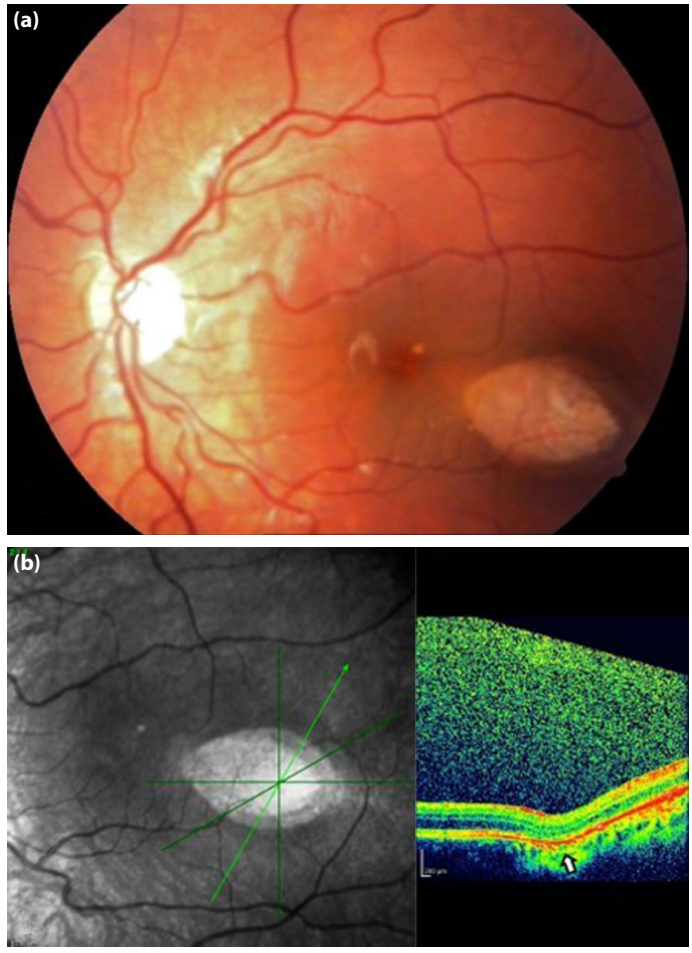

Fig. 2. **(a)** Color fundus photo of the left eye shows a well-circumscribed, hypopigmented, and torpedo-shaped lesion in the left temporal macula. **(b)** Disruption and thinning of outer retina with increased choroidal reflectivity in the region and a focal choroidal excavation (arrow) are prominent in optical coherence tomography.

coherence tomography (OCT) scan of the lesion revealed a thin outer retina with increased choroidal reflectivity under the lesion with a prominent focal choroidal excavation (Fig. 2b). There was no associated subretinal cleft.

Case 3– A 61-year-old Caucasian woman was consulted for a right macular lesion. Her VA's were 20/20 in both eyes. While the left fundus was normal, there was a torpedo-shaped hypopigmented lesion with a slight pigmentation at its temporal tail in the right eye (Fig. 3a). OCT of the lesion revealed a large subretinal cleft with a choroidal excavation. The upper roof of cleft had a brushy appearance (Fig. 3b). A well-defined window defect-like lesion exhibiting some staining was noted with fluorescein angiography (FA) (Fig. 3c). The lesion was apparent on the outer retina and choriocapillaris slabs on optical coherence tomography angiography (OCTA) (Fig. 4).

Verbal informed consent was obtained in all cases.

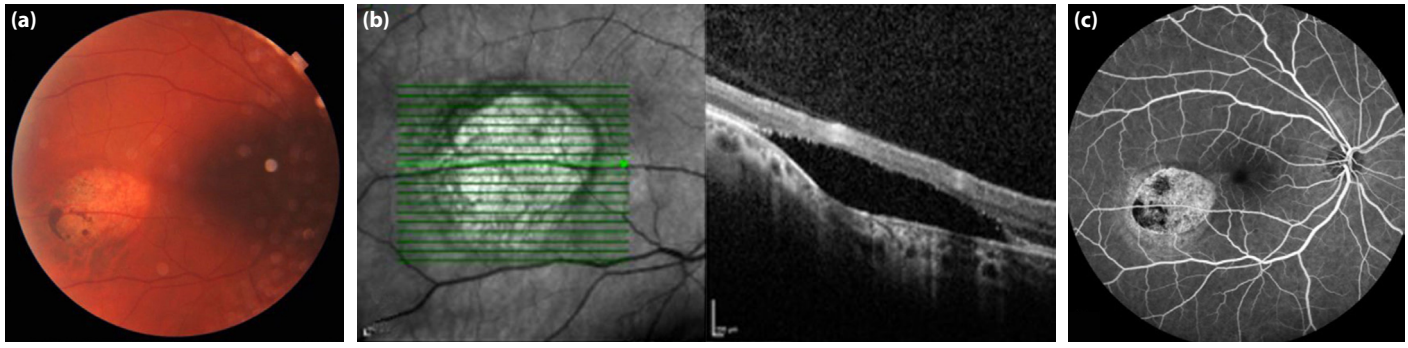

Fig. 3. **(a)** Color fundus photo of right eye demonstrates a torpedo-shaped hypopigmented lesion with segmental hyperpigmentation to its temporal edge. **(b)** Optical coherence tomography shows a large subretinal cleft and outer retinal excavation with thinning of outer retinal layers. **(c)** Fundus fluorescein angiography reveals a well-defined hyperfluorescent lesion with temporal hypofluorescence corresponding to hyperpigmented areas of torpedo lesion. Lesion shows no leakage in late-phase frames.

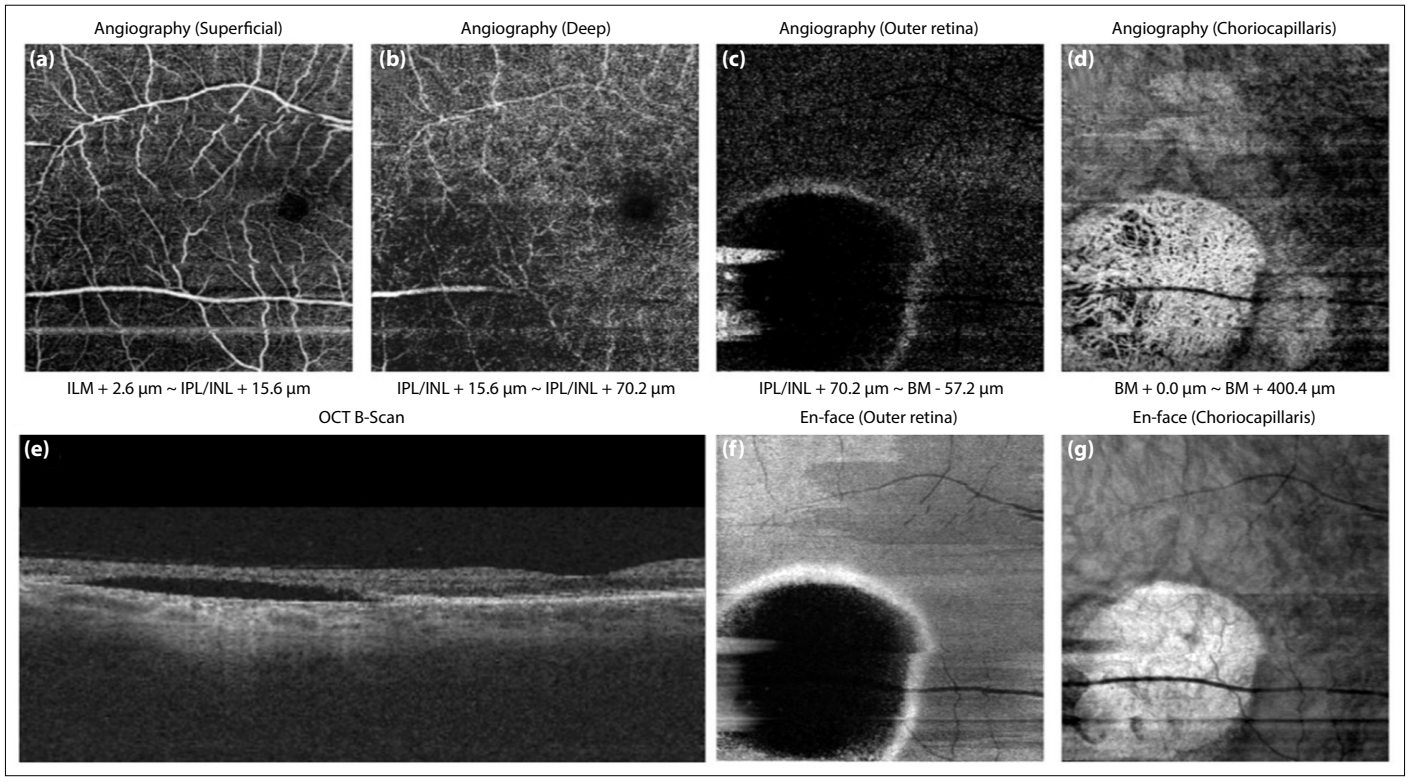

Fig. 4. **(a-d)** Optical coherence tomography angiography reveals normal superficial and deep plexi, and a convoluted pattern of fine vessels with some hyporeflective spaces between them on the choriocapillaris slab. **(e)** A subretinal cleft is prominent in swept-source optical coherence tomography (OCT). **(f-g)** En face OCT slabs of outer retinal layers and choroid show a homogeneous hyporeflective area corresponding to the subretinal cleft.

Discussion

TM is usually diagnosed incidentally during the ophthalmic examination as it is almost often asymptomatic. Patients can be at any age at the time of diagnosis (range, 6 months–72 years) and there is no predilection for a particular gender or race.[6,7] The youngest of our cases was 2 years old, whereas the oldest was 61. Although bilateral cases are reported, most of the TM lesions are typically unilateral. So far, all reported TM lesions were temporal to the macula, with one exception presenting with a nasal lesion.[8] In our case series, all TM lesions were unilateral and located temporally to macula. Although known as a benign lesion, it has been rarely associated with MNV and visual prognosis was good with intravitreal anti-VEGF injections according to case reports.[5,7] MNV was not observed in any of our cases.

Multimodal imaging has provided a better understanding of the structure of TM lesions. The characteristic OCT finding is an increase in choroidal reflectivity, with or without RPE hy-

perreflectivity, seen in the presence of normal inner retinal layers. The outer retina may be irregular due to RPE thinning and photoreceptor loss, and subretinal cleft may be present. Wong et al.[9] categorized TM according to the OCT findings into two subtypes. Having increased signal transmission to choroid and normal inner retinal structure in common, type 1 TM included the lesions without outer retinal cavitation, whereas type 2 TM included the lesions with outer retinal cavitation, which may be associated with inner choroidal excavation. Tripathy et al.[10] provided the most up-to-date classification of TM by defining a third type in which focal choroidal excavation is seen without cavitation. According to these definitions, while the OCT findings of Patient 1 and Patient 3 were compatible with type 2 TM, the lesion of Patient 2 could be classified as type 3 TM. Papastefanou et al.[11] described the characteristics of torpedo lesions with OCTA and observed hyporeflectivity at choriocapillaris level, indicating the atrophy, which in turn showed a correlation with subretinal cleft area on the OCT. In accordance with this description, there was a convoluted pattern of fine vessels with some hyporeflective spaces in between them in the choriocapillaris layer, while superficial and deep retinal layers appeared normal on the OCTA examination of Patient 3. Moreover, OCTA may reveal the increased density of choroidal vasculature due to increased signal transduction of thin RPE in cases of TM without subretinal cleft.[12] In most cases, FA revealed a well-defined hyperfluorescent window defect-like stained lesion without any leakage that probably indicates a loss of functional RPE. To date, no histopathologic evidence exists to confirm the true etiology of TM.

Differential diagnosis of TM includes other pigment-related lesions such as inactive toxoplasma retinochoroiditis, amelanotic nevus and/or melanoma of choroid, solitary congenital hypertrophy of RPE, and congenital RPE lesions having the potential of malignancy as in Gardner's syndrome.[7] Therefore, it is of utmost importance for the physician to recognize the lesion correctly.

Conclusion

TM usually presents as a hypopigmented "torpedo-like" lesion temporal to macula. Although retinal thinning, structural changes in the outer retinal layers and choriocapillaris atrophy are observed with multimodal imaging, VA is typically not affected. In some cases, it has been associated with conditions requiring treatment such as MNV. Various retinochoroidal lesions should be considered in its differential diagnosis, including tumors with systemic involvement. With this report, we want to share our observations on TM and to remind the ophthalmologists about the entity.

Informed Consent: Written informed consent was obtained from the parents and the case for the publication of this case report and accompanying images.

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