www.oftalmoloji.org

E-ISSN: 2149-8709

TURKISH JOURNAL OF OPHTHALMOLOGY

TURKISH JOURNAL OF OPHTHALMOLOGY TJO

March April 2021
51 Volume
Issue 2

galenos

TURKISH JOURNAL OF OPHTHALMOLOGY

TJO

www.oftalmoloji.org

Publishing House
Molla Gürani Mah. Kaçamak Sokak No: 21,
34093 Fındıkzade-İstanbul-Turkey
Publisher Certificate Number: 14521
Phone: +90 212 621 99 25 **Fax:** +90 212 621 99 27
E-mail: info@galenos.com.tr
Online Publishing Date: April 2021
International scientific journal published bimonthly.
E-ISSN: 2149-8709

The Turkish Journal of Ophthalmology is an official journal of the Turkish Ophthalmological Association.

On Behalf of Turkish Ophthalmological Association Owner

İzzet CAN
Private Practice, Ankara, Turkey

TURKISH JOURNAL OF OPHTHALMOLOGY

TJO

www.oftalmoloji.org

ABOUT US

The Turkish Journal of Ophthalmology (TJO) is the only scientific periodical publication of the Turkish Ophthalmological Association and has been published since January 1929. In its early years, the journal was published in Turkish and French. Although there were temporary interruptions in the publication of the journal due to various challenges, the Turkish Journal of Ophthalmology has been published continually from 1971 to the present.

The Turkish Journal of Ophthalmology is currently published in Turkish and English languages. TJO is an independent international periodical journal based on single-blind peer-review principle. TJO is regularly published six times a year and special issues are occasionally released. The aim of TJO is to publish original research papers of the highest scientific and clinical value at an international level. Furthermore, review articles, case reports, editorial comments, letters to the editor, educational contributions and congress/meeting announcements are released.

The target audience includes specialists and physicians in training in ophthalmology in all relevant disciplines.

The editorial policies are based on the "Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals (ICMJE Recommendations)" by the International Committee of Medical Journal Editors (2013, archived at http://www.icmje.org/) rules.

The Turkish Journal of Ophthalmology is indexed in the **PubMed/MEDLINE, PubMed Central (PMC), Web of Science-Emerging Sources Citation Index (ESCI), Scopus, TUBITAK/ULAKBIM, Directory of Open Access Journals (DOAJ), EBSCO Database, CINAHL, Proquest, Embase, British Library, Index Copernicus, J-Gate, ROOT INDEXING, IdealOnline, Turk Medline, Hinari, GOALI, ARDI, OARE** and **Turkish Citation Index.**

Open Access Policy

This journal provides immediate open access to its content on the principle that making research freely available to the public supports a greater global exchange of knowledge.

Open Access Policy is based on the rules of the Budapest Open Access Initiative (BOAI) http://www.budapestopenaccessinitiative.org/. By "open access" to peer-reviewed research literature, we mean its free availability on the public internet, permitting any users to read, download, copy, distribute, print, search, or link to the full texts of these articles, crawl them for indexing, pass them as data to software, or use them for any other lawful purpose, without financial, legal, or technical barriers other than those inseparable from gaining access to the internet itself. The only constraint on reproduction and distribution, and the only role for copyright in this domain, should be to give authors control over the integrity of their work and the right to be properly acknowledged and cited.

Subscription Information

TJO is sent free of charge to subscribers. Address changes should be immediately reported to the affiliates and to the managing editor. Subscribers who do not receive the journal in the relevant time period should contact the managing editor. All published volumes in full text can be reached free of charge through the website www.oftalmoloji.org. Requests for subscription should be addressed to the Turkish Ophthalmological Association.

Manuscripts can only be submitted electronically through the Journal Agent website (http://journalagent.com/tjo/) after creating an account. This system allows online submission and review.

Membership Procedures

Turkish Ophthalmological Association
Bank Account: Yapı Kredi Bankası, Şehremini Şubesi 65774842
IBAN: TR10 0006 7010 0000 0065 7748 42
Annual Subscription: Domestic: 100.-TL (Tax Incl)
Abroad: 100 USD (Tax Incl.)

Correspondence Address

Editor-in-Chief, Murat İrkeç, MD, Professor in Ophthalmology
Hacettepe University Faculty of Medicine, Department of Ophthalmology
06100 Sıhhiye-Ankara-Turkey
Phone: +90 212 801 44 36/37 Fax: +90 212 801 44 39
E-mail: mirkec@hacettepe.edu.tr

Secretary, Selvinaz Arslan
E-mail: dergi@oftalmoloji.org - sekreter@oftalmoloji.org
Address: Avrupa Konutları Kale, Maltepe Mah. Yedikule Çırpıcı Yolu Sk. 9. Blok No: 2 Kat:1 Ofis:1 Zeytinburnu-İstanbul-Turkey
Phone: +90 536 656 87 26 Fax: +90 212 801 44 39
Web Page: www.oftalmoloji.org

Permissions

Requests for permission to reproduce published material should be sent to the editorial office.
Editor-in-Chief: Murat İrkeç, MD, Professor in Ophthalmology
Address: Avrupa Konutları Kale, Maltepe Mah. Yedikule Çırpıcı Yolu Sk. 9. Blok No: 2 Kat:1 Ofis:1 Zeytinburnu-İstanbul-Turkey
Phone: +90 212 801 44 36/37 Fax: +90 212 801 44 39
Web Page: www.oftalmoloji.org
E-mail: dergi@oftalmoloji.org - sekreter@oftalmoloji.org

Advertisement

Applications for advertisement should be addressed to the editorial office.
Address: Avrupa Konutları Kale, Maltepe Mah. Yedikule Çırpıcı Yolu Sk. 9. Blok No: 2 Kat:1 Ofis:1 Zeytinburnu-İstanbul-Turkey
Phone: +90 212 801 44 36/37 Fax: +90 212 801 44 39
Web Page: www.oftalmoloji.org
E-mail: dergi@oftalmoloji.org - sekreter@oftalmoloji.org

Publisher Corresponding Address

Publisher: Erkan Mor
Galenos Yayınevi Tic. Ltd. Şti.
Address: Molla Gürani Mah. Kaçamak Sk. No: 21, 34093 Fındıkzade-İstanbul-Turkey
Phone: +90 212 621 99 25 Fax: +90 212 621 99 27
E-mail: info@galenos.com.tr

Instructions for Authors

Instructions for authors are published in the journal and on the website www.oftalmoloji.org

Material Disclaimer

The author(s) is (are) responsible for the articles published in the Turkish Journal of Ophthalmology.
The editor, editorial board and publisher do not accept any responsibility for the articles.

The journal is printed on acid-free paper.

TURKISH JOURNAL OF OPHTHALMOLOGY

TJO

www.oftalmoloji.org

INSTRUCTIONS TO AUTHORS

The Turkish Journal of Ophthalmology is an official peer-reviewed publication of the Turkish Ophthalmological Association. Accepted manuscripts are printed in Turkish and published online in both Turkish and English languages. Manuscripts written in Turkish should be in accordance with the Turkish Dictionary and Writing Guide ("Türkçe Sözlüğü ve Yazım Kılavuzu") of the Turkish Language Association. Turkish forms of ophthalmology-related terms should be checked in the TODNET Dictionary ("TODNET Sözlüğü" http://www.todnet.org/sozluk/) and used accordingly.

The Turkish Journal of Ophthalmology does not charge any article submission or processing charges.

A manuscript will be considered only with the understanding that it is an original contribution that has not been published elsewhere.

Reviewed and accepted manuscripts are translated either from Turkish to English or from English to Turkish by the Journal through a professional translation service. Prior to publishing, the translations are submitted to the authors for approval or correction requests, to be returned within 7 days. If no response is received from the corresponding author within this period, the translation is checked and approved by the editorial board.

The abbreviation of the Turkish Journal of Ophthalmology is TJO, however, it should be denoted as Turk J Ophthalmol when referenced. In the international index and database, the name of the journal has been registered as Turkish Journal of Ophthalmology and abbreviated as Turk J Ophthalmol.

The scientific and ethical liability of the manuscripts belongs to the authors and the copyright of the manuscripts belongs to the Turkish Journal of Ophthalmology. Authors are responsible for the contents of the manuscript and accuracy of the references. All manuscripts submitted for publication must be accompanied by the Copyright Transfer Form. Once this form, signed by all the authors, has been submitted, it is understood that neither the manuscript nor the data it contains have been submitted elsewhere or previously published and authors declare the statement of scientific contributions and responsibilities of all authors.

All manuscripts submitted to the Turkish Journal of Ophthalmology are screened for plagiarism using the 'iThenticate' software. Results indicating plagiarism may result in manuscripts being returned or rejected.

Experimental, clinical and drug studies requiring approval by an ethics committee must be submitted to the Turkish Journal of Ophthalmology with an ethics committee approval report confirming that the study was conducted in accordance with international agreements and the Declaration of Helsinki (revised 2013) (https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/). The approval of the ethics committee and the fact that informed consent was given by the patients should be indicated in the Materials and Methods section. In experimental animal studies, the authors should indicate that the procedures followed were in accordance with animal rights as per the Guide for the Care and Use of Laboratory Animals (http://oacu.od.nih.gov/regs/guide/guide.pdf) and they should obtain animal ethics committee approval.

Authors must provide disclosure/acknowledgment of financial or material support, if any was received, for the current study.

If the article includes any direct or indirect commercial links or if any institution provided material support to the study, authors must state in the cover letter that they have no relationship with the commercial product, drug, pharmaceutical company, etc. concerned; or specify the type of relationship (consultant, other agreements), if any.

Authors must provide a statement on the absence of conflicts of interest among the authors and provide authorship contributions.

The Turkish Journal of Ophthalmology is an independent international journal based on single-blind peer-review principles. The manuscript is assigned to the Editor-in-Chief, who reviews the manuscript and makes an initial decision based on manuscript quality and editorial priorities. Manuscripts that pass initial evaluation are sent for external peer review, and the Editor-in-Chief assigns an Associate Editor. The Associate Editor sends the manuscript to three reviewers (internal and/or external reviewers). The reviewers must review the manuscript within 21 days. The Associate Editor recommends a decision based on the reviewers' recommendations and returns the manuscript to the Editor-in-Chief. The Editor-in-Chief makes a final decision based on editorial priorities, manuscript quality, and reviewer recommendations. If there are any conflicting recommendations from reviewers, the Editor-in-Chief can assign a new reviewer.

The scientific board guiding the selection of the papers to be published in the Journal consists of elected experts of the Journal and if necessary, selected from national and international authorities. The Editor-in-Chief, Associate Editors, biostatistics expert and English language consultant may make minor corrections to accepted manuscripts that do not change the main text of the paper.

In case of any suspicion or claim regarding scientific shortcomings or ethical infringement, the Journal reserves the right to submit the manuscript to the supporting institutions or other authorities for investigation. The Journal accepts the responsibility of initiating action but does not undertake any responsibility for an actual investigation or any power of decision.

The Editorial Policies and General Guidelines for manuscript preparation specified below are based on "Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals (ICMJE Recommendations)" by the International Committee of Medical Journal Editors (2013, archived at http://www.icmje.org/).

Preparation of research articles, systematic reviews and meta-analyses must comply with study design guidelines:

CONSORT statement for randomized controlled trials (Moher D, Schultz KF, Altman D, for the CONSORT Group. The CONSORT statement revised recommendations for improving the quality of reports of parallel group randomized trials. JAMA 2001; 285: 1987-91) (http://www.consort-statement.org/);

PRISMA statement of preferred reporting items for systematic reviews and meta-analyses (Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 2009; 6(7): e1000097.) (http://www.prisma-statement.org/);

STARD checklist for the reporting of studies of diagnostic accuracy (Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig LM, et al., for the STARD Group. Towards complete and accurate reporting of studies of diagnostic accuracy: the STARD initiative. Ann Intern Med 2003;138:40-4.) (http://www.stard-statement.org/);

STROBE statement, a checklist of items that should be included in reports of observational studies (http://www.strobe-statement.org/);

MOOSE guidelines for meta-analysis and systemic reviews of observational studies (Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting Meta-analysis of observational Studies in Epidemiology (MOOSE) group. JAMA 2000; 283: 2008-12).

GENERAL GUIDELINES

Manuscripts can only be submitted electronically through the Journal Agent website (http://journalagent.com/tjo/) after creating an account. This system allows online submission and review.

The manuscripts are archived according to ICMJE, Index Medicus (Medline/PubMed) and Ulakbim-Turkish Medicine Index Rules.

Format: Manuscripts should be prepared using Microsoft Word, size A4 with 2.5 cm margins on all sides, 12 pt Arial font and 1.5 line spacing.

Abbreviations: Abbreviations should be defined at first mention and used consistently thereafter. Internationally accepted abbreviations should be used; refer to scientific writing guides as necessary.

Cover letter: The cover letter should include statements about manuscript type, single-journal submission affirmation, conflict of interest statement, sources of outside funding, equipment (if applicable), approval of language for articles in English and approval of statistical analysis for original research articles.

REFERENCES

Authors are solely responsible for the accuracy of all references.

In-text citations: References should be indicated as a superscript immediately after the period/full stop of the relevant sentence. If the author(s) of a reference is/are indicated at the beginning of the sentence, this reference should be written as a superscript immediately after the author's name. If relevant research has been conducted in Turkey or by Turkish investigators, these studies should be given priority while citing the literature.

Presentations presented in congresses, unpublished manuscripts, theses, Internet addresses, and personal interviews or experiences should not be indicated as references. If such references are used, they should be indicated in parentheses at the end of the relevant sentence in the text, without reference number and written in full, in order to clarify their nature.

References section: References should be numbered consecutively in the order in which they are first mentioned in the text. All authors should be listed regardless of number.

TURKISH JOURNAL OF OPHTHALMOLOGY

TJO

www.oftalmoloji.org

INSTRUCTIONS TO AUTHORS

The titles of journals should be abbreviated according to the style used in the Index Medicus.

Reference Format

Journal: Last name(s) of the author(s) and initials, article title, publication title and its original abbreviation, publication date, volume, the inclusive page numbers. Example: Collin JR, Rathbun JE. Involutional entropion: a review with evaluation of a procedure. Arch Ophthalmol. 1978;96:1058-1064.

Book: Last name(s) of the author(s) and initials, chapter title, book editors, book title, edition, place of publication, date of publication and inclusive page numbers of the extract cited.
Example: Herbert L. The Infectious Diseases (1st ed). Philadelphia; Mosby Harcourt; 1999:11;1-8.

Book Chapter: Last name(s) of the author(s) and initials, chapter title, book editors, book title, edition, place of publication, date of publication and inclusive page numbers of the cited piece.
Example: O'Brien TP, Green WR. Periocular Infections. In: Feigin RD, Cherry JD, eds. Textbook of Pediatric Infectious Diseases (4th ed). Philadelphia; W.B. Saunders Company;1998:1273-1278.
Books in which the editor and author are the same person: Last name(s) of the author(s) and initials, chapter title, book editors, book title, edition, place of publication, date of publication and inclusive page numbers of the cited piece.
Example: Solcia E, Capella C, Kloppel G. Tumors of the exocrine pancreas. In: Solcia E, Capella C, Kloppel G, eds. Tumors of the Pancreas. 2nd ed. Washington: Armed Forces Institute of Pathology; 1997:145-210.

TABLES, GRAPHICS, FIGURES, AND IMAGES

All visual materials together with their legends should be located on separate pages that follow the main text.

Images: Images (pictures) should be numbered and include a brief title. Permission to reproduce pictures that were published elsewhere must be included. All pictures should be of the highest quality possible, in
JPEG format, and at a minimum resolution of 300 dpi.

Tables, Graphics, Figures: All tables, graphics or figures should be enumerated according to their sequence within the text and a brief descriptive caption should be written. Any abbreviations used should be defined in the accompanying legend. Tables in particular should be explanatory and facilitate readers' understanding of the manuscript, and should not repeat data presented in the main text.

BIOSTATISTICS

To ensure controllability of the research findings, the study design, study sample, and the methodological approaches and applications should be explained and their sources should be presented.
The "P" value defined as the limit of significance along with appropriate indicators of measurement error and uncertainty (confidence interval, etc.) should be specified. Statistical terms, abbreviations and symbols used in the article should be described and the software used should be defined. Statistical terminology (random, significant, correlation, etc.) should not be used in non-statistical contexts.
All results of data and analysis should be presented in the Results section as tables, figures and graphics; biostatistical methods used and application details should be presented in the Materials and Methods section or under a separate title.

MANUSCRIPT TYPES

Original Articles

Clinical research should comprise clinical observation, new techniques or laboratories studies. Original research articles should include title, structured abstract, key words relevant to the content of the article, introduction, materials and methods, results, discussion, study limitations, conclusion references, tables/figures/images and acknowledgement sections. Title, abstract and key words should be written in both Turkish and English. The manuscript should be formatted in accordance with the above-mentioned guidelines and should not exceed sixteen A4 pages.

Title Page: This page should include the title of the manuscript, short title, name(s) of the authors and author information. The following descriptions should be stated in the given order:
1. Title of the manuscript (Turkish and English), as concise and explanatory as possible, including no abbreviations, up to 135 characters
2. Short title (Turkish and English), up to 60 characters
3. Name(s) and surname(s) of the author(s) (without abbreviations and academic titles) and affiliations
4. Name, address, e-mail, phone and fax number of the corresponding author
5. The place and date of scientific meeting in which the manuscript was presented and its abstract published in the abstract book, if applicable

Abstract: A summary of the manuscript should be written in both Turkish and English. References should not be cited in the abstract. Use of abbreviations should be avoided as much as possible; if any abbreviations are used, they must be taken into consideration independently of the abbreviations used in the text. For original articles, the structured abstract should include the following sub-headings:
Objectives: The aim of the study should be clearly stated.
Materials and Methods: The study and standard criteria used should be defined; it should also be indicated whether the study is randomized or not, whether it is retrospective or prospective, and the statistical methods applied should be indicated, if applicable.
Results: The detailed results of the study should be given and the statistical significance level should be indicated.
Conclusion: Should summarize the results of the study, the clinical applicability of the results should be defined, and the favorable and unfavorable aspects should be declared.

Keywords: A list of minimum 3, but no more than 5 key words must follow the abstract. Key words in English should be consistent with "Medical Subject Headings (MESH)" (www.nlm.nih.gov/mesh/MBrowser.html). Turkish key words should be direct translations of the terms in MESH.
Original research articles should have the following sections:
Introduction: Should consist of a brief explanation of the topic and indicate the objective of the study, supported by information from the literature.
Materials and Methods: The study plan should be clearly described, indicating whether the study is randomized or not, whether it is retrospective or prospective, the number of trials, the characteristics, and the statistical methods used.
Results: The results of the study should be stated, with tables/figures given in numerical order; the results should be evaluated according to the statistical analysis methods applied. See General Guidelines for details about the preparation of visual material.
Discussion: The study results should be discussed in terms of their favorable and unfavorable aspects and they should be compared with the literature. The conclusion of the study should be highlighted.
Study Limitations: Limitations of the study should be discussed. In addition, an evaluation of the implications of the obtained findings/results for future research should be outlined.
Conclusion: The conclusion of the study should be highlighted.
Acknowledgements: Any technical or financial support or editorial contributions (statistical analysis, English/Turkish evaluation) towards the study should appear at the end of the article.
References: Authors are responsible for the accuracy of the references. See General Guidelines for details about the usage and formatting required.

Case Reports

Case reports should present cases which are rarely seen, feature novelty in diagnosis and treatment, and contribute to our current knowledge. The first page should include the title in Turkish and English, an unstructured summary not exceeding 150 words, and key words. The main text should consist of introduction, case report, discussion and references. The entire text should not exceed 5 pages (A4, formatted as specified above).

Review Articles

Review articles can address any aspect of clinical or laboratory ophthalmology. Review articles must provide critical analyses of contemporary evidence and provide directions of current or future research. Most review articles are commissioned, but other review submissions are also welcome. Before sending a review, discussion with the editor is recommended.
Reviews articles analyze topics in depth, independently and objectively. The first chapter should include the title in Turkish and English, an unstructured summary and key words. Source of all citations should be indicated. The entire text should not exceed 25 pages (A4, formatted as specified above).

Letters to the Editor

Letters to the Editor should be short commentaries related to current developments in ophthalmology and their scientific and social aspects, or may be submitted to ask questions or offer further contributions in response to work that has been published in the Journal. Letters do not include a title or an abstract; they should not exceed 1,000 words and can have up to 5 references.

CORRESPONDENCE

All correspondence should be directed to the TJO editorial board:
Post: Turkish Ophthalmological Association
Avrupa Konutları Kale, Maltepe Mah. Yedikule Çırpıcı Yolu Sk. 9. Blok No: 2 Kat:1 Ofis:1 Zeytinburnu-İstanbul-Turkey
Phone: +90 212 801 44 36/37 Fax: +90 212 801 44 39
Web Page: www.oftalmoloji.org
E-mail: dergi@oftalmoloji.org / sekreter@oftalmoloji.org

TURKISH JOURNAL OF OPHTHALMOLOGY

TJO

www.oftalmoloji.org

CONTENTS

TURKISH JOURNAL OF OPHTHALMOLOGY

TJO

www.oftalmoloji.org

EDITORIAL

2021 Issue 2 at a Glance:

Esteemed colleagues,

This issue of our journal features 6 original studies, 1 review, and 5 case reports examining different topics.

Vitiligo is an acquired depigmentation disorder of the skin and mucous membranes that affects approximately 0.5-1% of the global population. The most accepted mechanism for the pathogenesis of diffuse vitiligo is the autoimmune theory, which implicates autoimmune-mediated destruction of melanocytes. Vitiligo patients exhibit retinal hypopigmentation, retinal pigment epithelium atrophy, and retinal electrophysiological dysfunction. Some studies have also demonstrated ocular surface changes and tear film abnormalities in vitiligo patients with periocular involvement. In their study titled "Dry Eye and Meibomian Glands in Vitiligo", Taheri et al. determined that vitiligo patients had lower Schirmer test and strip meniscometry values, while there was no difference in tear break-up time or meibomian gland loss measured by meibography. The authors concluded that vitiligo was associated with a decrease in aqueous tear film production but did not affect meibomian gland structure and function (see pages 70-74).

Keratoconus (KC) is a corneal disease characterized by non-inflammatory stromal thinning, corneal protrusion, and irregular astigmatism. There are studies in the literature suggesting that OCT can reveal macular changes in KC patients that are undetectable in slit-lamp examination. In a study by Özsaygılı and Yıldırım titled "The Relationship Between Keratoconus Stage and the Thickness of the Retinal Layers", measurements obtained by spectral domain optical coherence tomography were compared in 40 healthy eyes and 85 KC eyes according to disease stage. Measurements of the retinal nerve fiber layer, ganglion cell layer, inner plexiform layer, and outer plexiform layer did not differ between KC and healthy eyes. However, higher KC stage was associated with increased thickness of the inner nuclear layer, which contains neuroglial cell bodies, and reduced thickness of the outer retinal layers, especially the retinal pigment epithelium (see pages 75-82).

Low vision is defined as a distance visual acuity of less than 20/60 or a visual field of 20° or less in the better-seeing eye after refractive correction and if necessary, medical or surgical treatment. In their study titled "Comparison of Quality of Life Questionnaires in Patients with Low Vision", Şahlı and İdil assessed 64 low vision patients using the Low Vision Quality of Life Questionnaire (LVQOL) and the National Eye Institute Visual Function Questionnaire (NEI VFQ-25) and examined the compatibility between them. They found that total scores of the two questionnaires were strongly correlated and concluded that comparisons could be made between studies using these instruments, both of which have been validated in Turkish (see pages 83-88).

Gedar Totuk et al. share a study titled "Intense Pulsed Light Treatment for Moderate to Severe Acute Blepharitis or Blepharoconjunctivitis: A Retrospective Case Series", in which 11 patients underwent periocular intense pulsed light therapy and showed significant improvement in Ocular Surface Disease Index (OSDI) symptom score, lipid layer thickness, and meibography results 10 weeks later. There were greater than 50% reductions in scores in eyelid compression and ocular surface staining grading systems, and non-invasive tear film break-up time and tear meniscus height were also increased. The patients showed improvement in biomicroscopic signs of blepharitis or blepharoconjunctivitis and had no treatment-related adverse effects (see pages 89-94).

Kavadarlı and Mutlu surveyed 161 ophthalmologists in their study, "Effects of the COVID-19 Pandemic on Turkish Ophthalmologists." Half of the study group, which included mostly specialist ophthalmologists, stated that their weekly working hours were reduced, half were attending routine outpatient clinic appointments, 52.8% were working in COVID-19-related units, 67.1% continued emergency surgeries only, and 52% stated that the follow-up of patients with chronic eye disease was disrupted. Sixty-four percent of the ophthalmologists considered themselves in a high-risk group and 99% reported using a mask during examinations. Ninety-one percent of the respondents had high anxiety about the pandemic and the most common cause of concern (83%) was the risk of infecting family members (see pages 95-101).

Eales' disease is an idiopathic occlusive retinal vasculitis that usually occurs in young men and affects the peripheral retinal veins. The disease may present with periphlebitis with or without arthritis, peripheral capillary non-perfusion, retinal and disc neovascularization, retinal vein occlusion, vitreous hemorrhage, retinal detachment, and neovascular glaucoma. In an original study by Ersöz et al. titled "Vitrectomy Due to Vitreous Hemorrhage and Tractional Retinal Detachment Secondary to Eales' Disease", 22 eyes of 21 patients had a higher mean best corrected visual acuity (BCVA) after vitrectomy (BCVA increased in 72.7% of eyes). In multivariate linear regression analysis, final BCVA was negatively associated with preoperative or postoperative proliferative vitreoretinopathy stage C (PVR-C), preoperative detachment involving the macula, postoperative neovascular glaucoma, and longer

TURKISH JOURNAL OF OPHTHALMOLOGY

TJO

www.oftalmoloji.org

EDITORIAL

preoperative disease duration. The rate of primary anatomic success was 81.8% and the final anatomical success rate was reported as 90.9%. The authors concluded that in Eales' disease, good visual outcomes can be obtained with vitreoretinal surgery if the detachment area does not involve the macula and PVR-C does not develop preoperatively or postoperatively (see pages 102-106).

In the review selected for this issue, titled "Congenital Cataracts and Its Genetics: The Era of Next-Generation Sequencing", Şekeroğlu and Utine present a detailed overview of the literature on the epidemiology, etiology, classification, and genetics of congenital cataract, with particular focus on the role of next-generation sequencing (see pages 107-113).

In the first case report of this issue, titled "Cytarabine-Induced Corneal Toxicity: Clinical Features and Relief of Symptoms with Loteprednol Etabonate 0.5% in Two Patients'', Özcan and Uçakhan detected toxic keratopathy characterized by ocular discomfort, photophobia, blurred vision, and central corneal epithelial cysts in 2 patients who received high-dose cytarabine chemotherapy for acute myeloid leukemia. In vivo confocal microscopy revealed disseminated hyperreflective granular and irregular intraepithelial opacities concentrated in the basal epithelial layers. After 2-3 weeks of treatment with topical loteprednol etabonate 0.5%, both the symptoms and the epithelial microcysts on confocal microscopy had resolved (see pages 114-117).

A case report by Cespedes et al. titled "Utility of the Glabellar Flap in the Reconstruction of Medial Canthal Tumors after Mohs Surgery" presents two patients with basal cell carcinoma in the medial canthal region who underwent tumor excision by Mohs surgery followed by reconstruction with a glabellar flap alone in one case and glabellar and cheek advancement flaps in the other case (see pages 118-122).

In a case report titled "A Case of Multiple Optic Disc Pits: 21-Year Follow-up", Ceylan et al. discuss a 25-year-old female patient with partially accommodative esotropia and two optic disc pits in the right eye and one in the left eye with 21 years of follow-up fundus photographs, visual field, spectral-domain optical coherence tomography, and multifocal electroretinography examinations (see pages 123-126).

In a study by Nikandish and Saremi titled "ANCA-Negative Churg-Strauss Syndrome Presenting as Bilateral Central Retinal Artery Occlusion: A Case Report", a 42-year-old man with bilateral central retinal artery occlusion, visual acuity at the level of hand motions in the right eye and counting fingers in the left eye, and retinal whitening and cherry red spot on fundoscopy is presented. When eosinophilia was detected in addition to his right limb weakness, purpura on the right foot, and mononeuritis multiplex on electromyography, the patient was diagnosed as having Churg-Strauss syndrome according to the American College of Rheumatology diagnostic criteria and treatment with intravenous methylprednisolone 1 g/day for 3 days and cyclophosphamide was initiated. Although his systemic symptoms improved, there was no increase in visual acuity (see pages 127-130).

In the final case report, titled "Solar Retinopathy Presenting with Outer Retinal Defects Among Habitants of High Altitude", Sharma et al. described 3 patients living at high altitudes who presented during the winter months with visual field scotoma after a prolonged time in the sun. Tomography revealed discontinuity in the ellipsoid zone and outer retinal layer defects (see pages 131-133).

We hope that the articles selected for this issue will be interesting and enjoyable reading.

Respectfully on behalf of the Editorial Board,

Banu Bozkurt, MD

DOI: 10.4274/tjo.galenos.2020.78027
Turk J Ophthalmol 2021;51:70-74

Original Article

Dry Eye and Meibomian Glands in Vitiligo

Ahmad Reza Taheri*, Elahe Allahyari**, Borhan Haghi Rudi***, Malihe Nikandish***

*Mashhad University of Medical Sciences, Cutaneous Leishmaniasis Research Center, Mashhad, Iran
**Birjand University of Medical Sciences School of Health, Social Determinants of Health Research Center, Department of Epidemiology and Biostatistics, Birjand, Iran
***Birjand University of Medical Sciences Valiasr Hospital, Department of Ophthalmology, Birjand, Iran

Abstract

Objectives: To evaluate aqueous and lipid tear film parameters and the meibomian glands (MGs) with non-contact meibography in patients with vitiligo.

Materials and Methods: This case-control study was conducted in the right (OD) and left (OS) eyes of 43 patients with vitiligo and 43 controls in Birjand, Iran. In addition to demographic information and skin disease characteristics, the Ocular Surface Disease Index (OSDI) questionnaire was completed for each patient, followed by eye examinations including slit lamp examination, Schirmer test, strip meniscometry (SMTube), and tear break-up time (TBUT) measurement. The MGs were also imaged using a non-contact meibography system (SBM System, Italy). The data were analyzed using SPSS version 22.0 with a significant level of less than 0.05.

Results: Patients had higher OSDI score than controls but it was not significant (10.90±13.03 vs. 5.57±6.85; p=0.07). There were significant differences between the groups in mean Schirmer test values for both eyes (OD: 8.07±5.47 vs. 17.37±6.52; OS: 7.60±5.00 vs. 17.30±6.44, p<0.001) and mean SMTube results (OD: 4.49±2.40 vs. 9.74±3.67; OS: 4.30±2.81 vs. 9.65±4.52; p<0.001). However, mean TBUT did not differ between the groups (OD: 9.14±3.17 vs. 10.12±2.08, p=0.27; OS: 9.16±3.30 vs. 10.05±2.10, p=0.25). Meibography also showed no significant difference in MG dropout between the groups (OD: 20.86±9.79 vs. 21.05±12.07; p=0.74; OS: 18.16±8.83 vs. 19.53±10.30; p=0.51).

Conclusion: Vitiligo is associated with a reduction in the production of aqueous tear film, but does not affect the structure and function of the MGs.

Keywords: Vitiligo, dry eye, meibomian glands

Introduction

Vitiligo is an acquired depigmentation disorder of the skin and mucous membranes affecting approximately 0.5-1% of individuals worldwide. It is characterized by well-circumscribed white macules and patches that may appear at any age. Vitiligo can be divided into two major subgroups: non-segmental (NSV), which is more common and often symmetrical, and segmental (SV), which occurs in a unilateral distribution.[1] NSV is a multifactorial skin disorder with an immune-mediated melanocyte destructive mechanism. In contrast, SV is presumably a mosaic genetic skin disorder.[2]

The main hypotheses proposed for the pathogenesis of vitiligo are the autoimmune theory, the neural theory, and the cytotoxic theory. The autoimmune mechanism is believed to play a main role in the pathogenesis of NSV, while the neural mechanism has been implicated in SV. The autoimmune theory, which involves autoimmune-mediated destruction of melanocytes, is the most accepted mechanism for the pathogenesis of generalized vitiligo. The coexistence of vitiligo with several systemic and cutaneous

Address for Correspondence: Malihe Nikandish, Birjand University of Medical Sciences Valiasr Hospital, Department of Ophthalmology, Birjand, Iran
E-mail: malihenikandish@yahoo.com **ORCID-ID:** orcid.org/0000-0002-6180-637X
Received: 07.06.2020 **Accepted:** 23.07.2020

Cite this article as: Taheri AR, Allahyari E, Rudi BH, Nikandish M. Dry Eye and Meibomian Glands in Vitiligo. Turk J Ophthalmol 2021;51:70-74

autoimmune diseases supports this theory.[3] A cross-sectional study revealed that nearly 20% of patients with vitiligo had at least one comorbid autoimmune disease, with the most common being thyroid disease and alopecia areata.[4] The coexistence of vitiligo and Sjögren's syndrome, which includes dry eye as a diagnostic criterion, has also been reported.[5]

Melanocytes are present in other organs such as the eyes, ears, heart, and nervous system. As a result, these organ systems may be involved in pigmentation disorders. Vitiligo has been associated with systemic disorders such as Vogt-Koyanagi-Harada disease and Alezzandrini syndrome. Therefore, since the uveal tract and retinal epithelium are rich in melanocytes, it is not surprising that vitiligo has ocular comorbidities.[6]

Several studies have been conducted on the visual manifestations of vitiligo and have reported findings such as retinal hypopigmentation, retinal pigment epithelial atrophy, and impaired retinal electrophysiological function.[7] However, few studies have investigated ocular surface alterations and tear film abnormalities in people with vitiligo, particularly those with periocular involvement.[8]

Dry eye disease is one of the most common ocular morbidities, with as many as 4.3 million Americans older than 65 years affected to some degree. The impact of dry eye on quality of life was rated to be equivalent to unstable angina using utility assessments.[9] The meibomian glands (MGs) are large sebaceous glands located in the tarsal plates of the eyelids that secrete the lipid layer of the tear film, which plays a key role in retarding tear evaporation.[10] The assessment of MGs in various conditions such as dermatologic disorders has become a research topic since the recent introduction of infrared technology for MG imaging.

We hypothesize that tear film parameters worsen in vitiligo patients. Accordingly, we evaluated tear film parameters and MGs with non-contact meibography in vitiligo and compared these results with healthy individuals in the Iranian population.

Materials and Methods

Population and Study Design

This case-control study was conducted on both the right (OD) and left (OS) eyes of 43 patients with vitiligo and 43 controls in Birjand, Iran. The study protocol and examinations were reviewed and approved by the Ethics Committee of Birjand University of Medical Sciences (Ir.BUMS.REC.1396.302), and written informed consent was obtained from all subjects. Patients with vitiligo diagnosed clinically by a dermatologist (A.R.T.) were included. Subjects with a systemic or ocular disease, recent use of drugs affecting the lacrimal unit, or current use of contact lenses were excluded.

In addition to demographic information and skin disease characteristics, the Ocular Surface Disease Index (OSDI) questionnaire was completed for each patient. This was followed by eye examinations including slit lamp examination, tear break-up time (TBUT) measurement, Schirmer test, and strip meniscometry (SM) using the SMTube (Takagi Seiko Co., Nakano City, Japan). None of the patients used topical artificial tear drops within 2 hours before the examinations. The MGs were also imaged using BG-4M non-contact meibography system (SBM System, Turin, Italy). All ophthalmic examinations were done by the same ophthalmologist (M.N.).

Ocular Examinations

The OSDI questionnaire includes 12 questions related to experiences during the previous week, which are subdivided into 3 domains related to ocular symptoms, how these symptoms disturb visual function, and ocular reactions to environmental triggers. The OSDI is scored on a scale of 0 to 100, with higher scores demonstrating greater disability.[11]

TBUT was measured as the time (in seconds) between the last blink and the appearance of a dry spot in the fluorescein-stained tear film viewed under a cobalt blue filter. The mean of 3 measurements was recorded as the final result. Lower TBUT indicates tear film instability. Ten seconds or longer is considered normal. According to the study protocol, TBUT was performed first, followed by SM and Schirmer tests. A 30-min interval was applied between each examination to prevent disruption of the results.

In the Schirmer test, a strip is placed at the junction of the middle and lateral thirds of the lower eyelid and the length of tear wetting is measured in millimeters after 5 minutes.[11] We performed Schirmer test I without topical anesthesia.

SM is a promising new and non-invasive method that is expected to find application in the diagnosis and evaluation of treatment outcomes in dry eye patients.[12] The SMTube was shown to have acceptable sensitivity and specificity for assessing tear meniscus volume.[13]

Meibography is the visualization of the glands through trans-illumination of the eyelid with infrared light. The SBM System detects the length and width of MGs imaged by infrared meibography without requiring any input from the user. The images are then automatically classified. We performed lower eyelid meibography for the convenience and cooperation of patients (Figure 1 and 2).

Statistical Analysis

The collected data were entered into SPSS 22 software (IBM Corp, Armonk, NY, USA) and analyzed using appropriate statistical tests. The normality of distribution was assessed using the Shapiro-Wilk test. The Mann-Whitney U test was used to compare the means in non-normal distributions and independent t-test for normal distributions. Chi-square and Fisher's Exact tests were used to compare categorical data. Pearson correlation analysis was performed to evaluate the relationships between vitiligo duration and facial involvement and the patients' ocular parameters. The significance level was accepted as a p value less than 0.05.

Results

The mean age was 31.51±13.30 years in the vitiligo group and 33.23±12.46 years in the control group. In the group of patients with vitiligo, 10 (23.3%) were men and 33 (76.7%) were women, and the control group consisted of 17

men (39.5%) and 26 women (60.5%). The two groups were similar in age (p=0.47) and gender distribution (p=0.10). The mean duration of vitiligo was 7.26±5.03 years, and the mean involvement area was 11.70±9.49% of the total body surface area. There were 31 patients (72.1%) with facial involvement, 3 of whom had bilateral upper and lower eyelids lesions.

The results of ocular examinations are outlined in Table 1. Patients had higher OSDI score than controls but the difference was not significant (10.90±13.03 vs. 5.57±6.85; p=0.07). There were significant differences between mean Schirmer test (OD: 8.07±5.47 vs. 17.37±6.52 mm; OS: 7.60±5.00 vs. 17.30±6.44 mm; p<0.001) and SM results (OD: 4.49±2.40 vs. 9.74±3.67 mm; OS: 4.30±2.81 vs. 9.65±4.52 mm; p<0.001) in both eyes of the vitiligo and control groups. The mean TBUT of both eyes did not differ significantly between groups (OD: 9.14±3.17 vs. 10.12±2.08 s; p=0.27; OS: 9.16±3.30 vs. 10.05±2.10 s; p=0.25).

Meibography also showed no significant difference in MG atrophy rate between the groups (OD: 20.86±9.79% vs. 21.05±12.07%; p=0.74; OS: 18.16±8.83% vs. 19.53±10.30%; p=0.51).

Participants with OSDI higher than or equal to 13 and TBUT lower than 10 s were categorized as having dry eye. According to this new definition of dry eye, the prevalence of dry eye did not differ significantly between the vitiligo and control groups (11.6% vs. 9.3%, respectively; p=0.73). Finally, Pearson correlation test showed that facial involvement and disease duration had non-significant correlations with OSDI score, Schirmer test, SM, TBUT, and MG loss in the studied patients (Table 2).

Discussion

The concurrence of vitiligo and ocular abnormalities has been investigated in several studies, some of which have focused on ocular surface and dry eye evaluation in vitiligo. We employed Schirmer test and SM to assess the aqueous tear film and TBUT to evaluate tear film stability. In addition, we studied the structure of the MGs using SBM System.

Diagnosing dry eye presents many challenges to the medical practitioner due the absence of a gold standard protocol for diagnosis, the poor reliability of many common tests, and lack of well-defined cut-off values to distinguish disease from normal. The new definition of dry eye assigns an essential role to TBUT assessment in addition to the importance of visual impairment. According to the new definition, dry eye disease is diagnosed by the combination of symptoms (OSDI ≥13) and unstable tear film (TBUT <10 s).[14]

In this study, we observed that patients with vitiligo might have reduced production of aqueous tear film; however, there

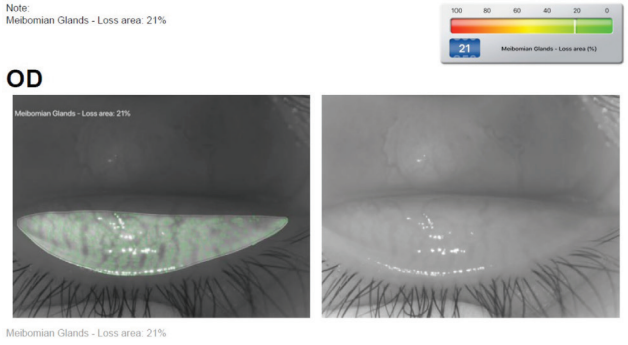

Figure 1. Meibography imaging of the right lower lid using SBM System in a normal control that shows minimal loss (21%) of meibomian glands

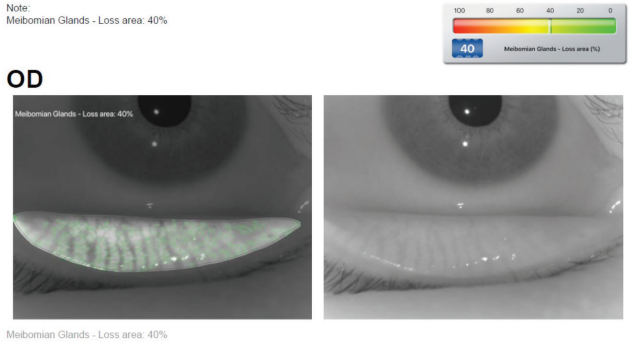

Figure 2. Meibography imaging of the right lower lid using SBM System that shows meibomian gland atrophy and dropout (40% loss) in a patient with vitiligo

Table 1. Dry eye parameters and meibography results of the groups

	Control group		Vitiligo group		p-value
	Mean ± SD	Range (min-max)	Mean ± SD	Range (min-max)	
OSDI score	10.90±13.03	52.08 (0-52.08)	5.57±6.85	29.17 (0-29.17)	0.07
Schirmer test (mm)	OD: 17.37±6.52 OS: 17.30±6.44	22 (5-27) 24 (6-30)	OD: 8.07±5.47 OS: 7.60±5.00	26 (0-26) 25 (0-25)	<0.001* <0.001*
SM (mm)	OD: 9.74±3.67 OS: 9.65±4.52	12 (3-15) 17 (3-20)	OD: 4.49±2.40 OS: 4.30±2.81	12 (1-13) 14 (2-16)	<0.001* <0.001*
TBUT (s)	OD: 10.12±2.08 OS: 10.05±2.10	11 (4-15) 11 (4-15)	OD: 9.14±3.17 OS: 9.16±3.30	13 (2-15) 13 (2-15)	0.27 0.25
MG loss (%)	OD: 21.05±12.07 OS: 19.53±10.30	64 (4-68) 48 (3-51)	OD: 20.86±9.79 OS: 18.16±8.83	37 (4-41) 30 (4-34)	0.74 0.51#

OSDI: Ocular Surface Disease Index, SM: Strip meniscometry, TBUT: Tear film break-up time, MG: Meibomian gland, SD: Standard deviation, *Mann-Whitney U test, #Independent t-test

Table 2. Association of vitiligo facial involvement and disease duration with OSDI score, Schirmer test, SM, TBUT, and MG loss, presented as Pearson correlation coefficients followed by p-values in parentheses

	OSDI score	Schirmer test		SM		TBUT		MG loss	
		OD	OS	OD	OS	OD	OS	OD	OS
Facial involvement	0.28 (0.07)	-0.26 (0.09)	-0.18 (0.25)	-0.13 (0.43)	-0.15 (0.34)	0.23 (0.14)	0.22 (0.16)	-0.19 (0.23)	-0.10 (0.53)
Disease duration	-0.11 (0.48)	-0.10 (0.51)	-0.09 (0.56)	0.14 (0.37)	0.05 (0.73)	-0.03 (0.84)	0.003 (0.98)	-0.13 (0.42)	0.01 (0.94)

OSDI: Ocular Surface Disease Index, SM: Strip meniscometry, TBUT: Tear film break-up time, MG: Meibomian gland

was no significant difference between patients and controls according to the new dry eye diagnostic criteria. This result is reasonable considering the key role of OSDI and TBUT in the new definition of dry eye and the lack of a significant association between these parameters and vitiligo in our study.

Studies investigating tear film parameters in vitiligo have yielded different and sometimes contradictory results. Karadag et al.[15] evaluated only Schirmer test as a tear film parameter in vitiligo and similarly showed a statistically significant difference between the vitiligo and control groups.

Güngör et al.[16] investigated TBUT and Schirmer test in 34 patients with different types of vitiligo. They found that the Schirmer test values in patients with vitiligo were insignificantly lower than those in the control subjects. However, the TBUT values of patients with vitiligo were significantly lower. A study by Dogan et al.[17] showed higher OSDI score, shorter TBUT, and shorter Schirmer test distance in vitiligo patients but the results were not statistically significant. Recently, Erdur et al.[18] evaluated ocular surface and tear film parameters in vitiligo patients with and without periocular involvement and compared them with controls. They showed that patients with vitiligo had higher OSDI score, lower TBUT, and higher tear osmolality, but there was no significant difference in Schirmer test and ocular surface staining between the groups. Moreover, they concluded that ocular involvement was associated with higher tear osmolarity values. The results of these studies were inconsistent with our results. However, we also performed SM, a novel test for tear production assessment, which showed significantly lower tear meniscus volume in vitiligo.

Palamar et al.[19] reported that OSDI score was higher while mean TBUT and Schirmer values were lower in vitiligo. The latter finding is similar to our results. To our knowledge, that is the only study investigating MG morphology in vitiligo patients. They showed significant differences in MG morphology in patients with vitiligo when compared to those without vitiligo. They evaluated the upper and lower eyelids using infrared biomicroscope images (Topcon, SL-D701, IJssel, Netherlands) and their morphologic results contradict our findings. Notably, we examined only the lower eyelid and employed a different device (SBM System, Turin, Italy), and the sample size in our study was twice as large. The mean extent of MG atrophy in the eyes of our vitiligo patients was greater than in the control group but the difference was not statistically significant.

Facial involvement in vitiligo might affect the eye, but this issue is more significant in patients with eyelid lesions. The association of periocular involvement with ophthalmic parameters was not assessed in this study due to small number of patients with eyelid lesions.

Study Limitations

The limitations of this study were a small sample size and lack of more comprehensive ocular surface investigations. Moreover, our meibography findings were limited to the lower eyelids. Despite these limitations, we believe that this study has the potential to guide future studies.

Conclusion

Vitiligo is associated with a reduction in the production of aqueous tear film, but does not affect MG structure and function.

Acknowledgements

The authors would like to thank the Clinical Research Development Unit of Valiasr Hospital (Birjand University of Medical Sciences), Ghaem Hospital, and the Research Chancellor (Mashhad University of Medical Sciences) for their support, cooperation, and assistance throughout the study. The authors would also like to thank Mahbube Haghi Rudi, Mostafa Zeinaly, Hakimeh Malaki-moghadam, and Nasrin Javan for their invaluable contributions to the study.

Ethics

Ethics Committee Approval: The study protocol and examinations were reviewed and approved by the Ethics Committee of Birjand University of Medical Sciences (Ir.BUMS.REC.1396.302).

Informed Consent: Obtained.

Peer-review: Externally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: A.R.T., B.H.R., M.N., Concept: A.R.T., E.A., B.H.R., M.N., Design: A.R.T., E.A., B.H.R., M.N., Data Collection or Processing: A.R.T., E.A., B.H.R., M.N., Analysis or Interpretation: A.R.T., E.A., B.H.R., M.N., Literature Search: A.R.T., E.A., B.H.R., M.N., Writing: A.R.T., E.A., B.H.R., M.N.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: This work was supported by the Research Chancellor of Birjand University of Medical Sciences [grant numbers 455461].

References

1. Alikhan A, Felsten LM, Daly M, Petronic-Rosic V. Vitiligo: a comprehensive overview Part I. Introduction, epidemiology, quality of life, diagnosis,

differential diagnosis, associations, histopathology, etiology, and work-up. J Am Acad Dermatol. 2011;65:473-491.
2. Speeckaert R, van Geel N. Vitiligo: An Update on Pathophysiology and Treatment Options. Am J Clin Dermatol. 2017;18:733-744.
3. Dahir AM, Thomsen SF. Comorbidities in vitiligo: comprehensive review. Int J Dermatol. 2018;57:1157-1164.
4. Gill L, Zarbo A, Isedeh P, Jacobsen G, Lim HW, Hamzavi I. Comorbid autoimmune diseases in patients with vitiligo: A cross-sectional study. J Am Acad Dermatol. 2016;74:295-302.
5. Montes LF, Pfister R, Elizalde F, Wilborn W. Association of vitiligo with Sjögren's syndrome. Acta Derm Venereol. 2003;83:293.
6. Ahluwalia J, Correa-Selm LM, Rao BK. Vitiligo: Not Simply a Skin Disease. Skinmed. 2017;15:125-127.
7. Shoeibi N, Taheri AR, Nikandish M, Omidtabrizi A, Khosravi N. Electrophysiologic evaluation of retinal function in patients with psoriasis and vitiligo. Doc Ophthalmol. 2014;128:131-136.
8. Serin D, Buttanri IB, Parlak AH, Boran C, Tirak E. Impression cytology of the ocular surface and tear function in patients with periocular vitiligo. Eur J Ophthalmol. 2012;22:734-738.
9. Schiffman RM, Walt JG, Jacobsen G, Doyle JJ, Lebovics G, Sumner W. Utility assessment among patients with dry eye disease. Ophthalmology. 2003;110:1412-1419.
10. Yin Y, Gong L. The quantitative measuring method of meibomian gland vagueness and diagnostic efficacy of meibomian gland index combination. Acta Ophthalmol. 2019;97:403-409.
11. Mian SI, Dougherty Wood S. Diagnostic Tools for Dry Eye Disease. European Ophthalmic Review. 2016;10:101.
12. Dogru M, Ishida K, Matsumoto Y, Goto E, Ishioka M, Kojima T, Goto T, Saeki M, Tsubota K. Strip meniscometry: a new and simple method of tear meniscus evaluation. Invest Ophthalmol Vis Sci. 2006;47:1895-1901.
13. Ibrahim OM, Dogru M, Ward SK, Matsumoto Y, Wakamatsu TH, Ishida K, Tsuyama A, Kojima T, Shimazaki J, Tsubota K. The efficacy, sensitivity, and specificity of strip meniscometry in conjunction with tear function tests in the assessment of tear meniscus. Invest Ophthalmol Vis Sci. 2011;52:2194-2198.
14. Craig JP, Nelson JD, Azar DT, Belmonte C, Bron AJ, Chauhan SK, de Paiva CS, Gomes JAP, Hammitt KM, Jones L, Nichols JJ, Nichols KK, Novack GD, Stapleton FJ, Willcox MDP, Wolffsohn JS, Sullivan DA. TFOS DEWS II Report Executive Summary. Ocul Surf. 2017;15:802-812.
15. Karadag R, Esmer O, Karadag AS, Bilgili SG, Cakici O, Demircan YT, Bayramlar H. Evaluation of ocular findings in patients with vitiligo. Int J Dermatol. 2016;55:351-355.
16. Güngör Ş, Nurözler A, Akbay G, Ekşioğlu M. Tear functions in patients with vitiligo. Int J Dermatol. 2015;54:466-468.
17. Dogan AS, Atacan D, Durmazlar SP, Acar M, Gurdal C. Evaluation of dry eye findings in patients with vitiligo. Pak J Med Sci. 2015;31:587-591.
18. Erdur SK, Aydin R, Balevi A, Ozsutcu M, Kocabora MS. Dry Eye Assessment in Patients With Vitiligo. Cornea. 2018;37:412-415.
19. Palamar M, Kiyat P, Ertam I, Yagci A. Evaluation of dry eye and meibomian gland dysfunction with meibography in vitiligo. Eye (Lond). 2017;31:1074-1077.

DOI: 10.4274/tjo.galenos.2020.84748
Turk J Ophthalmol 2021;51:75-82

Original Article

The Relationship Between Keratoconus Stage and the Thickness of the Retinal Layers

Cemal Özsaygılı, Yener Yıldırım

Kayseri City Hospital, Clinic of Ophthalmology, Kayseri, Turkey

Abstract

Objectives: To examine the relationship between keratoconus (KC) stage and the thickness of the retinal layers.

Materials and Methods: Retinal layer thicknesses were compared between 85 eyes of 85 KC patients and 40 eyes of 40 controls similar in age, sex, and axial length. KC patients were staged as stage 1, 2, or 3 according to the Amsler-Krumeich staging system, and segmentation of the retinal layers was performed with spectral domain optical coherence tomography automatic segmentation program. The thickness of the retinal nerve fiber layer (RNFL), ganglion cell layer (GCL), inner plexiform layer (IPL), inner nuclear layer (INL), outer plexiform layer (OPL), outer nuclear layer (ONL), and retinal pigment epithelium (RPE) in the central 1 mm Early Treatment Diabetic Retinopathy Study subfield was analyzed.

Results: There was no significant difference between the control and KC groups in the segmentation of the RNFL, GCL, IPL, or OPL (p=0.306; p=0.661; p=0.893, p=0.664, respectively). The INL differed significantly between control and stage 2 KC, control and stage 3 KC, stage 1 and 2 KC, and stage 2 and 3 KC, increasing in thickness with higher stage (p=0.004; p=0.005: p=0.001; p=0.002, respectively). The RPE also differed significantly between control and stage 2 KC, control and stage 3 KC, stage 1 and 2 KC, and stage 2 and 3 KC, showing decreased thickness with higher stage (p=0.03; p=0.001; p=0.001; p<0.001, respectively). The ONL also thinned as stage increased, but the results were not statistically significant (p=0.051).

Conclusion: More advanced KC stage was associated with increased thickness of the INL layer, where the neuroglial cell bodies are located, and decreased thickness in the outer retinal layers, especially the RPE.

Keywords: Keratoconus, oxidative stress, optical coherence tomography, retinal layer thickness

Introduction

Keratoconus (KC) is a generally bilateral but asymmetrical corneal disease characterized by non-inflammatory stromal thinning, corneal protrusion, and irregular astigmatism.[1] The prevalence of KC is estimated to be 86 per 100,000 population. Although it can occur in all age groups, it is more common between the ages of 10 and 20 years.[2] KC can reduce visual acuity (VA) and quality to varying degrees depending on disease stage. VA can be improved with spectacles in the early stages of KC, whereas rigid gas-permeable contact lenses or corneal transplantation may be required to compensate for anterior corneal surface irregularity in the advanced stages.[3]

The current software of optical coherence tomography (OCT) imaging devices enables the objective measurement of macular thickness changes. These changes are helpful in the diagnosis and follow-up of various diseases such as diabetic retinopathy, macular degeneration, and retinal vascular occlusion.[4,5] OCT imaging can now be used to investigate the presence of accompanying macular pathologies, not only in posterior segment pathologies, but also in other ocular problems related to the anterior segment, such as myopia or KC. While there are studies in the literature

Address for Correspondence: Cemal Özsaygılı, Kayseri City Hospital, Clinic of Ophthalmology, Kayseri, Turkey
E-mail: cemalozsaygili@hotmail.com **ORCID-ID:** orcid.org/0000-0002-8236-1728
Received: 22.02.2020 **Accepted:** 27.07.2020

Cite this article as: Özsaygılı C, Yıldırım Y. The Relationship Between Keratoconus Stage and the Thickness of the Retinal Layers. Turk J Ophthalmol 2021;51:75-82

showing that mean macular thickness did not change with refractive error,[6,7] others showed that mean macular volume and thickness decreased with higher myopia.[8] There are also a few studies in the literature on OCT imaging in patients with KC. Moschos et al.[9] reported that patients with KC may have macular changes undetectable by biomicroscopy. Another study showed that mean thickness in the central fovea, inner macula, and outer macula was significantly greater in patients with KC compared to a control group.[10] However, this study did not investigate the relationship between KC stage and thicknesses of the fovea or the individual retinal layers, or determine which retinal layer was responsible for the increase in thickness.

The present study aimed to evaluate whether macular layer segmentation differs in healthy volunteers and patients with KC and to evaluate the relationship between KC stage and retinal layer thicknesses.

Materials and Methods

Study Design

This observational clinical study was conducted in the Corneal and Retinal Units of the Kayseri Training and Research Hospital Ophthalmology Clinic in accordance with the principles of the Declaration of Helsinki after obtaining ethics committee approval (decision no: 00106647458). All participants were informed about the study and provided their written informed consent. The study included patients diagnosed with KC in our clinic and individuals without KC who presented to the outpatient clinic between January 2019 and December 2019.

All participants underwent a thorough ophthalmological examination including manifest refraction measurement, VA evaluated with Snellen chart, slit-lamp biomicroscopy and anterior segment evaluation, intraocular pressure measurement, and dilated fundus examination. Corneal topography (Pentacam TM, Oculus Inc., Lynnwood, WA, USA) was used to diagnose and stage KC, spectral domain-OCT (SD-OCT) (Spectralis, Heidelberg Engineering, Inc., Heidelberg, Germany) was used to obtain segmentation of the macular layers, and non-contact partial coherence interferometry (IOL Master, Zeiss, Jena, Germany) was used to measure axial length. KC patients were classified as stage 1, stage 2, or stage 3 according to the Amsler-Krumeich Classification.[11]

Of the patients with KC confirmed by clinical examination and corneal topography in at least one eye and the healthy controls, those with complete ophthalmological examination records including axial length measurement, corneal topography, and SD-OCT imaging were included in the study. Topographic findings in favor of KC were the presence of focal steepening greater than 47 diopters (D) and more than 1.4 D asymmetry between the midperipheral and inferior/superior corneal regions on the topographic map.[12] Exclusion criteria included the presence of non-KC corneal pathology such as corneal degeneration and keratectasia in either eye, any retinal pathology such as age-related macular degeneration or retinal vascular occlusion, age less than 18 or over 40 years, myopia greater than -6 diopters, axial length longer than 26 mm, any systemic disease, and optic nerve diseases (optic neuritis, optic atrophy). In addition, patients with severe corneal problems (e.g., corneal scarring, previous corneal surgery) that precluded SD-OCT or Pentacam imaging and participants with vitreoretinal interface pathology (e.g., vitreoretinal traction, retinoschisis, epiretinal membrane, and lamellar macular hole) that could affect segmentation in SD-OCT scans were excluded from the study. Patients who had undergone corneal cross-linking (CXL) were also excluded due to its potential effects on the retinal layers. Therefore, 2 patients with inadequate image quality due to advanced KC, 21 patients with history of CXL, 5 patients with myopia greater than -6 diopters, 1 patient with collagen tissue disease, and 4 patients younger than 18 years of age were excluded from the study.

Corneal Topography and Screening Analysis

A Pentacam corneal topographer was used to evaluate anterior segment parameters. All images were acquired by an experienced nurse (G.C.) at the same time of day (between 9 and 10 a.m.) and evaluated by an experienced refractive surgeon (Y.Y.).

All participants were screened with the SD-OCT Fast Macular Thickness program to show the macular structure and analyze the thickness of the individual retinal layers. Signal-to-noise ratio was maximized using automatic real-time averaging mode. OCT image was classified according to signal strength ranging from 0 (low-quality image) to 40 (high-quality image) and patients with SD-OCT image quality lower than 20 were excluded from the study. One eye of each KC patient was randomly selected using randomization software (http://random-allocation-software.software.informer.com/2.0/) for comparison with the right eyes of the healthy controls. All OCT scans were performed by the same experienced nurse (S.E.) at the same time of day and the automated OCT segmentation (Segmentation Technology; Heidelberg Engineering, Inc) was validated by an experienced retinal specialist (C.O.). After imaging, all images were checked to ensure that the foveal depression was evident in the center of the scan. The segmentation application automatically divided the retina into 7 separate layers with a single horizontal foveal scan of the retinal layers and calculated the average thickness of each layer. Patients with severe corneal distortions due to advanced KC were advised to wear contact lenses during image acquisition; images that were not suitable despite this were not included in the analysis. The mean thickness values of the retinal nerve fiber layer (RNFL), ganglion cell layer (GCL), inner plexiform layer (IPL), inner nuclear layer (INL), outer plexiform layer (OPL), outer nuclear layer (ONL), and retinal pigment epithelium (RPE) within the central 1 mm Early Treatment Diabetic Retinopathy Study subregion as determined by automatic segmentation were analyzed.

Outcome Measures

The primary outcome measures were differences in retinal layer thicknesses in the central macular region between patients with KC and healthy volunteers. The secondary outcome

measures were correlations between keratometric and clinical values and retinal layer thickness.

Statistical Analysis

All analyses were performed using SPSS version 22.0 for Windows software package (IBM Corp, Armonk, NY). Distribution of the variables was assessed using Kolmogorov-Smirnov test. Descriptive data were expressed as mean ± standard deviation (SD). Analysis of variance (ANOVA) was used for parametric data and Kruskal-Wallis H test for non-parametric data. Spearman correlation analysis was performed to evaluate relationships between non-parametric variables and Pearson correlation analysis for parametric variables. Chi-square test was used to analyze quantitative data. P values less than 0.05 were accepted as statistically significant.

Results

Participant Characteristics

This study included 85 eyes of 85 KC patients and 40 eyes of 40 non-KC controls. The mean age of the control group was 26.25±7.14 years and the female/male distribution was 21/19. According to the Amsler-Krumeich staging system, there were 40 stage 1 KC patients (mean age: 27.32±7.43, female/male distribution: 14/26), 27 stage 2 KC patients (mean age: 28.18±8.25, female/male distribution: 14/13), and 18 stage 3 KC patients (mean age: 29.94±10.34, female/male distribution: 9/9). The groups had statistically similar demographic characteristics, axial length values, and SD-OCT image quality scores. The demographic and descriptive data of the groups are shown in Table 1.

Retinal Segmentation Results

Table 2 shows the comparison of retinal segmentation results between the groups. There were no significant differences in RNFL, GCL, IPL, or OPL between the control and KC groups (p=0.306; p=0.661; p=0.893; p=0.664, respectively). INL thickness increased with higher KC stage and differed significantly between the control and stage 2 KC groups (p=0.004), control and stage 3 KC groups (p=0.005), stage 1 and 2 KC groups (p=0.001), and stage 1 and 3 KC groups (p=0.002) (Figure 1a, b).

RPE thickness decreased with higher KC stage and differed significantly between the control and stage 2 KC groups (p=0.03), control and stage 3 KC groups (p=0.001), stage 1 and 2 KC groups (p=0.001), and stage 1 and 3 KC groups (p<0.001) (Figure 2a,b).

Mean thickness of the ONL also showed a marked decrease as KC stage increased, but the result narrowly missed statistical significance (p=0.051).

Correlation Analysis

Correlation analysis was performed between all retinal layers and mean keratometric value (Kmean), maximum keratometric value (Kmax), thinnest corneal thickness, topographic cylinder, axial length, age, and gender (Table 3). Kmean was positively correlated with INL thickness (r=0.305, p=0.001) and negatively correlated with RPE thickness (r=-0.386, p<0.001).

Topographic cylinder also correlated positively with INL thickness (r=0.244, p=0.006) and negatively with RPE thickness (r=-0.270, p=0.002).

Similar correlations were detected in the analysis of relationships between Kmax and retinal layer thicknesses. There were no significant correlations between the retinal layers and age, axial length, or thinnest corneal thickness values.

Discussion

KC is a degenerative corneal disorder characterized by defects in Bowman's layer and ectasia associated with iron deposits in the form of Fleischer rings in the epithelial basal membrane.[13] Environmental, genetic, and mechanical factors such as oxidative ultraviolet (UV) radiation, genetic susceptibility, contact lens use, atopy, and eye rubbing play an important role in the pathogenesis and progression of KC.[14,15] Compared to normal corneal specimens, human corneas with KC were found to have high levels of nitrotyrosine, a marker of superoxide and peroxynitrite production, and increased endothelial nitric oxide synthesis (eNOS) at sites of breaks in Bowman's layer.[16] The formation of increased reactive oxygen species (ROS) leads to oxidative stress, resulting in mitochondrial DNA (mtDNA) degradation in KC corneas.[14] In KC corneas, increased mtDNA damage affects the protein-encoding mtDNA regions

Table 1. Demographic and descriptive data

	Control n=40	Stage 1 n=40	Stage 2 n=27	Stage 3 n=18	P
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	
Age (years)	26.25±7.14	27.32±7.43	28.18±8.25	29.94±10.34	0.592
Axial length (mm)*	23.72±1.02	23.34±0.61	23.66±0.65	23.48±0.85	0.581
Kmean (diopters)	43.74±1.56	44.77±1.70	49.47±1.18	54.49±2.79	<0.001
Thinnest corneal thickness (µm)*	525.85±37.21	450.17±69.33	421.81±60.89	387.16±55.03	<0.001
Topographic cylinder (diopters)	1.20±0.77	2.71±1.54	3.68±1.98	5.98±3.13	<0.001
Sex (M/F)α	19/21	26/14	13/14	9/9	0.376
Image quality score	25.61±3.52	24.80±2.29	23.72±2.53	22.91±1.37	0.310

Kmean: Mean keratometry value, M: Male, F: Female; Kruskal-Wallis Test, *One-way ANOVA, αChi-square test

and disrupts mitochondrial oxidative phosphorylation, thereby causing deviations in the expression of oxidative phosphorylation proteins, incorrect ATP synthesis, increased ROS formation, and more oxidative damage. Reduced antioxidant defenses in KC corneas also result in keratocyte apoptosis and adverse changes in the extracellular matrix, leading to corneal thinning and deformation. In addition to accelerating keratocyte apoptosis in the anterior segment, oxidative stress may also have important effects on the lens tissue and the retina in the posterior segment.[17]

Oxidative stress in the lens tissue occurs not only due to oxidant-antioxidant imbalance but also as the result of an imbalanced redox state in the lens epithelial cells. Lens

Table 2. Retinal segmentation results of the control group and the KC group according to stage

	Control n=40[a]	Stage 1 n=40[b]	Stage 2 n=27[c]	Stage 3 n=18[d]	p
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	
Total retina (µm)*	271.17±22.19	265.55±23.66	273.11±23.92	270.77±29.24	0.615
RNFL (µm)	12.87±2.31	12.12±2.30	13.48±3.27	12.77±4.03	0.306
GCL (µm)	17.37±8.45	15.72±6.56	17.14±6.59	16.27±7.62	0.661
IPL (µm)	21.10±5.02	20.15±3.86	20.81±4.50	20.44±5.57	0.893
INL (µm)	19.07±5.65	18.37±5.85	23.11±6.06	25.50±9.19	**<0.001**
OPL (µm)	26.60±8.07	25.62±6.78	27.59±6.19	27.88±9.13	0.664
ONL (µm)*	86.85±10.10	86.80±11.87	78.50±12.22	77.52±17.59	0.051
RPE (µm)	16.95±1.86	17.70±2.51	15.85±1.83	15.11±1.87	**<0.001**

RNFL: Retinal nerve fiber layer, GCL: Ganglion cell layer, IPL: Inner plexiform layer, INL: Inner nuclear layer, OPL: Outer plexiform layer, ONL: Outer nuclear layer, RPE: Retinal pigment epithelium; Kruskal-Wallis Test, *One-way ANOVA; INL p: [a-c]: 0.004, [a-d]: 0.005, [b-c]: 0.001, [b-d]: 0.002, RPE p: [a-c]: 0.030, [a-d]: 0.001, [b-c]: 0.001, [b-d]: <0.001

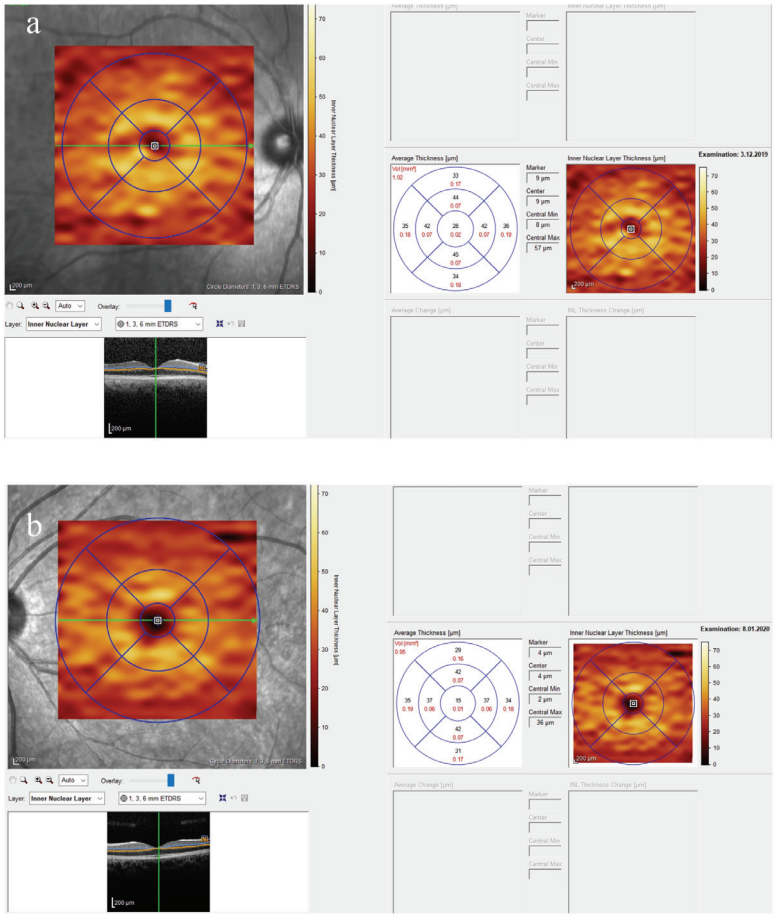

Figure 1. Automatic segmentation showing that the inner nuclear layer tends to be thicker in a patient with advanced keratoconus (a) compared to the control group (b)

epithelial cells contain abundant mitochondria, consume 90% of the oxygen entering the lens, are major sources of endogenous ROS, converting 1-5% of uptaken oxygen into ROS, and their oxidative damage plays an important role in cataractogenesis.[18] Therefore, the mitochondrial dysfunction and ROS imbalance that can be present in patients with KC may also play a role in the pathogenesis of cataract development by inducing oxidative damage of cellular components.

ROS reduces levels of brain-induced neurotrophic factor (BDNF), which regulates axonal growth, synaptic activity, and neuron survival. Synaptic transmitter damage and neurotrophic factor inhibition by excessive ROS levels lead to neuronal apoptosis, visual impairment, and impaired vision quality.[19] It has been reported that central macular thickness showed no difference between pediatric KC patients and a control group.[20] However, the thickness of the individual retinal layers was not evaluated, and no detailed study to determine whether retinal layer segmentation differs in adult KC patients compared to a control group has been conducted to date. Uzunel et al.[21] evaluated peripapillary RNFL measurement, ganglion cell analysis, and total macular thickness and reported that all parameters decreased compared to the control group as KC stage increased. However, they did not analyze the individual retinal layers in the central macular area. Cankaya et al.[22] similarly reported that RNFL thickness values were more comparable than optic nerve head parameters. The present study also aimed to investigate whether factors involved in the pathogenesis and progression of KC lead to posterior segment changes in addition to problems affecting the anterior segment. Müller cells provide architectural support to the retina and are known to play a key role in the retinal physiology. However, macroglia stimulated by oxidative stress indirectly contribute to retinal excitotoxicity by increasing glial fibrillary acidic

Table 3. Correlation analysis

	r	p
Kmean		
INL	0.305	0.001
RPE	-0.386	<0.001
Topographic cylinder		
INL	0.244	0.006
RPE	-0.270	0.002

Kmean: Mean keratometry value, INL: Inner nuclear layer, RPE: Retinal pigment epithelium

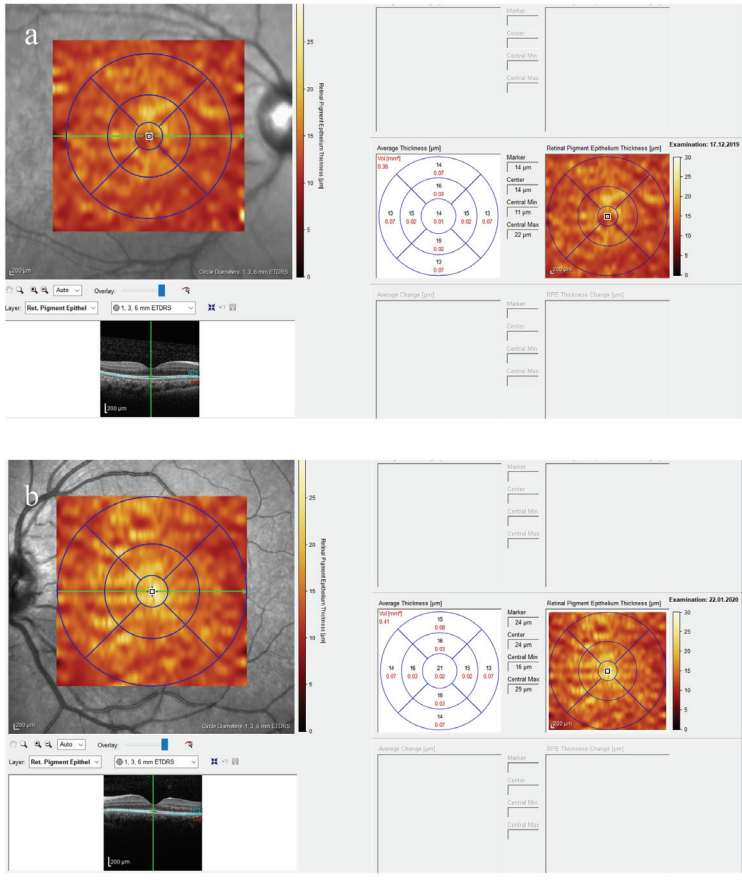

Figure 2. Automatic segmentation showing that the retinal pigment epithelium layer tends to be thinner in a patient with advanced keratoconus (a) compared to the control group (b)

protein expression, nitric oxide production, and glutamate synthesis.[23] The INL is known to contain Müller cells, bipolar cells, and the bodies of horizontal and amacrine cells. We believe that the increase in INL thickness with more advanced KC stage observed in the present study is likely due to the response from Müller cells that are present in higher numbers and activated as a result of increased oxidative stress. To the best of our knowledge, there are no previous reports on this subject in the literature.

Increased ROS levels and reduced antioxidant cell defense systems cause damage to photoreceptors and RPE cells through apoptosis.[24] As KC progresses, it can be expected that the adverse effects on the outer retinal layers will also increase, because these layers are more susceptible to UV radiation and blue light, which are involved in the pathogenesis and progression of KC. As the cell membranes of photoreceptors are rich in polyunsaturated fatty acids that are easily oxidized, this is one of the reasons why they are more susceptible to oxidative damage. In our study, we observed that the ONL, which comprises the nuclei of photoreceptor cells, thinned as KC stage advanced. However, the difference did not reach statistical significance, probably due to the small number of patients. Photoreceptors are cells that have high metabolic activity and high oxygen and nutrient demand. Due to their high oxygen consumption, any mitochondrial dysfunction results in a high rate of ROS production. Photoreceptors and RPE cells, which are postmitotic cells with high metabolic activity, show a reduction in number and thickness in the presence of increased oxidative stress.[25] In the present study, we observed significant thinning of the RPE layer in eyes with KC compared to the control group and in the advanced stages of KC. We believe that this difference between groups with similar central macular thickness is also clinically significant.

When examining retinal layer thickness in patients with KC, other common factors besides the oxidative stress mechanism that could affect the anterior and posterior ocular structures should also be investigated. KC is a complex, multifactorial pathology whose etiology involves both genetic and environmental factors. Currently, genetic risk factors that may play a role in the development of KC are mostly being investigated by analyzing genes identified as important in other complex eye diseases. In a genotyping study of DNA extracted from the blood or saliva samples of 248 KC and 366 control patients, single nucleotide polymorphisms in two gene loci that have been implicated in AMD, rs6795735 (*ADAMTS9*) and rs5749482 (*TIMP3*), were significantly associated with KC and were reported to potentially play a role in the pathogenesis of KC.[26] Another study reported that these two genes encoded enzymes involved in proteoglycan and extracellular matrix metabolism and were expressed at a lower rate in KC patients compared to the control group.[27] Determining the relationship between this genetic relationship and the RPE layer thinning observed in this study, especially in patients with advanced KC, and whether it causes a clinical predisposition to atrophy at a younger age than expected remains to be clarified in future studies.

When conducting retinal layer segmentation, it is also necessary to evaluate for distortions and artifacts that may lead to possible errors. Increasing astigmatism as KC progresses can lead to artifacts in different parts of the retina. Langenbucher et al.[28] reported that high astigmatism may lead to changes in peripapillary RNFL measurements due to elliptical distortion of the retinal image in different quadrants and that image size may vary according to meridian. They also stated that increased scanning distance from the optic disc could affect RNFL measurements around the optic disc head. Similarly, Hwang et al.[29] reported that RNFL measurements in the superior/inferior peripapillary regions and those obtained from the nasal/temporal areas may be affected differently. Leonard et al.[30] investigated objective scattering index and retinal image quality in KC patients using point spread function analysis. They reported that image quality was close to normal in mild to moderate KC patients, while in advanced KC the retinal image could assume an ellipsoid shape, resulting in lower image quality. The authors concluded that the use of this objective analysis in the clinic may be effective in the early diagnosis of patients with KC and in treatment decision-making during preoperative management.[30] As mentioned above, Uzunel et al.[21] reported that peripapillary RNFL measurements decreased as KC stage advanced, but their study did not include macular measurements. Similarly, Cankaya et al.[22] reported that RNFL thickness measurements obtained by OCT in KC and normal individuals were more comparable than optic nerve head parameters obtained by scanner laser ophthalmoscope. Furthermore, other studies in the literature suggested that astigmatism had no significant effect on macular thickness measurements.[31,32] Finally, in a meta-analysis examining the reliability of retinal layer thickness measurements performed with different OCT devices in patients with different demographic characteristics (e.g., refractive error, age), it was reported that segmentation measurements obtained within the central 6 mm zone were highly reliable and that the OCT devices could be used in clinical research.[33] Based on this information, we believe that a possible artifact would not significantly affect the results of our automatic segmentation of the central macular region in a similar meridian.

Another important parameter to keep in mind when evaluating the retinal layers is axial length. Studies evaluating the effect of axial length on macular layer analysis have yielded different results. In some of these studies, macular thickness parameters measured by OCT were reported to decrease with increased axial length.[34,35] Xie et al.[35] reported that the mean macular thickness was significantly thinner in the myopia group compared to the emmetropia group. Lim et al.[7] reported that the mean macular thickness did not change with myopia, while the parafovea was thinner and the fovea was thicker. Choi et al.[36] reported that longer axial length was associated with increased foveal thickness. In our study, the similarity between the groups in terms of other clinical parameters such as axial length, age, and sex ensured that the potential effects on the retinal layers were also similar.

There are also studies in the literature examining the relationship between KC and other posterior ocular structures. Akkaya and Küçük[37] found that the lamina cribrosa was significantly thinner in patients with KC compared to the control group and suggested that the structural features of the cornea may be associated with the sclera and optic nerve. In another study, subfoveal choroidal thickness was reported to be significantly higher in KC patients than controls, and this change was attributed to the natural course of the disease.[38] Considering our findings of different effects on the retinal layers, the relationship between KC and the posterior ocular structures and the possible underlying mechanisms are an important subject for future research.

Study Limitations

This study has certain limitations. Further studies with more advanced KC cases are needed to determine whether changes in macular parameters consistently follow these patterns and to confirm the current findings. It has been reported in the literature that astigmatism may affect peripapillary RNFL measurements but does not change the signal strength of macular parameters measured with SD-OCT devices.[22,31] However, the correlation between astigmatism severity and peripapillary RNFL and thickness analyses in the macular region must be confirmed in future studies. The strength of our study is that it is the first study showing that potential factors involved in the progression of KC, such as UV radiation, oxidative stress, and genetic predisposition, may also have different effects on the retinal layers.

Conclusion

Another important question worth investigating through long-term follow-up is whether patients with advanced KC are predisposed to AMD due to RPE dysfunction. Further studies at the molecular level could reveal that KC may also be accompanied by retinal pathologies that can affect vision level and quality.

Ethics

Ethics Committee Approval: Kayseri City Training and Research Hospital (ethics committee decision approval: 00106647458)

Informed Consent: Obtained.

Peer-review: Externally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: C.Ö., Y.Y., Concept: C.Ö., Design: C.Ö., Data Collection or Processing: Y.Y., Analysis or Interpretation: Y.Y., Literature Search: C.Ö., Writing: C.Ö.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Krachmer JH, Feder RS, Belin MW. Keratoconus and related noninflammatory corneal thinning disorders. Surv Ophthalmol. 1984;28:293-322.
2. Romero-Jimenez M, Santodomingo-Rubido J, Wolffsohn JS. Keratoconus: a review. Cont Lens Anterior Eye. 2010;33:157-166.
3. Tuft SJ, Moodaley LC, Gregory WM, Davison CR, Buckley RJ. Prognostic factors for the progression of keratoconus. Ophthalmology. 1994;101:439-447.
4. Hee MR, Puliafito CA, Wong C, Duker JS, Reichel E, Rutledge B, Schuman JS, Swanson EA, Fujimoto JG. Quantitative assessment of macular edema with optical coherence tomography. Arch Ophthalmol.1995;113:1019-1029.
5. Schaudig UH, Glaefke C, Scholz F, Richard G. Optical coherence tomography for retinal thickness measurement in diabetic patients without clinically significant macular edema. Ophthalmic Surg Lasers. 2000;31:182-186.
6. Wakitani Y, Sasoh M, Sugimoto M, Ito Y, Ido M, Uji Y. Macular thickness measurements in healthy subjects with different axial lengths using optical coherence tomography. Retina. 2003;23:177-182.
7. Lim MC, Hoh ST, Foster PJ, Lim TH, Chew SJ, Seah SK, Aung T. Use of optical coherence tomography to assess variations in macular retinal thickness in myopia. Invest Ophthalmol Vis Sci. 2005;46:974-978.
8. Luo HD, Gazzard G, Fong A, Aung T, Hoh ST, Loon SC, Healey P, Tan DT, Wong TY, Saw SM. Myopia, axial length, and OCT characteristics of the macula in Singaporean children. Invest Ophthalmol Vis Sci. 2006;47:2773-2781.
9. Moschos MM, Chatziralli IP, Koutsandrea C, Siasou G, Droutsas D. Assessment of the macula in keratoconus: an optical coherence tomography and multifocal electroretinography study. Ophthalmologica. 2013;229:203-207.
10. Sahebjada S, Amirul Islam FM, Wickremasinghe S, Daniell M, Baird PN. Assessment of Macular Parameter Changes in Patients with Keratoconus Using Optical Coherence Tomography. J Ophthalmol. 2015;2015:245953.
11. Alió JL, Shabayek MH. Corneal higher order aberrations: A method to grade keratoconus. J Refract Surg. 2006;22:539-545.
12. Piñero DP, Nieto JC, Lopez-Miguel A. Characterization of corneal structure in keratoconus. J Cataract Refract Surg. 2012;38:2167-2183.
13. Sherwin T, Brookes NH. Morphological changes in keratoconus:pathology or pathogenesis. Clinical and Experimental Ophthalmology. 2004;32:211-217.
14. Arnal E, Peris-Martínez C, Menezo JL, Johnsen-Soriano S, Romero FJ. Oxidative stress in keratoconus? Invest Ophthalmol Vis Sci. 2011;52:8592-8597.
15. Burdon KP, Vincent AL. Insights into keratoconus from a genetic perspective. Clin Exp Optom. 2013;96:146-154.
16. Buddi R, Lin B, Atilano SR, Zorapapel NC, Kenney MC, Brown DJ. Evidence of oxidative stress in human corneal diseases. J Histochem Cytochem. 2002;50:341-351.
17. Chwa M, Atilano SR, Hertzog D, Zheng H, Langberg J, Kim DW, Kenney MC. Hypersensitive response to oxidative stress in keratoconus corneal fibroblasts. Invest Ophthalmol Vis Sci. 2008;49:4361-4369.
18. Huang L, Yappert MC, Jumblatt MM, Borchman D. Hyperoxia and thyroxine treatment and the relationships between reactive oxygen species generation, mitochondrial membrane potential, and cardiolipin in human lens epithelial cell cultures. Curr Eye Res. 2008;33:575-586.
19. Ozawa Y, Kurihara T, Sasaki M, Ban N, Yuki K, Kubota S, Tsubota K. Neural degeneration in the retina of the streptozotocin-induced type 1 diabetes model. Exp Diabetes Res. 2011;2011:108328.
20. Yilmaz I, Saracoglu Yilmaz B, Guleryuz NB, Perente I, Ozkaya A, Taskapili M. Assessment of the macula and choroid in pediatric keratoconus patients. Saudi J Ophthalmol. 2018;32:126-129.
21. Uzunel UD, Küsbeci T, Yüksel B. Does the Stage of Keratoconus Affect Optical Coherence Tomography Measurements? Semin Ophthalmol. 2017;32:676-681.
22. Cankaya AB, Beyazyildiz E, Ileri D, Yilmazbas P. Optic disc and retinal nerve fiber layer parameters of eyes with keratoconus. Ophthalmic Surg Lasers Imaging. 2012;43:401-407.
23. Sasaki M, Ozawa Y, Kurihara T, Kubota S, Yuki K, Noda K, Kobayashi S, Ishida S, Tsubota K. Neurodegenerative influence of oxidative stress in the retina of a murine model of diabetes. Diabetologia. 2010;53:971-979.
24. Lu L, Hackett SF, Mincey A, Lai H, Campochiaro PA. Effects of different types of oxidative stress in RPE cells. J Cell Physiol. 2006;206:119-125.
25. De La Paz MA, Anderson RE. Anderson. Lipid peroxidation in rod outer segments: role of hydroxyl radical and lipid hydroperoxides. Invest Ophthalmol Vis Sci.1992;33:2091-2096.

26. Cao K, Sahebjada S, Richardson AJ, Baird BN. Do age-related macular degeneration genes show association with keratoconus? Eye Vis (Lond). 2019;6:38.
27. Lee JE, Oum BS, Choi HY, Lee SU, Lee JS. Evaluation of differentially expressed genes identified in keratoconus. Mol Vis. 2009;15:2480-2487.
28. Langenbucher A, Viestenz A, Seitz B, et al. Computerized calculation scheme for retinal image size after implantation of toric intraocular lenses. Acta Ophthalmol Scand. 2007;85:92-98.
29. Hwang YH, Lee SM, Kim YY, Lee JY, Yoo C. Astigmatism and optical coherence tomography measurements. Graefes Arch Clin Exp Ophthalmol. 2012;250:247-254.
30. Leonard AP, Gardner SD, Rocha KM, Zeldin ER, Tremblay DM, Waring GO 4th. Double-Pass Retina Point Imaging for the Evaluation of Optical Light Scatter, Retinal Image Quality, and Staging of Keratoconus. J Refract Surg. 2016;32:760-765.
31. Hwang YH, Lee JY, Kim YY. The effect of head tilt on the measurements of retinal nerve fiber layer and macular thickness by spectral-domain optical coherence tomography. Br J Ophthalmol. 2011;95:1547-1551.
32. Campbell RJ, Coupland SG, Buhrmann RR, Kertes PJ. Effect of eccentric and inconsistent fixation on retinal optical coherence tomography measures. Arch Ophthalmol. 2007;125:624-627.
33. Oberwahrenbrock T, Weinhold M, Mikolajczak J, Zimmermann H, Paul F, Beckers I, Brandt AU. Reliability of Intra-Retinal Layer Thickness Estimates. PLoS One. 2015;10:e0137316.
34. Röck T, Bartz-Schmidt KU, Bramkamp M, Röck D. Influence of axial length on thickness measurements using spectral-domain optical coherence tomography. Invest Ophthalmol Vis Sci. 2014;55:7494-7498.
35. Xie R, Zhou XT, Lu F, Chen M, Xue A, Chen S, Qu J. Correlation between myopia and major biometric parameters of the eye: A retrospective clinical study. Optom Vis Sci. 2009;86:503-508.
36. Choi SW, Lee SJ. Thickness changes in the fovea and peripapillary retinal nerve fiber layer depend on the degree of myopia. Korean J Ophthalmol. 2006;20:215-219.
37. Akkaya S, Küçük B. Lamina Cribrosa Thickness in Patients With Keratoconus. Cornea. 2017;36:1509-1513.
38. Akkaya S. Macular and Peripapillary Choroidal Thickness in Patients With Keratoconus. Ophthalmic Surg Lasers Imaging Retina. 2018;49:664-673.

DOI: 10.4274/tjo.galenos.2020.99975
Turk J Ophthalmol 2021;51:83-88

Original Article

Comparison of Quality of Life Questionnaires in Patients with Low Vision

Esra Şahlı, Şefay Aysun İdil

Ankara University Faculty of Medicine, Department of Ophthalmology, Ankara, Turkey

Abstract

Objectives: To compare the quality of life assessed by the Low Vision Quality of Life Questionnaire (LVQOL) and National Eye Institute Visual Function Questionnaire (NEI VFQ-25) in patients with low vision.

Materials and Methods: A total of 64 consecutive patients who presented to the Ankara University Low Vision Rehabilitation Department for the first time were included in the study. Patients aged 18 or older who had a best-corrected visual acuity of less than 20/60 or a visual field of equal to or less than 20° from the fixation point in the better eye were included. After examination, the patients were asked to complete the LVQOL and NEI VFQ-25 questionnaires.

Results: A very strong correlation was found between the total scores of the two questionnaires. A strong correlation was found between the "distance vision" subscale score of LVQOL and "distance activities" subscale score of NEI VFQ-25. There was also a strong correlation between the "reading and fine work" subscale score of LVQOL and "near activities" subscale score of NEI VFQ-25. There was a weak correlation between the LVQOL total score and visual acuity. There were moderate negative correlations between age at disease onset and the total scores of the two questionnaires.

Conclusion: Both the LVQOL and NEI VFQ-25 are able to quantify the quality of life of individuals with low vision and it is possible to compare the studies carried out with these two questionnaires which are validated in Turkish.

Keywords: Low vision, quality of life, LVQOL, NEI VFQ-25

Introduction

The approach to low vision and blindness is very important as it impacts the quality of life, cognitive function, and well-being of the individual as well as society. It is associated with employment, education opportunities, and health economics.[1] According to 2010 statistics from the World Health Organization (WHO), there were an estimated 285 million people with visual impairment worldwide. Of these, 39 million were reported as blind and 246 million as having low vision. The prominent causes of visual impairment (80%) are uncorrected refractive errors and treatable causes such as cataracts. In developed countries, the most common causes are age-related macular degeneration (AMD), glaucoma, and diabetic retinopathy.[2]

Low vision is defined as a distance visual acuity of less than 20/60 or a visual field of equal to or less than 20° in the better eye after refractive correction and medical or surgical treatment if necessary. Low vision is the main problem targeted by the Vision 2020 program, a global collaborative initiative by the WHO and International Agency for the Prevention of Blindness that aimed to eliminate preventable blindness.[3] It was reported

Address for Correspondence: Esra Şahlı, Ankara University Faculty of Medicine, Department of Ophthalmology, Ankara, Turkey
E-mail: esracansizoglu@gmail.com **ORCID-ID:** orcid.org/0000-0002-1355-7284
Received: 30.05.2020 **Accepted:** 27.07.2020

Cite this article as: Şahlı E, İdil ŞA. Comparison of Quality of Life Questionnaires in Patients with Low Vision. Turk J Ophthalmol 2021;51:83-88

that 65% of people with visual impairment and 82% of those with blindness were aged 50 years or older.[2] In addition, more people will be at risk in the future due to the increasing age of the population worldwide. Visual rehabilitation is an effective method of increasing the quality of life of people with low vision and blindness that cannot be prevented or treated.

Visual impairment is associated with performance and difficulty in everyday tasks related to vision.[4] The effects of visual impairment on an individual include visual, functional, psychological, social, and economic issues. These issues can cause limitations in performing tasks that require vision in educational, occupational, and recreational activities, and these limitations reduce the quality of life of individuals with low vision.[5,6,7,8]

Quality of life means the degree to which a person is independent, productive, healthy, and able to participate in or enjoy life events. The WHO has defined quality of life as an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards, and concerns.[9] Using quality of life questionnaires in patients with low vision may represent a viable option to better understand the impact of low vision on an individual's daily functioning, well-being, needs, and goals. At the same time, quality of life in patients with low vision and the effect of rehabilitation programs on these patients should be measured in order to improve low vision services.[10]

Most studies have focused on objective assessments including visual acuity at near and far distance, reading speed, duration, and fluency, contrast sensitivity, and visual field. But these objective assessments of vision do not cover every aspect of visual function and cannot measure the patient's perception of their disease. Applying quality of life instruments may help the clinician in this regard.

Quality of life instruments consist of a set of questions used to assess daily functioning and health-related quality of life. There are a few quality of life instruments which provide a functional, social, and psychological evaluation and are appropriate for use in the evaluation of low vision services.[10] Two of them, the Low Vision Quality of Life Questionnaire (LVQOL) and the National Eye Institute Visual Function Questionnaire (NEI VFQ-25), have been translated into Turkish and validated.[11,12]

The LVQOL was developed by Wolffsohn and Cochrane[13] specifically for patients with low vision and includes 25 items in 4 dimensions: distance vision, mobility, and lighting; adjustment; reading and fine work; and activities of daily living. This instrument is used in the clinical evaluation of patients with low vision in order to determine the needs of patients in daily life and whether these needs can be met by low vision rehabilitation. Patients are asked to respond on a 5-point scale on which 5 represents no difficulty and 1 great difficulty. The total score ranges from 0 to 125, with higher scores indicating a higher quality of life. The LVQOL was shown to be a reliable, internally consistent, and sensitive measure of quality of life in patients with low vision.[13]

The LVQOL was adapted into Turkish by Idil et al.[11] One item in the "adjustment" dimension that had a low validity value was excluded from the questionnaire. After removing the item "How well has your eye condition been explained to you", all dimensions of the LVQOL were shown to be reliable, valid, and suitable for use in Turkish patients with low vision. As a result, the Turkish version of the questionnaire consists of 24 items and is evaluated out of a total score of 120.[11]

The NEI VFQ-25 can assess the impact of a wide spectrum of eye diseases on quality of life. It includes 13 subscales (general health, general vision, ocular pain, vision expectations, near activities, distance activities, vision-specific social functioning, vision-specific mental health, vision-specific role difficulties, vision-specific dependency, driving, peripheral vision, and color vision).[14] The 25-item NEI VFQ was translated into Turkish and validated by Toprak et al.[12] and found useful in measuring the impact of visual impairment on affected individuals' quality of life.

The purpose of the present study was to compare quality of life assessed with the LVQOL and NEI VFQ-25 in patients with low vision. Comparing the two questionnaires and evaluating the correlation between them will provide the opportunity to compare the results of studies that used these questionnaires. To our knowledge, there is only one previous study (Chieh JJ, et al. IOVS 2006;47:ARVO E-Abstract 2106) comparing the results obtained from these questionnaires, and it evaluated quality of life in a small group of patients with AMD.

Materials and Methods

This was a randomized methodological study to evaluate the consistency between the two questionnaires. Ethical approval was obtained from the Ankara University Faculty of Medicine Clinical Trials Ethics Committee (approval number: 15-1022-18). A total of 64 consecutive patients who presented to the Ankara University Low Vision Rehabilitation Department for the first time were included in the study. Patients aged 18 years or older whose better eye had a best-corrected visual acuity (BCVA) of less than 20/60 (0.48 logMAR) or a visual field equal to or less than 20° from the fixation point were included.

All patients underwent a complete ophthalmologic examination including BCVA, near visual acuity, slit lamp biomicroscopy, fundus examination, applanation tonometry, and low vision examination. The patient's visual acuity in the better-seeing eye was recorded as their visual acuity. After the examination, the patients were asked to complete the LVQOL and NEI VFQ-25 questionnaires. The questions were asked to all participants by the same employee (B.S.) due to their inadequate near visual acuity for reading. An informed consent form was signed by each participant before data collection.

The 24 items of the Turkish LVQOL were asked to obtain a total score out of 120 points and 4 subscale scores for each participant. According to the 25 questions and 13 additional questions in the NEI VFQ, 12 subscale scores as well as a combined total score were obtained for each participant. Each subscale was calculated according to the instructions described by the NEI VFQ developers.[15] The scores can range from 0 to 100, where 0 is the worst and 100 shows no disability related to vision. Demographic data including age, sex, diagnosis, and disease duration were also collected. Total scores and related subscale scores of the LVQOL and NEI VFQ-25 were assessed for correlation.

Statistical Analysis

The total score and the subscale scores of the two questionnaires were compared using the non-parametric Mann-Whitney U test. Correlations between the scores were calculated using Spearman rank analysis. P<0.05 was considered significant. The strength of correlations was described according to the guide recommended by Evans[16] for the absolute correlation coefficient (r): 0.00-0.19 as very weak, 0.20-0.39 as weak, 0.40-0.59 as moderate, 0.60-0.79 as strong, and 0.80-1.00 as very strong.

Results

There were 31 women (48%) and 33 men (52%). The mean age was 58.7 years (range: 21-87 years). The mean BCVA was 1.3 logMAR (range: 0.3-3.1 logMAR). Thirty percent of the patients had AMD, 25% of the patients had retinitis pigmentosa. The other diagnoses were diabetic retinopathy (9%), Stargardt disease (9%), hereditary optic neuropathies (6%), glaucoma (5%), albinism (3%), macula dystrophies (5%), and degenerative myopia (3%).

The total score on the LVQOL ranged from 10.6 to 72.0 with a mean of 42.31±16.19. The mean total score for the NEI VFQ-25 was 46.45±24.24 (range 8 to 97). The Spearman correlation coefficient between the total score of the LVQOL and NEI VFQ-25 was 0.842 (p<0.001), indicating a very strong correlation between the total scores of the two questionnaires. A strong correlation was found between the LVQOL "distance vision" subscale score and the NEI VFQ-25 "distance activities" subscale (r=0.660, p<0.001). There was also a strong correlation between the LVQOL "reading and fine work" subscale score and NEI VFQ-25 "near activities" subscale score (r=0.768, p<0.001). Table 1 shows the total and subscale scores for the two questionnaires and correlations between total scores and related subscale scores.

There was a weak correlation between LVQOL total score and visual acuity (r=0.277, p<0.05) but no relationship between the NEI VFQ-25 total score and visual acuity (r=0.237, p=0.06). A weak correlation was demonstrated between the NEI VFQ-25 "distance activities" subscale score and visual acuity (r=0.261, p<0.05). There were strong correlations between the LVQOL "adjustment" subscale and NEI VFQ-25 "mental health", "role

Table 1. NEI VFQ-25 and LVQOL total and subscale scores and correlations between related scores

NEI VFQ-25 total and subscale scores	Mean ± SD	LVQOL total and subscale scores	Mean ± SD	Correlations
Overall score	56.02±20.23	Overall score (max. 120)	46.45±24.24	r=0.842 p<0.001
Distance activities	34.25±22.22	Distance vision, mobility and lighting (max. 60)	25.42±11.82	r=0.660 p<0.001
Near activities	32.56±20.20	Reading and fine work (max. 25)	6.98±5.8	r=0.768 p<0.001
Vision-specific mental health	40.77±19.28	Adjustment (max. 15)	6.97±3.78	r=0.647 p<0.001
Vision-specific role difficulties	38.06±20.85			r=0.521 p<0.001
Vision-specific dependency	52.42±26.08			r=0.665 p<0.001
Vision-specific social functioning	51.19±26.38	Activities of daily living (max. 20)	7.55±6.1	
General health	53.78±16.41			
General vision	33.12±14.10			
Ocular pain	61.32±26.51			
Driving	5.85±16.96			
Color vision	70.70±26.73			
Peripheral vision	61.72±26.34			

NEI VFQ-25: National Eye Institute Visual Function Questionnaire 25, LVQOL: Low Vision Quality of Life Questionnaire, SD: Standard deviation, max: Maximum

limitations due to vision", and "dependency on others due to vision" subscales (r=0.647; r=0.521; r=0.665, respectively, p<0.001).

Total LVQOL and NEI VFQ-25 scores showed moderate negative correlation with age at disease onset (r=0.370 and r=0.387, respectively, p<0.05) but not with disease duration. No relationship was found between the total scores of the two questionnaires and age, sex, or diagnosis.

Discussion

Low vision examination includes many tests to objectively measure visual function, such as visual acuity, reading speed, contrast sensitivity, and visual field, but these measurements do not describe an individual's visual status exactly. Therefore, there is also a need to assess subjective visual function and outcomes of low vision rehabilitation in patients with low vision.

The success of a low vision service has been defined as reducing the level of difficulty in visual tasks. Stelmack[17] declared that self-reported quality of life is a significant measure of the impact of low vision rehabilitation, and it has long been recognized that visual acuity measurements do not always correlate with the actual daily performance of patients with low vision.[8]

Various questionnaires have been developed and used to assess quality of life in patients with glaucoma, AMD, retinitis pigmentosa, cataract, and optic neuritis, but none of them are specific for patients with untreatable visual impairment. Wolffsohn and Cochrane[13] developed the LVQOL in 2000 to measure the quality of life of those with low vision and determine the effects of low vision rehabilitation. The items of this questionnaire are related to difficulties that people with low vision have in performing daily activities, and it is reported to be one of the best tools for use in low vision patients. LVQOL scores were found to be correlated with visual acuity and other vision-related quality of life questionnaires, and its subscales showed satisfactory construct validity.[18,19] The Turkish version of LVQOL was shown to be internally consistent, reliable, and sensitive in the measurement of quality of life.[11]

The 25-item NEI VFQ was also developed and became one of the most widely used visual function questionnaires.[20] The NEI VFQ-25 has been used in well-known eye surveys including the Age-Related Eye Disease Study, the Wisconsin Epidemiologic Study of Diabetic Retinopathy, and Optic Neuritis Treatment Trial.[21,22,23] It has been translated and validated in several languages. This instrument showed good psychometric properties including reliability and construct validity in a mixed population of patients with various eye diseases and visual impairment.[14] Marella et al.[20] suggest that although the overall scale of NEI VFQ-25 was psychometrically satisfactory, the 12-subscale feature of the NEI VFQ-25 had limited psychometric validity in a low vision population. The items of general health, pain, and driving were found not to fit the overall scale. Sivaprasad et al.[24] demonstrated that the overall scale and the near and distance activities subscales showed good internal consistency reliability, test-retest reliability, and convergent validity with maximum reading speed and functional reading independency index score in patients with geographic atrophy. Good reliability and construct validity of the NEI VFQ-25 were also demonstrated in patients with AMD in several studies.[25,26] The Turkish version of the NEI VFQ-25 was found to be reliable and valid for the assessment of quality of life in patients with various chronic eye diseases.[14]

Chieh et al. reported a strong correlation (correlation coefficient=0.724) between the LVQOL and NEI VFQ-25 and significant correlations between similar LVQOL and NEI VFQ-25 questions in patients with bilateral severe macular degeneration. They concluded that the LVQOL is a useful additional tool to assess AMD patients with severe vision loss (Chieh JJ, et al. IOVS 2006;47:ARVO E-Abstract 2106). We found a very strong correlation between the total scores of the LVQOL and NEI VFQ-25 in low vision patients. There was a strong correlation between the "distance vision" subscale score of the LVQOL and the "distance activities" subscale score of the NEI VFQ-25. There was also a strong correlation between the "reading and fine work" subscale score of the LVQOL and "near activities" subscale score of the NEI VFQ-25 in our study.

Chieh et al. demonstrated a low correlation between LVQOL composite and subscale scores and visual function including distance and near visual acuity, reading speed, and contrast sensitivity (Chieh JJ, et al. IOVS 2006;47:ARVO E-Abstract 2106). Owen et al.[27] reported that the NEI VFQ-25 subscales for general vision, social functioning, visual dependency, near vision, and color vision were strongly and independently associated with visual impairment in a large group of older people. They demonstrated that although visual acuity was strongly associated with NEI VFQ scores in older adults, it explained less than a fifth of the variation in total score, indicating that visual acuity provides a relatively limited measure of visual performance.

In another study, it was demonstrated that NEI VFQ-25 overall composite score, near activities, distance activities, and vision-specific dependency scores were correlated with BCVA, reading speed, and contrast sensitivity in AMD patients.[25] Although we could not detect a relationship between NEI VFQ-25 and visual acuity, there was a weak correlation between LVQOL total score and visual acuity in low vision patients with several diagnoses. In fact, quality of life instruments provide additional information to visual function measures, so they are not expected to be strongly correlated. The patient's well-being in visual rehabilitation is a more important indicator than the visual functions measured.

Correlational analysis showed that the total scores and related subscale scores for the two questionnaires were strongly to very strongly correlated. These results suggest that both questionnaires would provide accurate information for assessing quality of life in patients with low vision and evaluating the outcome of low vision rehabilitation.

In our opinion, the NEI VFQ-25 may provide more useful details regarding quality of life than the LVQOL due to the greater number of items in the NEI VFQ-25, but it is more difficult and time-consuming to calculate the total score and subscale scores of NEI VFQ-25, which reduces its practicality. Nevertheless, the LVQOL and NEI VFQ-25 are both useful tools for assessing quality of life.

Study limitations

Studies on quality of life questionnaires have mostly focused on older populations because of the increased prevalence of low vision in advanced age. We evaluated people in a wide age group with various chronic eye diseases that cause low vision. To our knowledge, no direct comparison of instruments evaluating quality of life in patients with low vision specifically has been reported in the literature. The inclusion of patients with various diseases that cause low vision can be considered a strength of our study as well as a limitation. The patients we included in our study were not homogeneously distributed according to their diagnoses.

Conclusion

We observed a very strong correlation between LVQOL and NEI VFQ-25 total scores and strong correlations between their related subscale scores. They both can provide important information in addition to objective visual measurements when evaluating a patient. Both the LVQOL and NEI VFQ-25 are able to quantify the quality of life of individuals with low vision and will be useful in assessing the effectiveness of low-vision rehabilitation. Therefore, these questionnaires should be combined with objective methods of assessing visual function in a low vision clinic. It is possible to compare studies carried out with these two questionnaires, both of which are validated in Turkish.

Ethics

Ethics Committee Approval: Ethical approval for the study was received from the Ankara University Faculty of Medicine Clinical Trials Ethics Committee (approval number: 15-1022-18).

Informed Consent: Obtained.

Peer-review: Externally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: E.Ş., Ş.A.İ., Concept: Ş.A.İ., Design: Ş.A.İ., Data Collection or Processing: E.Ş., Analysis or Interpretation: E.Ş., Ş.A.İ., Literature Search: E.Ş., Writing: E.Ş.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Sabel BA, Flammer J, Merabet LB. Residual vision activation and the brain-eye-vascular triad: dysregulation, plasticity and restoration in low vision and blindness - a review. Restor Neurol Neurosci. 2018;36:767-791.
2. World Health Organization, Global Data on Visual Impairments 2010. http://www.who.int/blindness/GLOBALDATAFINALforweb.pdf?ua=1.
3. World Health Organization. Vision 2020: The right to sight: Global initiative for the elimination of avoidable blindness. Action Plan 2006 – 2011. Geneva: World Health Organization; 2007.
4. Rubin GS, Bandeen-Roche K, Huang GH, Munoz B, Schein OD, Fried LP, West SK. The association of multiple visual impairments with self-reported visual disability: SEE project. Invest Ophthalmol Vis Sci. 2001;42:64-72.
5. Wang JJ, Mitchell P, Smith W. Vision and low self-rated health: The Blue Mountains Eye Study. Invest Ophthalmol Vis Sci. 2000;41:49-54.
6. O'Connor P, Keefe J. Focus on low vision. Melbourne: Centre for Eye Research; 2007:16-17.
7. McCarthy CA, Nanjan MB, Taylor HR. Vision impairment predicts five-year mortality. Br J Ophthalmol. 2001;85:322-326.
8. Ovenseri-Ogbomo G, Osafo-Agyei H, Akpalaba REU, Ovenseri EO. Impact of low vision services on the quality of life of low vision patients in Ghana. Afr Vision Eye Health. 2016;75:1-5.
9. World Health Organization, Health statistics and information systems. WHOQOL: Measuring Quality of Life. https://www.who.int/health info/survey/whoqol-qualityof life/en/
10. Jackson AJ. Assessment of functional vision. In: Jackson AJ, Wolffsohn JS, eds. Low Vision Manual. 1st ed. Philadelphia: Elsevier Ltd; 2007:167-182.
11. Idil A, Ozen M, Atak N, Elhan A, Pehlivan. Validity and reliability study of Turkish version on low vision with Quality of life questionnaire. Int J Ophthalmol. 2011;4:546-551.
12. Toprak AB, Eser E, Guler C, Baser FE, Mayali H. Cross-validation of the Turkish version of the 25-item National Eye Institute Visual Functioning Questionnaire (NEIU-VFQ 25). Ophthalmic Epidemiol. 2005;12:259-269.
13. Wolffsohn JS, Cochrane AL. Design of the Low Vision Quality of Life Questionnaire (LVQOL) and measuring the outcome of low-vision rehabilitation. Am J Ophthalmol. 2000;130:793-802.
14. Mangione CM, Lee PP, Gutierrez PR, Spritzer K, Berry S, Hays RD; National Eye Institute Visual Function Questionnaire Field Test Investigators. Development of the 25-item National Eye Institute Visual Function Questionnaire. Arch Ophthalmol. 2001;119:1050-1058.
15. Mangione CM. NEI VFQ-25 Scoring Algorithm. Rockville, MD: National Eye Institute; 2000.
16. Evans JD. Straightforward Statistics for the Behavioral Sciences (1st ed). Pacific Grove, California; Brooks/Cole Publishing; 1996.
17. Stelmack JA. Quality of life of low-vision patients and outcomes of low-vision rehabilitation. Optom Vis Sci. 2001;128:335-342.
18. de Boer MR, Moll AC, de Vet HC, Terwee CB, Völker-Dieben HJ, van Rens GH. Psychometric properties of vision-related quality of life questionnaires: a systematic review. Ophthalmic Physiol Opt. 2004;24:257-273.
19. de Boer MR, Terwee CB, de Vet HC, Moll AC, Völker-Dieben HJ, van Rens GH. Evaluation of cross-sectional and longitudinal construct validity of two vision-related quality of life questionnaires: The LVQOL and VCM1. Qual Life Res. 2006;15:233-248.
20. Marella M, Pesudovs K, Keeffe JE, O'Connor PM, Rees G, Lamoureux EL. The psychometric validity of the NEI VFQ-25 for use in a low-vision population. Invest Ophthalmol Vis Sci. 2010;51:2878-2884.
21. Clemons TE, Chew EY, Bressler SB, McBee W; Age-Related Eye Disease Study Research Group. National Eye Institute Visual Function Questionnaire in the Age-Related Eye Disease Study (AREDS): AREDS Report No. 10. Arch Ophthalmol. 2003;121:211-217.
22. Klein R, Moss SE, Klein BE, Gutierrez P, Mangione CM. The NEIVFQ-25 in people with long-term type 1 diabetes mellitus: the Wisconsin Epidemiologic Study of Diabetic Retinopathy. Arch Ophthalmol. 2001;119:733-740.
23. Cole SR, Beck RW, Moke PS, Gal RL, Long DT. The National Eye Institute Visual Function Questionnaire: experience of the ONTT; Optic Neuritis Treatment Trial. Invest Ophthalmol Vis Sci. 2000;41:1017-1021.
24. Sivaprasad S, Tschosik E, Kapre A, Varma R, Bressler NM, Kimel M, Dolan C, Silverman D. Reliability and construct validity of the NEI VFQ-25 in a subset of patients with geographic atrophy from the Phase 2 Mahalo Study. Am J Ophthalmol. 2018;190:1-8.

25. Orr P, Rentz AM, Margolis MK, Revicki DA, Dolan CM, Colman S, Fine JT, Bressler NM. Validation of the National Eye Institute Visual Function Questionnaire-25 (NEI VFQ-25) in age-related macular degeneration. Invest Ophthalmol Vis Sci. 2011;52:3354-3359.
26. Revicki DA, Rentz AM, Harnam N, Thomas VS, Lanzetta P. Reliability and validity of the National Eye Institute Visual Function Questionnaire-25 in patients with age-related macular degeneration. Invest Ophthalmol Vis Sci. 2010;51:712-717.
27. Owen CG, Rudnicka AR, Smeeth L, Evans JR, Wormald RPL, Fletcher AE. Is the NEI-VFQ-25 a useful tool in identifying visual impairment in an elderly population? BMC Ophthalmol. 2006;6:24.

DOI: 10.4274/tjo.galenos.2020.28924
Turk J Ophthalmol 2021;51:89-94

Original Article

Efficacy of Intense Pulsed Light Treatment for Moderate to Severe Acute Blepharitis or Blepharoconjunctivitis: A Retrospective Case Series

Özgün Melike Gedar Totuk*, Kerem Kabadayı**, Cihan Özkapı***, Ümit Aykan****

*Bahçeşehir University Faculty of Medicine, Department of Ophthalmology, İstanbul, Turkey
**Bahçeşehir University Faculty of Medicine, İstanbul, Turkey
***Üsküdar University, Health Services Vocational School, Department of Opticianry, İstanbul, Turkey
****Yakın Doğu University Faculty of Medicine, Department of Ophthalmology, Nicosia, Cyprus

Abstract

Objectives: We aimed to evaluate the efficacy of periocular intense pulsed light (IPL) therapy in the treatment of moderate to severe acute blepharitis or blepharoconjunctivitis.

Materials and Methods: This was a retrospective study performed in one institution. Eleven patients who received bilateral periocular IPL therapy using an IPL device (E>Eye, ESwin, Paris, France) were retrospectively evaluated. The following findings obtained at baseline and 10 weeks after the treatment were recorded: slit-lamp examinations; symptom scores of the Compression of the Eyelid (COTE) grading system and Ocular Surface Disease Index (OSDI); ocular surface staining with Oxford grading scale (OXFORD) scores; lipid layer thickness (LLT); and non-invasive tear meniscus test (TMH), non-invasive break up time measurement (NIBUT), and meibography performed by using I.C.P. Ocular Surface Analyzer (SBM System, Turin, Italy).

Results: Significant improvements in OSDI symptom scores ($p<0.0001$), LLT ($p<0.0001$), and meibography ($p<0.0001$) were obtained at 10 weeks after bilateral periocular IPL therapy. COTE and ocular surface staining scores decreased by 59.72% and 57.14% respectively, while NIBUT and TMH increased by 47.34% and 22.16%, respectively. In parallel to the improvement in OSDI, LLT, and meibography, findings of acute blepharitis or blepharoconjunctivitis improved in slit-lamp examination. There were no adverse effects.

Conclusion: Serial IPL therapy improves the clinical signs and symptoms of moderate to severe acute blepharitis or blepharoconjunctivitis, meibomian gland morphology, and secretion quality.

Keywords: Blepharitis, blepharoconjunctivitis, intense pulsed light treatment, meibography

Introduction

Meibomian gland dysfunction (MGD) refers to functional abnormalities of the meibomian glands such as chronic and diffuse terminal duct obstruction and qualitative or quantitative changes in the glandular secretion of the meibomian glands.[1,2] Blepharitis is the general term for inflammation of the eyelids as a whole. Acute blepharitis may be bacterial, viral, or parasitic in etiology. It often affects the anterior eyelid, with the most prominent changes centered on the meibomian glands.[1,2] Acute blepharitis associated with secondary conjunctival and corneal involvement is defined as acute blepharoconjunctivitis. MGD and severe chronic blepharitis may result in increased bacterial growth on the lid margin, ocular surface inflammation, and damage.[1,2]

The diagnosis of acute blepharitis or blepharoconjunctivitis is based on clinical signs and symptoms such as inflamed eyelids, anterior lid margin telangiectasia, accumulation of collarettes around the base of the cilia, recurrent episodes of chronic red eye, watering, photophobia, styes or meibomian cysts, and keratitis.

Address for Correspondence: Özgün Melike Gedar Totuk, Bahçeşehir University Faculty of Medicine, Department of Ophthalmology, İstanbul, Turkey
Phone: +90 533 336 79 86 E-mail: melikegedar@gmail.com **ORCID-ID:** orcid.org/0000-0003-1863-6501
Received: 08.12.2019 **Accepted:** 16.07.2020

Cite this article as: Gedar Totuk ÖM, Kabadayı K, Özkapı C, Aykan Ü. Efficacy of Intense Pulsed Light Treatment for Moderate to Severe Acute Blepharitis or Blepharoconjunctivitis: A Retrospective Case Series. Turk J Ophthalmol 2021;51:89-94

Clinical signs and symptoms are graded as mild, moderate, or severe.[1,2,3]

The common treatment approaches in moderate to advanced acute blepharitis or blepharoconjunctivitis, such as warm compresses, lid massage, daily lid hygiene, topical or systemic broad spectrum antibiotics, and topical corticosteroids, have limited efficacy.[1,2,3]

Intense pulsed light (IPL) therapy has been applied in the periocular area in dermatology for over a decade for the treatment of rosacea. During this period, it has been noticed that facial skin rosacea patients treated with IPL reported a significant improvement in their dry eye symptoms, thus the clinical application of IPL devices has been extended to include the treatment of MGD.[4,5,6,7] However, the effect of IPL treatment in patients with moderate to severe acute blepharitis or blepharoconjunctivitis has not been extensively studied.

In this study we aimed to evaluate the effect of a series of three bilateral IPL treatments, which was applied in addition to the standard clinical treatments, in patients with moderate to severe acute blepharitis or blepharoconjunctivitis.

Materials and Methods

Study Design and Patients

This was a single-center, retrospective study. Eleven patients with moderate to severe acute blepharitis or blepharoconjunctivitis who received bilateral IPL treatment using an IPL device (E>Eye, ESwin, Paris, France) in our clinic were retrospectively evaluated. Patients with moderate to severe acute blepharitis or blepharoconjunctivitis had moderate-marked hyperemia, diffuse or marked diffuse infiltration, tarsal conjunctival vessels just visible or no visible, moderate papillary hyperplasia and more than 5 follicles, as defined by Viswalingam et al.[2] None of the patients had prior treatment for acute blepharitis or blepharoconjunctivitis. Patients with excessive sun exposure in the last month, a history of herpes zoster infection, pregnancy, use of photosensitizing drugs or foods, or skin Fitzpatrick scale V/VI were excluded from the study.

Informed consent was obtained from all of the patients after explanation of the nature and possible consequences of the IPL treatment. The study was approved by the Institutional Ethics Committee of Bahçeşehir University (6 Nov 2019; 2019-16/04).

Study Procedures and Scales

The results of the following clinical evaluations performed at baseline and 10 weeks after the treatment were recorded: slit-lamp examinations; symptom scores of the Compression of the Eyelid (COTE) grading system and Ocular Surface Disease Index (OSDI); ocular surface staining with Oxford grading scale (OXFORD) scores; lipid layer thickness (LLT); and non-invasive tear meniscus height (TMH), non-invasive tear break-up time (NIBUT) measurement, and meibography performed using an I.C.P. Ocular Surface Analyzer (SBM System, Turin, Italy).

The OSDI is a self-administered questionnaire containing 12 items and scoring a range of 0 (no symptoms) to 100 (severe symptoms) points. It is evaluated using the following formula: OSDI=Dx25/E, where D is the sum of scores for all questions answered and E is the number of questions answered. A final score of 0 to 12 is interpreted as no disability, 13 to 22 as mild symptoms, 23 to 32 as moderate symptoms, and 33 to 100 as severe symptoms. The validated Turkish version of the OSDI was used in the study.

The Oxford grading scale divides corneal staining into six groups according to severity from 0 (absent) to 5 (severe).

TMH was measured using an I.C.P. Ocular Surface Analyzer with a high-power pre-shot image. Values less than 0.22 mm were considered below normal. As the tear volume was measured with TMH, we did not perform invasive Schirmer test for any of our patients.

NIBUT of the tear film was determined with a tear interferometer using the I.C.P. Ocular Surface Analyzer. The time between the last complete blink and the first indication of pattern break-up and image deformation of the Placido rings image detected with a special film in the interferometer was measured. Values equal to or greater than 10 s were considered normal.

Meibomian gland function was assessed with the COTE grading system and LLT.

The COTE test is performed at the slit lamp, using a nonpreserved, artificial tear-wetted or warm water-wetted cotton bud. On the basis of the nature and severity of expressed tarsal gland secretions, it is graded as follows: 1, clear oil; 2, easy or slow and difficult egress of pus; 3, thick toothpaste-like secretion (worm-like); 4, complete blockage of tarsal gland, no egress of secretion visualized.

LLT was assessed by interferometry using the I.C.P. Ocular Surface Analyzer and measured by analyzing the interference of images by using a color profile of the pre-ocular tear film in the blinking eyes. LLT was graded from F to 0 based on the comparison of the videos obtained to the classification installed in the device and seven short videos with different thicknesses of the tear film lipid layer (160-120 nm, 80-120 nm, 80 nm, 30-80 nm, 30 nm, 15 nm, <15 nm).

Meibomian gland morphological indexes were assessed by non-contact meibography using the I.C.P. Ocular Surface Analyzer.

Intense Pulsed Light Treatment

The IPL device (E>Eye, ESwin, Paris, France) has a proprietary treatment algorithm delivering light pulses with a spectral range of 580 to 1200 nm. At each treatment session, both eyes of the patient were closed with opaque safety goggles. An ultrasonic conductive gel was applied to the targeted periocular skin area reaching up to the inferior boundary of the eye shields. Four adjacent IPL flashes were administered to the skin area immediately below the lower eyelid and one IPL flash on the temple of both eyes with the E>Eye device.

Treatments were performed at baseline following baseline assessments, week 2, and week 6, adjusting the appropriate pulse intensity setting (range, 9.8-13 J/cm^2) following the

manufacturer's treatment protocol for the E>Eye device. Multiple homogenously sculpted light treatment pulse intensities were chosen based on the Fitzpatrick scale according to the manufacturer's guidelines (with very lightly pigmented Phototype 1 participants being treated at 13 J/cm^2 and individuals with dark brown complexions being treated at 9.8 J/cm^2).

Patients applied warm compresses with eyelid massage and lid hygiene with tea tree oil shampoo daily. In addition to IPL treatment, all patients received the following pharmacological treatment: 1% azithromycin ophthalmic solution (1 drop twice daily for 2 days followed by once daily dosing for 12 days) and 0.05% dexamethasone ophthalmic suspension (1 drop 4 times daily for 14 days).

Results

Twenty-two eyes of 11 patients with moderate to severe acute blepharitis or blepharoconjunctivitis (5 women and 6 men, mean age 50.54±19.39 years, age range 17-77 years) were included in the study. Cataract surgery had been performed on 4 eyes of 2 patients more than 3 years before, multiple chalazion surgeries had been performed on 6 eyes of 3 patients more than a year before, and pars plana vitrectomy surgery had been performed on 1 eye of 1 patient 7 years before the initiation of IPL therapy. Two patients had seborrheic skin type. There was no diagnosis of skin disease or previous skin therapy in any of the patients.

OSDI score (range, 0-100) was significantly improved at 10 weeks after serial IPL therapy compared with baseline score (29.73±4.58 vs. 12.36±1.40; p<0.0001). Over half of the eyes (55%) had OSDI scores higher than 12 (Table 1). Oxford grading scale (range, 0-5) did not show a significant decrease at 10 weeks after serial IPL therapy (1.91±0.75 vs. 0.82±0.39; p=0.12). However, the percentage of eyes showing an absence of corneal and ocular surface staining increased from 18% to 57.14% after serial IPL therapy (Table 1).

NIBUT (normal >10 s) was prolonged from 4.52±0.90 s to 6.66±1.50 s with serial IPL therapy, but this prolongation was not statistically significant (p=0.48, Table 1). At 10 weeks after serial IPL therapy, NIBUT was longer than 10 s in 9% eyes and the mean NIBUT increased by 47.34%. There was also an increase in the mean TMH score that was not statistically significant when compared with baseline (0.29±0.12 vs. 0.35±0.09; p=0.55) (Table 1). However, all of the eyes were within normal range (>0.22 mm) and TMH level increased by 22.16% at 10 weeks after serial IPL therapy.

LLT (range, 0-6) was significantly improved at 10 weeks after serial IPL therapy compared with baseline thickness (1.23±0.43 vs. 2.46±0.67; p<0.0001) showing improvement in all of the eyes (Table 1). In contrast, although the mean COTE score (graded 1-4) did not significantly decrease at 10 weeks after serial IPL therapy (3.27±0.77 vs. 1.32±0.48; p=0.11) (Table 1), 59.72% of eyes had decreased COTE score and 68% had clear oil secretion.

Meibomian gland loss area (range, 0-100%) significantly decreased both in upper eyelids and lower eyelids at 10 weeks after serial IPL therapy compared with baseline (p<0.0001) (Table 1). In 36% of the eyelids, meibomian gland loss completely resolved after serial IPL therapy.

Discussion

In the present study, we primarily found that the subjective symptoms and objective signs of acute blepharitis or blepharoconjunctivitis were significantly improved after a series of IPL treatments combined with short-term medical therapy.

MGD is an important clinical condition which can lead to hyperosmolarity and instability of the tear film, increased bacterial growth on the lid margin, eye irritation, ocular surface inflammation, and dry eye.[8] MGD causes more viscous meibum production than usual, and patients can experience severe inflammation and bacterial overgrowth that exacerbates abnormal meibum production.[1,2] Inflammation of the meibomian glands leads to acute blepharitis or blepharoconjunctivitis, which can be treated with warm compresses, lid massage, and topical antibiotics.[4,5,6] Treatment modalities for blepharitis include eyelid hygiene (i.e., warm compresses, eyelid massage, and eyelid scrubs), meibomian gland expression and probing, topical corticosteroid drops to decrease inflammation in acute exacerbations, topical antibiotics for up to eight weeks for staphylococcal and seborrheic blepharitis, and increasing dietary intake of essential fatty acids, specifically omega-3 fatty acid, in cases of mild-to-severe MGD.[3] For severe cases, topical steroids and systemic antibiotics are needed. Most acute blepharitis or blepharoconjunctivitis cases result from underlying MGD. Treatment is often long-term and requires patient adherence, yet despite diverse treatment modalities, complete and lasting relief of the signs and symptoms of MGD could not be obtained.[9] Recurrence during follow-up is common and requires repeating the treatment.[10,11,12,13] Additionally, long-term antibiotic and

Table 1. Signs and symptom scores before and 10 weeks after serial intense pulsed light (IPL) therapy

Score (range)	Baseline	10 weeks post-IPL	p value[a]
COTE grade (1-4)	3.27±0.77	1.32±0.48	0.11
OSDI score (0-100)	29.73±4.58	12.36±1.40	<0.0001
OXFORD scale (0-5)	1.91±0.75	0.82±0.39	0.12
NIBUT (> or <10 s)	4.52±0.90	6.66±1.50	0.48
LLT (0-F[b])	1.23±0.43	2.46±0.67	<0.0001
MGL (0-100%)			
UL	31.86±13.08	9.82±10.58	<0.0001
LL	26.59±9.94	7.41±7.56	<0.0001
TMH (> or <0.22 mm)	0.29±0.12	0.35±0.09	0.55

COTE: Compression of the Eyelid, OSDI: Ocular Surface Disease Index, OXFORD: Ocular surface staining with Oxford grading scale, NIBUT: Non-invasive break-up time, LLT: Lipid layer thickness, MGL: Meibomian gland loss, UL: Upper eyelids, LL: Lower eyelids, TMH: Tear meniscus height; [a]Paired t test. [b]LLT is scored as follows: A=1, B=2, C=3, D=4, E=5, and F=6

corticosteroid therapy bears the potential risk of serious side effects.[9] Although there is no standard concomitant medical therapy after IPL procedure, our patients were treated with warm compresses with eyelid massage, lid hygiene with tea tree oil shampoo daily, and short-term topical antibiotic and corticosteroid drops. The decreased number of medications is a critical factor increasing patients' adherence to treatment and decreasing the risk of potential side effects of systemic medications. Although the cost of IPL therapy is relatively high and not covered by health insurance, it is balanced by reduced medication costs.

Since IPL therapy was accidentally found to treat dry eye due to MGD during its use for the treatment of facial rosacea, IPL has been used as an effective and well-tolerated treatment option for improvement of subjective symptoms and objective findings of mild to moderate MGD or dry eye.[4,5,13,14,15,16] This relatively novel treatment modality utilizes non-coherent, polychromatic light in a wavelength spectrum of 500-1200 nm applied to the periocular skin for selective thermolysis. The light absorbed by chromophores (e.g., melanin), hemoglobin, and water in the skin transforms into heat, causing thrombosis and ablation of superficial blood vessels.[17]

The mechanisms underlying the effect of IPL treatment in MGD are not clearly understood. Multiple possible mechanisms of action have been proposed:

1. Thrombosis of abnormal erythematous blood vessels removes the major source of inflammation in the eyelids and meibomian glands through facial artery and orbital vessels.[17]

2. IPL therapy causes a temperature increase up to 45-70 °C in small blood vessels, which in turn raises the eyelid skin temperature above the phase-transition temperature, which is 4 °C higher in MGD patients than healthy subjects. This thermal response unclogs the meibomian glands, liquefies the meibum and facilitates distribution over the ocular surface.[18,19]

3. The reduction in epithelial turnover with IPL therapy decreases the accumulation of debris on the lid margin and eliminates the risk of physical meibomian gland obstruction.[20]

4. Photomodulation (intracellular changes at the gene and protein levels by means of visible and infrared light induction) starts a cascade of excitation of cytochrome C oxidase, induction of redox potentials of mitochondrial respiratory chain and electron transfer, increase in cytoplasmic ATP levels, and finally increase in intracellular free calcium concentration, which stimulates specific physiological reactions for cell development and growth.[21,22,23]

5. Photomodulation increases the proliferation rate of fibroblasts and enhances the synthesis of collagen genes.[23,24]

6. The light delivered during IPL therapy is absorbed by pigmented chromophores in the exoskeleton of *Demodex folliculum*, a potential mediator of blepharitis, causing coagulation and necrosis of the ectoparasite.[25,26] Eradication of *Demodex* decreases the microbial load, particularly commensal bacteria *Bacillus olerinus,* which contributes to chronic inflammation of the eyelids.[27]

7. IPL therapy interferes with the positive feedback loop underlying the inflammatory cycle by upregulating anti-inflammatory agents like interleukin (IL)-10 and transforming growth factor beta (TGF-β) and/or downregulation of proinflammatory ones like IL-6 and tumor necrosis factor alpha (TNF-α).[28,29,30]

8. IPL indirectly suppresses one of the major protein families in the pathogenesis of dry eye disease, matrix metalloproteinases, by downregulating TNF-α.[31]

9. High-dose light irradiation causes attenuation of reactive oxygen species levels and decreases oxidative stress and inflammation.[7,32]

The E>Eye device, which we used in our study, is one of the specifically configured periocular IPL therapy devices (intense regulated pulsed light, IRPL) with regulated wavelengths, pulse duration, pulse intervals, and fluence depending on the patient's skin Fitzpatrick score. IPL therapy is not recommended for patients with a Fitzpatrick score higher than IV to avoid the risk of melanin damage and hypopigmentation.[33,34]

The non-invasive nature of the IPL device is favorable for both patient and ophthalmologist. However, incorrect use can cause devastating intraocular complications such as acute iridocyclitis due to neglecting the use of eye shields, permanent iris atrophy, posterior synechia, pupillary block, and secondary angle closure glaucoma due to absorption of light by the pigmented iris.[35,36,37,38,39] Other side effects are transient blistering, cheek swelling, conjunctival cyst, floaters, hair loss on the brow and forehead, light sensitivity, redness of face, purpura, and hyperpigmentation.[16,33,40] We observed no adverse effects in any of our patients.

Toyos et al.[16] reported that tear break-up time (TBUT) and meibum secretion were improved in 86% and 94% of patients with MGD-associated dry eye disease treated with IPL and meibomian gland expression (MGX), and the rate of patient satisfaction with treatment was 93%. Gupta et al.[41] showed a significant decrease in meibum viscosity and OSDI score and a significant increase in meibum flow and TBUT in MGD patients who underwent IPL therapy. Mejía et al.[42] demonstrated that IPL therapy effectively improves dry eye symptoms and objective scores of TBUT, Schirmer test, ocular surface staining in both evaporative and aqueous-deficient dry eye disease. Albietz and Schmid[43] reported sustained improvements in meibum expression, TBUT, ocular surface staining, and OSDI 6 weeks after final treatment with IPL/MGX, but not in Schirmer test or tear osmolarity. Arita et al.[15] showed significant improvement in Standard Patient Evaluation of Eye Dryness (SPEED) score, NIBUT, TBUT, meibum grade, and ocular surface staining in refractory MGD cases at 6 to 32 weeks of IPL/MGX. Choi et al.[44] reported that in addition to improvements in meibum score, TBUT, ocular surface staining, and OSDI, there is a correlation between meibomian gland function in patients with MGD and decreased inflammatory cytokines levels after IPL therapy. Dell et al.[45] reported that TBUT, corneal staining, tear film osmolarity, SPEED score, and meibomian gland score were improved but LLT was unchanged after 4 sessions of IPL/MGX in moderate

to severe MGD. Jiang et al.[46] reported significant improvement in symptom scores, TBUT, and meibomian gland score in MGD eyes, with no adverse effects. Karaca et al.[47] also reported improvement in Schirmer test, TBUT, OSDI, and SPEED scores, but not in Oxford scale or meibomian gland score after 3 sessions of IPL therapy in patients with MGD. Li et al.[40] observed a larger increase in TBUT and OSDI scores in younger MGD patients with Fitzpatrick skin types III-IV after IPL therapy. Seo et al.[5] indicated that improvements in meibomian gland score and ocular symptoms persisted for 12 months in patients with rosacea-associated MGD after 4 sessions of IPL treatment. Craig et al.[48] reported significant increase in LLT and NIBUT, but not in TMH or tear evaporation rate in MGD eyes treated with IPL.

To our knowledge, this is the first study in the English literature showing the effects of IPL therapy on moderate to severe acute blepharitis or blepharoconjunctivitis. We primarily observed clinical improvement in moderate to severe acute blepharitis or blepharoconjunctivitis patients without any side effects. We also found that ocular surface indexes (OSDI scores, ocular surface staining, non-invasive TMH, and NIBUT), meibomian gland functional indexes (COTE grading system and LLT), and meibomian gland morphological indexes determined using the non-contact meibography system with I.C.P. Ocular Surface Analyzer were improved, consistent with the literature.

Study Limitations

The main limitations of the study are its retrospective and single-arm design, small number of patients, concomitant drug treatment, and short follow-up time. Further prospective controlled studies with larger sample size and longer follow-up duration will be necessary to assess the long-term effectiveness and safety of IPL treatment for acute blepharitis or blepharoconjunctivitis.

Conclusion

In conclusion, our results suggest that in patients with moderate to severe acute blepharitis or blepharoconjunctivitis, serial IPL therapy in addition to conventional treatments effectively improves clinical signs, meibomian gland morphology, and secretion quality.

Ethics

Ethics Committee Approval: The study was approved by the Institutional Ethics Committee of Bahçeşehir University (6 Nov 2019; 2019-16/04).

Informed Consent: Retrospective study.

Peer-review: Externally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: Ö.M.G.T., Concept: Ö.M.G.T., Ü.A., Design: Ö.M.G.T., Ü.A., Data Collection or Processing: Ö.M.G.T., K.K., C.Ö., Analysis or Interpretation: Ö.M.G.T., K.K., C.Ö., Ü.A., Literature Search: Ö.M.G.T., K.K., C.Ö., Writing: Ö.M.G.T., Ü.A.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Nelson JD, Shimazaki J, Benitez-del-Castillo JM, Craig JP, McCulley JP, Den S, Foulks GN. The international workshop on meibomian gland dysfunction: report of the definition and classification subcommittee. Invest Ophthalmol Vis Sci. 2011;52:1930-1937.
2. Viswalingam M, Rauz S, Morlet N, Dart JKG. Blepharokeratoconjunctivitis in children: diagnosis and treatment. Br J Ophthalmol. 2005;89:400-403.
3. Lindsley K, Matsumura S, Hatef E, Akpek EK. Interventions for chronic blepharitis. Cochrane Database Syst Rev. 2012:CD005556.
4. Rong B, Tang Y, Liu R, Tu P, Qiao J, Song W, Yan X. Long-term effects of ıntense pulsed light combined with meibomian gland expression in the treatment of meibomian gland dysfunction. Photomed Laser Surg. 2018;36:562-567.
5. Seo KY, Kang SM, Ha DY, Chin HS, Jung JW. Long-term effects of intense pulsed light treatment on the ocular surface in patients with rosacea-associated meibomian gland dysfunction. Cont Lens Anterior Eye. 2018;41:430-435.
6. Vegunta S, Patel D, Shen JF. Combination therapy of ıntense pulsed light therapy and meibomian gland expression (IPL/MGX) can improve dry eye symptoms and meibomian gland function in patients with refractory dry eye: a retrospective analysis. Cornea. 2016;35:318-322.
7. Dell SJ. Intense pulsed light for evaporative dry eye disease. Clin Ophthalmol. 2017;11:1167-1173.
8. Küçümen RB, Utine CA, Görgün E, Yenerel NM, Ziylan S, Çiftçi F. Evaluation of tear film osmolarity in cases with chronic belpharitis. [In Turkish] Turk J Ophthalmol. 2015;45:5-8.
9. Alves M, Fonseca EC, Alves MF, Malki LT, Arruda GV, Reinach PS, Rocha EM. Dry eye disease treatment: a systematic review of published trials and a critical appraisal of therapeutic strategies. Ocul Surf. 2013;11:181-192.
10. Torkildsen GL, Cockrum P, Meier E, Hammonds WM, Silverstein B, Silverstein S. Evaluation of clinical efficacy and safety of tobramycin/dexamethasone ophthalmic suspension 0.3%/0.05% compared to azithromycin ophthalmic solution 1% in the treatment of moderate to severe acute blepharitis/blepharoconjunctivitis. Curr Med Res Opin. 2011;27:171-178.
11. Thode AR, Latkany RA. Current and emerging therapeutic strategies for the treatment of meibomian gland dysfunction. Drugs. 2015;75:1177-1185.
12. Akova YA, Asena L. Meibomian Gland Dysfunction: Review. Turkiye Klinikleri J Ophthalmol. 2014;23:172-183.
13. Geerling G, Tauber J, Baudouin C, Goto E, Matsumoto Y, O'Brien T, Rolando M, Tsubota K, Nichols KK. The International Workshop on Meibomian Gland Dysfunction: report of the subcommittee on management and treatment of meibomian gland dysfunction. Invest Ophthalmol Vis Sci. 2011;52:2050-2064.
14. Yin Y, Liu N, Gong L, Song N. Changes in the meibomian gland after exposure to intense pulsed light in meibomian gland dysfunction (MGD) patients. Curr Eye Res. 2018;43:308-313.
15. Arita R, Mizoguchi T, Fukuoka S, Morishige N. Multicenter study of intense pulsed light therapy for patients with refractory meibomian gland dysfunction. Cornea. 2018;37:1566-1571.
16. Toyos R, McGill W, Briscoe D. Intense pulsed light treatment for dry eye disease due to meibomian gland dysfunction; a 3-year retrospective study. Photomed Laser Surg. 2015;33:41-46.
17. Papageorgiou P, Clayton W, Norwood S, Chopra S, Rustin M. Treatment of rosacea with intense pulsed light: significant improvement and long-lasting results. Br J Dermatol. 2008;159:628-632.
18. Borchman D, Foulks G, Yappert M, Bell J, Wells E, Neravetla S, Greenstone V. Human meibum lipid conformation and thermodynamic changes with meibomian-gland dysfunction. IOVS. 2011;52:3805-3817.
19. Bäumler W, Vural E, Landthaler M, Muzzi F, Shafirstein G. The effects of intense pulsed light (IPL) on blood vessels investigated by mathematical modeling. Lasers Surg Med. 2007;39:132-139.

20. Henriquez A, Korb D. Meibomian glands and contact lens wear. Br J Ophthalmol. 1981;65:108-111.
21. Karu T. Primary and secondary mechanisms of action of visible to near-IR radiation on cells. J Photochem Photobiol B. 1999;49:1-17.
22. Farivar S, Malekshahabi T, Shiari R. Biological effects of low level laser therapy. J Lasers Med Sci. 2014;5:58-62.
23. Takezaki S, Omi T, Sato S, Kawana S. Ultrastructural observations of human skin following irradiation with visible red light-emitting diodes (LEDs): a preliminary in vivo report. Laser Ther. 2005;14:153-160.
24. Cuerda-Galindo E, Díaz-Gil G, Palomar-Gallego M, Linares-GarcíaValdecasas R. Increased fibroblast proliferation and activity after applying intense pulsed light 800–1200 nm. Ann Anat. 2015;198:66-72.
25. Prieto V, Sadick N, Lloreta J, Nicholson J, Shea C. Effects of intense pulsed light on sun-damaged human skin, routine, and ultrastructural analysis. Lasers Surg Med. 2002;30:82-85.
26. Kirn T. Intense pulsed light eradicates Demodex mites. Skin Allergy News. 2002;33:37.
27. O'Reilly N, Menezes N, Kavanagh K. Positive correlation between serum immunoreactivity to Demodex-associated Bacillus proteins and erythematotelangiectatic rosacea. Br J Dermatol. 2012;167:1032-1036.
28. Byun J, Choi H, Myung K, Choi Y. Expression of IL-10, TGF-β1 and TNF-α in cultured keratinocytes (HaCaT Cells) after IPL treatment or ALA-IPL photodynamic treatment. Ann Dermatol. 2009;21:12-17.
29. Lee S, Park K, Choi J, Kwon J, Lee DR, Shin MS, Lee JS, You CE, Park MY. A prospective, randomized, placebo-controlled, double-blinded, and split-face clinical study on LED phototherapy for skin rejuvenation: clinical, profilometric, histologic, ultrastructural, and biochemical evaluations and comparison of three different treatment settings. J Photochem Photobiol B. 2007;88:51-67.
30. Taylor M, Porter R, Gonzalez M. Intense pulsed light may improve inflammatory acne through TNF-α down-regulation. J Cosmet Laser Ther. 2014;16:96-103.
31. Wong WR, Shyu WL, Tsai JW, Hsu KH, Lee HY, Pang JH. Intense pulsed light modulates the expressions of MMP-2, MMP-14 and TIMP-2 in skin dermal fibroblasts cultured within contracted collagen lattices. J Dermatol Sci. 2008;51:70-73.
32. Lubart R, Lavi R, Friedmann H, Rochkind S. Photochemistry and photobiology of light absorption by living cells. Photomed Laser Surg. 2006;24:179-185.
33. Guilloto Caballero S, García Madrona JL, Colmenero Reina E. Effect of pulsed laser light in patients with dry eye syndrome. Arch Soc Esp Oftalmol. 2017;92:509-515.
34. Fitzpatrick TB. The validity and practicality of sun-reactive skin types I through VI. Arch Dermatol. 1988;124:869-871.
35. Crabb M, Chan WO, Taranath D, Huilgol SC. Intense pulsed light therapy (IPL) induced iritis following treatment for a medial canthal capillary malformation. Australas J Dermatol. 2014;55:289-291.
36. Lee WW, Murdock J, Albini TA, O'Brien TP, Levine ML. Ocular damage secondary to intense pulse light therapy to the face. Ophthal Plast Reconstr Surg. 2011;27:263-265.
37. Pang AL, Wells K. Bilateral anterior uveitis after intense pulsed light therapy for pigmented eyelid lesions. Dermatol Surg. 2008;34:1276-1279.
38. Goldman MP, Weiss RA, Weiss MA. Intense pulsed light as a nonablative approach to photoaging. Dermatol Surg. 2005;31:1179-1187.
39. Javey G, Schwartz SG, Albini TA. Ocular complication of intense. pulsed light therapy: iris photoablation. Dermatol Surg. 2010;36:1466-1468.
40. Li D, Lin S, Cheng B. Intense pulsed light treatment for meibomian gland dysfunction in skin types III/IV. Photobiomodul Photomed Laser Surg. 2019;37:70-76.
41. Gupta PK, Vora GK, Matossian C, Kim M, Stinnett S. Outcomes of intense pulsed light therapy for treatment of evaporative dry eye disease. Can J Ophthalmol. 2016;51:249-253.
42. Mejía LF, Gil JC, Jaramillo M. Intense pulsed light therapy: a promising complementary treatment for dry eye disease. Arch Soc Esp Oftalmol. 2019;94:331-336.
43. Albietz JM, Schmid KL. Intense pulsed light treatment and meibomian gland expression for moderate to advanced meibomian gland dysfunction. Clin Exp Optom. 2018;101:23-33.
44. Choi M, Han SJ, Ji YW, Choi YJ, Jun I, Alotaibi MH, Ko BY, Kim EK, Kim T, Nam SM, Seo KY. Meibum Expressibility improvement as a therapeutic target of intense pulsed light treatment in meibomian gland dysfunction and its association with tear infammatory cytokines. Sci Rep. 2019;9:1-8.
45. Dell SJ, Gaster RN, Barbarino SC, Cunningham DN. Prospective evaluation of intense pulsed light and meibomian gland expression efficacy on relieving signs and symptoms of dry eye disease due to meibomian gland dysfunction. Clin Ophthalmol. 2017;11:817-882.
46. Jiang X, Lv H, Song H, Zhang M, Liu Y, Hu X, Li X, Wang W. Evaluation of the safety and effectiveness of intense pulsed light in the treatment of meibomian gland dysfunction. J Ophthalmol. 2016;1910694.
47. Karaca EE, Kemer OE, Özek D. Intense regulated pulse light for the meibomian gland dysfunction. Eur J Ophthalmol. 2018;1-4.
48. Craig JP, Chen YH, Turnbull PRK. Prospective trial of intense pulsed light for the treatment of meibomian gland dysfunction. Invest Ophthalmol Vis Sci. 2015;56:1965-1970.

DOI: 10.4274/tjo.galenos.2020.52563
Turk J Ophthalmol 2021;51:95-101

Original Article

Effects of the COVID-19 Pandemic on Turkish Ophthalmologists

Işılay Kavadarlı*, Melek Mutlu**

*Dünyagöz Hospital, İstanbul, Turkey
** University of Health Sciences Turkey Gaziosmanpaşa Training and Research Hospital, Clinic of Ophthalmology, İstanbul, Turkey

Abstract

Objectives: To assess the effects of the coronavirus disease-2019 (COVID-19) pandemic on Turkish ophthalmologists.
Materials and Methods: In this survey study, an online questionnaire consisting of 40 questions was directed to actively working ophthalmologists. The questions asked about demographic characteristics, working conditions and schedule, follow-up of ophthalmology patients, and levels of knowledge and anxiety about the pandemic.
Results: This study included 161 ophthalmologists (78 women and 83 men). They were predominantly consultant ophthalmologists (71%), with 128 living in metropolitan areas. More than half (54.4%) reported decreased weekly working hours, 52.5% were attending routine outpatient clinics, 52.8% were working in COVID-19-related units, 67.1% were performing only emergency operations, and 52% reported disrupted follow-up of chronic eye patients. Sixty-four percent thought that ophthalmologists were in the high-risk group, and nearly all participants used masks while working (99%). Additionally, 91% expressed high anxiety regarding the pandemic, most commonly due to the risk of transmitting the disease to family (83%), and 12.5% considered their level of knowledge about the pandemic to be insufficient. Forty-six percent of the participants thought that daily life conditions would normalize in 2 to 5 months.
Conclusion: Close proximity during patient examination causes ophthalmologists concern about their risk. The increasing number of COVID-19 cases resulted in a proportional decrease in the number of patients and surgeries in ophthalmology clinics in our country. As a result, ophthalmologists are unwillingly appointed to high-risk units. The COVID-19 pandemic has caused a substantial increase in anxiety levels among Turkish ophthalmologists.
Keywords: COVID-19, pandemic, ophthalmologist, anxiety

Introduction

Coronavirus disease-2019 (COVID-19) is an acute respiratory disease caused by a novel coronavirus severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) first detected in Wuhan, China in December 2019. It is highly infectious and was recognized by the World Health Organization as an emergency pandemic that threatens public health due to its rapid international spread (http://www.euro.who.int/en/healthtopics/emergencies/pages/news/news/2020/01/2019-ncov-outbreak-is-an-emergency-of-international-concern).

Infected patients most commonly present with symptoms such as fever, dry cough, weakness, myalgia, and dyspnea. Transmission is thought to occur either through droplets from close contact with an infected person or by touching contaminated surfaces.[1,2] This virus, which navigates from mouth and nasal mucosa to the respiratory tract, has also been detected in conjunctival swabs and tears and reported to cause conjunctivitis.[3,4] Moreover, conjunctival congestion was

Address for Correspondence: Işılay Kavadarlı, Dünyagöz Hospital, İstanbul, Turkey
E-mail: isilay@kavadarli.com **ORCID-ID:** orcid.org/0000-0002-0057-8828
Received: 25.04.2020 **Accepted:** 23.07.2020

Cite this article as: Kavadarlı I, Mutlu M. Effects of the COVID-19 Pandemic on Turkish Ophthalmologists. Turk J Ophthalmol 2021;51:95-101

reported in 9 (0.8%) of 1,099 COVID-19 patients studied in China.[5]

As ophthalmologists, being in close proximity with the patient during biomicroscopic examination and possible contamination from used devices constitute high risk of infection and carriage of SARS-CoV-2. The purpose of this study was to evaluate Turkish ophthalmologists' knowledge, anxiety level, working conditions, and preventive measures related to the COVID-19 pandemic by online survey.

Materials and Methods

In this survey study, which was carried out using an online questionnaire (docs.google.com/forms), participants were not required to provide personal identity information data and were informed that the information they provided would be used solely for research purposes. The questions were directed to actively working ophthalmologists who volunteered for the study between 8 and 14 April 2020. These questions were categorized under the main topics of demographic features, characteristics of the institutions at which ophthalmologists were working, procurement and use of protective equipment, follow-up of ophthalmology patients, and levels of knowledge and anxiety about the COVID-19 pandemic.

Demographic data collected included age, gender, city, number of people in household, presence of chronic disease, and smoking status. Questions related to the institutions in which the ophthalmologists were working included the type of hospital, their title and years of professional experience, adequacy of equipment, change in the number of operations and outpatient visits, and exposure to COVID-19 patients. The use of masks, safety glasses, and gloves as protective equipment, installation of a protective shield on the biomicroscope, and cleaning of microscopes were also questioned. With respect to ophthalmology patients, the participant's approach to patients presenting with conjunctivitis, follow-up of chronic eye diseases, and their approach to patients using contact lenses were among the questions. Perceived adequacy of the participants' knowledge and their sources of information about the COVID-19 pandemic were questioned. In addition, there were questions about pandemic-related concerns such as infection and transmission anxiety, level of risk for ophthalmologists, and an estimate of how long the pandemic would last. Of the total 40 questions, 11 were yes/no questions, 24 required the participant to select the most suitable response option, and 5 allowed the participant to select multiple response options. The answers were collected by a single person and analyzed using the Microsoft Excel program.

Results

This study included 161 participants, of whom 78 were women and 83 were men, with 36.2% between 35 and 44 years of age (Figure 1). In terms of other demographic features, 13.1% were living alone, 20% had chronic diseases, and 9.4% were smokers. Regarding their institutions, 34% were working in private hospitals, 25.2% in education and research hospitals, 24.5% in state hospitals, and 15.1% in university hospitals. The majority of the participants (71.3%) were consultant ophthalmologists and 61.9% had more than 10 years of professional experience. One hundred twenty-eight of the participants were living in one of 30 metropolitan cities, with the highest number being from Istanbul (n=46). Most participants (76.9%) stated that there were COVID-19 cases in their institutions, and 52.8% were working in high-risk units/schedules such as night shifts, emergency rooms, and COVID-19 clinics. Among those who were working in these units, 80% lived in metropolitan cities, 80% were ≤45 years old, 41% were working in state hospitals, 36% in education and research hospitals, 17% in university hospitals, and 5% in private hospitals. Moreover, 22% were both attending routine ophthalmology clinics and working in units with a high risk of COVID-19 transmission.

Reduced weekly working hours was mentioned by 54.4% of the participants, while 52.5% were attending routine outpatient clinics. Although 67.1% of the participants were performing only emergency surgeries, 5.3% continued elective surgeries as necessary. Expectedly, 88% of those continuing elective surgeries worked in private hospitals. When asked whether protective equipment was sufficient in their institution, more than half of the participants (53.7%) said that protective equipment was generally sufficient despite some shortcomings (Figure 2). Of these, 40% were working in units that were risky in terms of COVID-19, 31% worked in private hospitals, and 50% were those continuing to perform elective surgeries. Regarding protective measures against infection and transmission, 91.8% had installed a biomicroscope shield for protective purposes, 55% were using protective glasses, 99.4% were using masks during examinations, 80% were providing masks to examined patients, 57.2% were changing gloves after every patient, and 82% were disinfecting their biomicroscopes after each

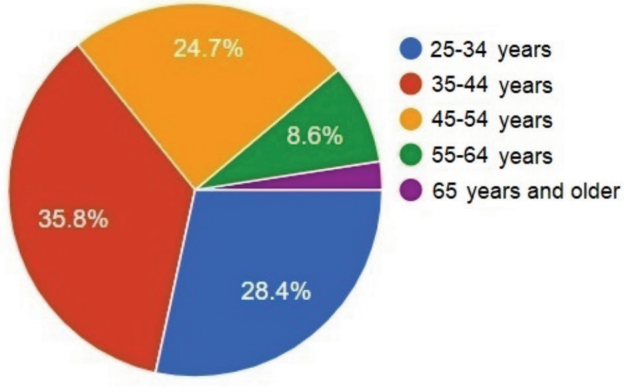

Figure 1. Age distribution of the participants

patient examination. The most commonly used mask type was surgical masks (67.5%), whereas others masks were FFP2 (20%) and FFP3 (12.5%). Most participants (75%) were not allowing patients' relatives in the examination room.

When asked whether they had concerns about COVID-19 and questioned additional symptoms when examining patients with conjunctivitis, 93.1% of the participants answered yes. More than half (51.9%) of the participants reported that the follow-up of patients with chronic eye diseases was disrupted during the pandemic (Figure 3). When asked which patients they considered most affected during the pandemic, the most frequent responses were patients with age-related macular degeneration and diabetic macular edema (Figure 4). Regarding their approach to contact lens users, 56.9% of participants strongly urged patients to use glasses instead of contact lenses, 33.1% only recommended the use of glasses, and 10% did not recommend the use of glasses at all to their patients.

Although 64.2% of the participants considered ophthalmology to be among the high-risk medical branches, 34.6% believed themselves to be in the medium risk group. When asked whether they would perform surgery on a patient diagnosed with COVID-19, 55.6% said they would perform urgent procedures with the necessary precautions, 24.4% said they would refer the patient to another institution, and 30.6% said they would insist on conservative treatment options.

The presence of anxiety during the pandemic was mentioned by 91.3% of the participants, and the most common reason cited for this anxiety was the risk of transmitting the disease to family members (83.1%) (Figure 5). Of those expressing concern about transmitting the disease to family, 43.1% were concerned and 23.8% were very concerned. Fifty-seven percent of the very concerned participants were working in high-risk COVID-19 units, while 84% of those who were not worried about the pandemic were living alone. Furthermore, 53.8% stated that they could not stay elsewhere, 23.7% could stay in another house if provided, and 22.4% could stay in guesthouses during the pandemic.

Perceived level of knowledge about the COVID-19 pandemic was rated as sufficient by 33.1%, partially sufficient by 54.4%, and insufficient by 12.5% of the participants. The most common sources of information were scientific articles (78.1%), Ministry of Health guidelines (60%), social media (45%), and hospital education programs (31.3%). None of the participants answered yes when asked if they believed the pandemic was being exaggerated, and 35.8% stated that the pandemic warranted even more attention. While 61.9% were satisfied with the information provided by national health specialty associations, 24.4% did not know about them. The largest proportion of participants (46%) estimated that conditions would normalize in 2 to 5 months (Figure 6).

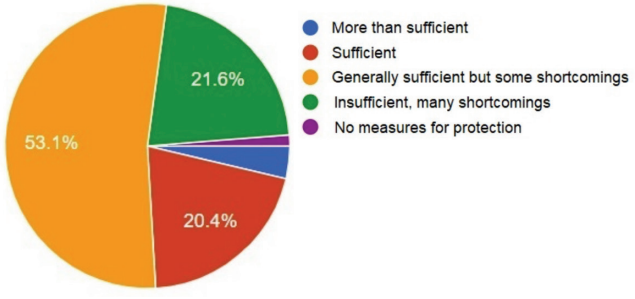

Figure 2. The participants' perceptions about the protective equipment and precautions against the COVID-19 pandemic in their institutions

COVID-19: Coronavirus disease-2019

Discussion

The novel coronavirus was first identified as the cause of an outbreak of pneumonia in China on January 7, 2020. The virus spread rapidly worldwide, escalating to a pandemic due to international travel by patients and carriers, and as of April 26, 2020, SARS-CoV-2 had been detected in nearly 2.8 million people and resulted in the deaths of 190,871 people worldwide (https://covid19.who.int/). The first case in our country was announced on March 11, 2020 and the numbers of confirmed cases and deaths as of April 14, 2020 were reported as 65,111 and 1,403, respectively (https://covid19.saglik.gov.tr/).

The rapid spread of COVID-19 impacted healthcare globally. Health workers in units with high risk of transmission required both more efficient protective equipment and changes in working conditions. In this study, 54% of the participants said that their weekly working hours were reduced, 52% were attending routine outpatient clinics, and 52% were working in risky units related to COVID-19. The decrease in the number of ophthalmology outpatient appointments and increase in the burden of work in COVID-19 units is likely due to the fact that most of the ophthalmologists lived in metropolitan cities and non-emergency hospital visits, especially to ophthalmology clinics, were reduced.

During the SARS epidemic of 2003, 21% of cases were reported to be healthcare professionals.[6] Likewise, a report published in China in February 2020 stated that 6 of 1,716 infected health workers died (https://www.who.int/dg/speeches/detail/whodirector-general-s-remarks-at-the-media-briefing-on-covid-2019outbreak-on-14-february-2020).[7] Among these victims was Dr. Li Wenliang, the ophthalmologist who was infected by an asymptomatic patient followed up for glaucoma (https://www.aao.org/headline/coronavirus-kills-chinese-whistleblower-ophthalmol).

The close proximity of ophthalmologists to the patient during biomicroscopic examination increases the risk of infection. In this study, 64% of the ophthalmologists reported that they thought they were in a high-risk branch of medicine. Similarly, in a survey of 100 people working in ophthalmology clinics in the UK, 80% thought they were in

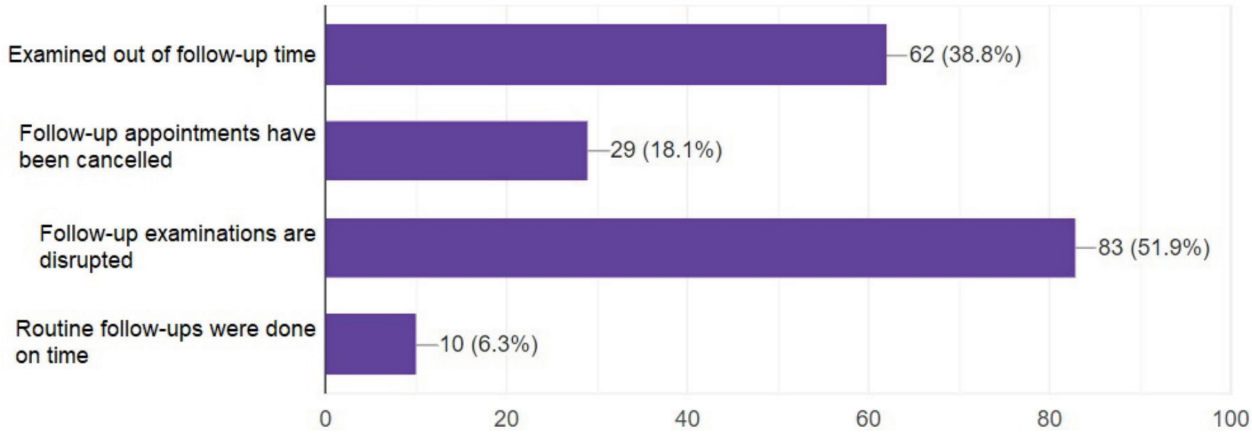

Figure 3. Follow-up periods of the patients with chronic eye diseases

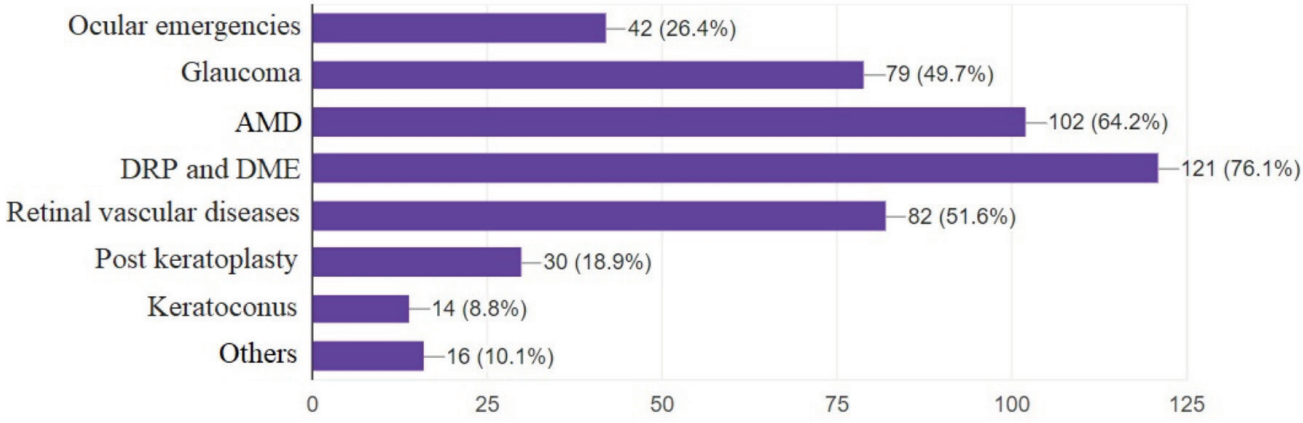

Figure 4. Ophthalmic patient groups considered to be most affected during the pandemic
AMD: Age-related macular degeneration, DRP: Diabetic retinopathy, DME: Diabetic macular edema

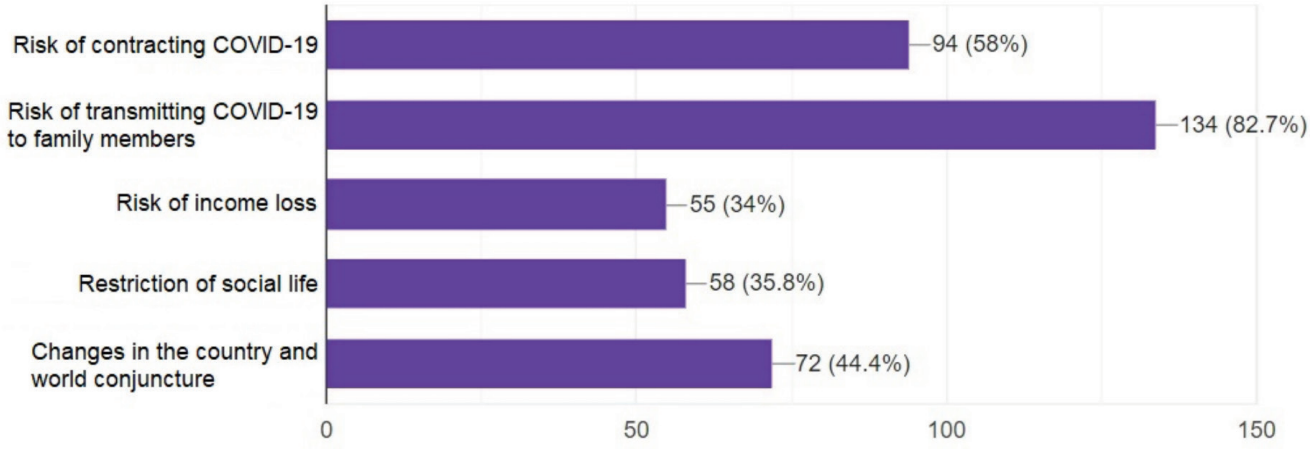

Figure 5. Reasons for the participants' anxiety related to the COVID-19 pandemic
COVID-19: Coronavirus disease-2019

the high-risk group.[8] Furthermore, in the same survey, 55% of respondents found the guidelines insufficient and 79% were not trained for efficient use of personal protective equipment (PPE). The study also revealed that most respondents did not trust guidelines that did not recommend ophthalmology practitioners to routine use PPE, and that there was insufficient explanation regarding the use of protective glasses, gowns, and FFP3 masks in patient examinations at close proximity (closer than 1 m). Consequently, eye hospitals started using acetate shields on all biomicroscopes for protection and provided FFP3 to all healthcare workers. In the present study, nearly all participants were using masks during examination (67% surgical masks), 80% provided masks to patients, 55% wore protective glasses, and 91% had installed protective shields on their biomicroscopes. Only 21% thought that their clinics were insufficient in terms of PPE. We believe that close cooperation between ophthalmology clinics, healthcare associations, and the Ministry of Health is required to eliminate these shortcomings. The use of masks, protective glasses, and a biomicroscope shield has been recommended in the guideline published by the American Academy of Ophthalmology (AAO) (https://www.aao.org/headline/d6e1ca3c-0c30-4b20-87e0-7668fa5bf906).

In a meta-analysis on the use of masks by healthcare workers, it was reported that surgical masks would provide protection from large droplets, whereas N95 masks would be protective in procedures such as bronchoscopy and intubation that cause aerosol scattering.[9] Romano et al.[10] recommended the use of FFP3 masks during ophthalmologic examinations of diagnosed or suspected COVID-19 cases. Although there are guideline-based recommendations for the use of mask types and PPE in ophthalmology practice, there is no definite consensus whatsoever.

Although 93% of the participants in our study reported that they would question patients presenting with conjunctivitis about additional COVID-19 symptoms, currently there is no consensus in the literature on ocular surface transmission of SARS-CoV-2. Xia et al.[3] investigated tear and conjunctival swab samples from 30 patients with coronavirus pneumonia using SARS-CoV-2 polymerase chain reaction (PCR) test and reported positive results only in the samples obtained from the one patient who had conjunctivitis. In another study conducted by Zhou et al.[11], PCR tests of conjunctival swab samples taken from 69 patients with COVID-19 pneumonia yielded only 1 positive and 2 possibly positive results, while the PCR result of the one patient with accompanying conjunctivitis was negative. On the other hand, Wu et al.[12] reported ocular symptoms such as hyperemia, chemosis, and epiphora in 12 of 38 COVID-19 patients with clinical symptoms, with positive PCR results for nasopharyngeal samples in 28 cases and nasopharyngeal and conjunctival swab samples in 2 cases. In the same study, although 11 patients with ocular symptoms had positive nasopharyngeal specimens, only 2 had positive conjunctival swab samples. In addition, levels of blood inflammatory markers were higher in the patients with ocular syptoms.[12] Despite detection of the virus in conjunctival swab and tear samples, currently there is no scientific evidence linking the virus and ocular symptoms directly. Consequently, it may be suggested that directing patients to eye clinics due to red eye may be the source of transmission.

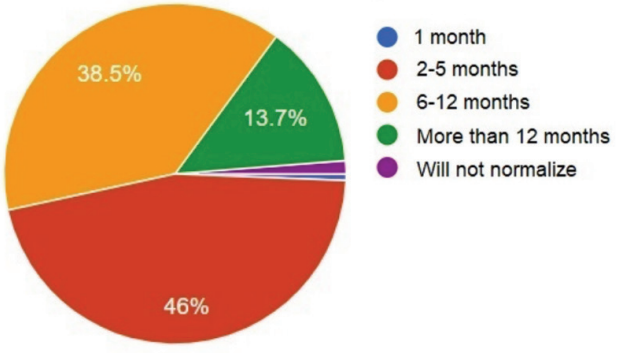

Figure 6. Participants' expectations of the time until normalization of conditions caused by the COVID-19 pandemic

COVID-19: Coronavirus disease-2019

Fifty-two percent of the participants in this study said that the follow-up of patients with chronic eye diseases was disrupted during the pandemic; only 6% said they were continuing routine follow-up as usual. The participants also speculated that this would mostly impact patients with age-related macular degeneration and diabetic macular edema. These diseases most commonly affect the older population, which is also among the high-risk groups with respect to COVID-19. This patient group has high mortality and has been advised not to go to hospitals except in emergencies to reduce the risk of infection.[13]

In another study conducted in China, it was reported that 34 previously asymptomatic COVID-19-positive patients became symptomatic after non-ocular surgeries, with lung tomography findings compatible with pneumonia in all patients and a mortality rate of 20% during the postoperative period.[14] Although the proportion of ophthalmologists performing elective surgeries was low in our study, it suggests that patients should be carefully evaluated for COVID-19 preoperatively. Guides regarding the procedures and surgeries classified as urgent during the pandemic have been published by both the Turkish Ophthalmological Association (TOA) and AAO (https://koronavirus.todnet.org/pandemi-nedeni-ile-acil-kabul-edilen-gz-ameliyatlar), (https://www.aao.org/headline/list-of-urgent-emergent-ophthalmic-procedures). While the TOA guidelines were found to be satisfactory by the majority of the participants, 24% did not know about the guidelines.

Fifty-seven percent of the participants in this study stated that they strongly recommended patients use glasses instead of contact lenses. Although not proven, the possibility of virus

transmission through the eye suggests that glasses may offer more protection against transmission through droplets, and hence may be more appropriate to use during the pandemic. Despite the fact that contact lens disinfection solutions have a virucidal effect, the information on this subject remains hypothetical. Patients continuing to use contact lenses should be informed in detail in accordance with the information from the TOA manual and other sources (https://koronavirus.todnet.org/kon).[15]

Ninety-one percent of the participants stated that their anxiety level increased due to the pandemic and they were mostly worried about infecting their families. In a survey of 1,210 people conducted in China, 54% of the participants expressed being moderately to severely affected psychologically, 75% experienced anxiety due to the risk of infecting their families, and the use of masks decreased the level of anxiety.[16] The high anxiety level in the present study may be related to the participants being highly educated and working in units with high COVID-19 risk. Likewise, Qiu et al.[17] observed that the level of pandemic-related stress was higher in those with higher education level.

Study Limitations

In this study, the most frequently used sources of information were scientific articles and Ministry of Health guidelines, indicating that the participants were trying to obtain the most accurate information possible. Fifty-four percent of the participants considered their level of knowledge about the pandemic as partly sufficient, whereas 12% considered it insufficient. This may be attributed to factors such as the rapid progression of the pandemic, the occupational stress experienced by health professionals, and the inability to sufficiently keep up with the flow of information. None of the participants thought that the pandemic was being exaggerated, and in fact the majority thought that more attention should be given to the COVID-19 pandemic. This indicates that awareness of the pandemic is high among ophthalmologists. The majority of the participants expected the pandemic to last up to 6 months.

Conclusion

Because ophthalmologists are always in close proximity to the patient, they are in the risk group for COVID-19. With the ongoing pandemic, anxiety levels have increased, work conditions have changed, and urgent examinations and interventional procedures have been prioritized. It is therefore necessary to provide up-to-date information on the use of PPE and procure materials. Although it is uncertain when the pandemic will end, following guidelines is immensely important for not only ourselves but also our patients.

Ethics

Ethics Committee Approval: Obtained.

Informed Consent: Obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: I.K., M.M., Design: I.K., M.M., Data Collection or Processing: I.K., Analysis or Interpretation: I.K., M.M., Literature Search: I.K., M.M., Writing: I.K., M.M.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, Qiu Y, Wang J, Liu Y, Wei Y, Xia J, Yu T, Zhang X, Zhang L. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020;395: 507-513.
2. Rothan HA, Byrareddy SN. The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. J Autoimmun. 2020;109:102433.
3. Xia J, Tong J, Liu M, Shen Y, Guo D. Evaluation of coronavirus in tears and conjunctival secretions of patients with SARS-CoV-2 infection. J Med Virol. 2020;92:589-594.
4. Cheema M, Aghazadeh H, Nazarali S, Ting A, Hodges J, McFarlane A, Kanji JN, Zelyas N, Damji KF, Solarte C. Keratoconjunctivitis as the initial medical presentation of the novel coronavirus disease 2019 (COVID-19). Can J Ophthalmol. 2020;55:125-129.
5. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, Liu L, Shan H, Lei CL, Hui DSC, Du B, Li LJ, Zeng G, Yuen KY, Chen RC, Tang CL, Wang T, Chen PY, Xiang J, Li SY, Wang JL, Liang ZJ, Peng YX, Wei L, Liu Y, Hu YH, Peng P, Wang JM, Liu JY, Chen Z, Li G, Zheng ZJ, Qiu SQ, Luo J, Ye CJ, Zhu SY, Zhong NS; China Medical Treatment Expert Group for Covid-19. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020;382:1708-1720.
6. Johnston LB, Conly JM. Severe acute respiratory syndrome: What have we learned two years later? Can J Infect Dis Med Microbiol. 2004;15:309-312.
7. Coronavirus kills Chinese whistleblower ophthalmologist. American Academy of Ophthalmology. https://www.aao.org/ headline/coronavirus-kills-chinese-whistleblower-ophthalmol. Accessed 15 Feb 2020 https://www.aao.org/headline/coronavirus-kills-chinese-whistleblower-ophthalmol
8. Minocha A, Sim SY, Than J, Vakros G. Survey of ophthalmology practitioners in A&E on current COVID-19 guidance at three major UK eye hospitals. Eye (Lond). 2020;34:1243-1245.
9. Bartoszko J, Farooqi MAM, Alhazzani W, Loeb M. Medical masks vs N95 respirators for preventing COVID-19 in health care workers a systematic review and meta-analysis of randomized trials. Influenza Other Respir Viruses. 2020;14:365-373.
10. Romano MR, Montericcio A, Montalbano C, Raimondi R, Allegrini D, Ricciardelli G, Angi M, Pagano L, Romano V. Facing COVID-19 in ophthalmology department. Curr Eye Res. 2020;45:653-658.
11. Zhou Y, Zeng Y, Tong Y, Chen C. Ophthalmologic evidence against the interpersonal transmission of 2019 novel coronavirus through conjunctiva. medRxiv. 2020.
12. Wu P, Duan F, Luo C, Liu Q, Qu X, Liang L, Wu K. Characteristics of ocular findings of patients with coronavirus disease 2019 (COVID-19) in Hubei Province, China. JAMA Ophthalmol. 2020;138:575-578.
13. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, Wang B, Xiang H, Cheng Z, Xiong Y, Zhao Y, Li Y, Wang X, Peng Z. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA. 2020;323:1061-1069.
14. Lei S, Jiang F, Su W, Chen C, Chen J, Mei W, Zhan LY, Jia Y, Zhang L, Liu D, Xia ZY, Xia Z. Clinical characteristics and outcomes of patients undergoing surgeries during the incubation period of COVID-19 infection. EClinicalMedicine. 2020;21:100331.

15. Jones L, Walsh K, Willcox M, Morgan P, Nichols J. The COVID-19 Pandemic: Important considerations for contact lens practitioners. Cont Lens Anterior Eye. 2020;43:196-203.
16. Wang C, Pan R, Wan X, Tan Y, Xu L, Ho CS, Ho RC. Immediate psychological responses and associated factors during the initial stage of the 2019 coronavirus disease (COVID-19) epidemic among the general population in China. Int J Environ Res Public Health. 2020;17:1729.
17. Qiu J, Shen B, Zhao M, Wang Z, Xie B, Xu Y. A nationwide survey of psychological distress among Chinese people in the COVID-19 epidemic: implications and policy recommendations. Gen Psychiatr. 2020;33:e100213.

DOI: 10.4274/tjo.galenos.2020.43709
Turk J Ophthalmol 2021;51:102-106

Original Article

Vitrectomy Due to Vitreous Hemorrhage and Tractional Retinal Detachment Secondary to Eales' Disease

M. Giray Ersöz, Mümin Hocaoğlu, Işıl Bahar Sayman Muslubaş, Serra Arf, Murat Karaçorlu

İstanbul Retina Institute, İstanbul, Turkey

Abstract

Objectives: To investigate visual and anatomical outcomes of vitreoretinal surgeries in patients with Eales' disease.

Materials and Methods: In this retrospective study, 22 eyes of 21 patients with vitreous hemorrhage (VH) or tractional retinal detachment (TRD) secondary to Eales' disease who underwent vitreoretinal surgery between January 1997 and December 2015 and had at least 1 year of follow-up were included.

Results: The mean best corrected visual acuity (BCVA) was significantly higher at final visit (0.6±0.9 logMAR) than the preoperative values (1.8±1.1 logMAR) ($p<0.001$). After surgery, BCVA was stable in 4 eyes (18.2%), increased in 16 eyes (72.7%), and decreased in 2 eyes (9.1%). Although the mean BCVA was better in the VH group (0.3±0.34 logMAR) than the TRD group (0.9±1.1 logMAR), the difference was not statistically significant ($p=0.1$). Multivariable linear regression analyses revealed that final BCVA was negatively associated with preoperative or postoperative proliferative vitreoretinopathy grade C (PVR-C), preoperative retinal detachment involving the macula, postoperative neovascular glaucoma, and long preoperative duration of disease, and positively associated with preoperative BCVA. Final BCVA was not associated with preoperative retinal and disc neovascularization, rubeosis iridis, total posterior hyaloid detachment, preoperative retinal laser photocoagulation, indication of surgery, diameter of sclerotomy (20 or 23 gauge), preoperative lens status, preoperative or postoperative epimacular membrane, peroperative iatrogenic retinal breaks, postoperative hypotony, cystoid macular edema, and new or recurrent retinal detachment. The primary anatomic success rate was 81.8% and the final anatomic success rate was 90.9%.

Conclusion: In Eales' disease, good visual results can be obtained with vitreoretinal surgery if the detachment area does not involve the macula and PVR-C does not develop pre- or postoperatively.

Keywords: Eales' disease, tractional retinal detachment, vitrectomy, vitreous hemorrhage

Introduction

Eales' disease is an idiopathic occlusive retinal vasculitis that mainly affects the peripheral retinal veins, usually in young men.[1] Findings that may be observed in Eales' disease include periphlebitis with or without arteritis, peripheral capillary nonperfusion, retinal neovascularization (NVE), disc neovascularization (NVD), central or branch retinal vein occlusion, vitreous hemorrhage (VH), tractional retinal detachment (TRD), combined TRD and rhegmatogenous retinal detachment (RRD), and neovascular glaucoma.[2] Active periphlebitis may be accompanied by anterior uveitis, posterior uveitis, and pars planitis.[1,3] Patients usually present with recurrent VH and involvement is generally bilateral.[3] Although defined as an idiopathic disease, it may be associated with *Mycobacterium tuberculosis* and hypersensitivity to tubercular antigen.[4,5]

Systemic steroid therapy is effective in controlling the active phase of Eales' disease.[3] Intravitreal steroids are useful in the treatment of periphlebitis and cystoid macular edema.[6,7]

Address for Correspondence: Murat Karaçorlu, İstanbul Retina Institute, İstanbul, Turkey
E-mail: mkaracorlu@gmail.com **ORCID-ID:** orcid.org/0000-0001-5561-3339
Received: 22.12.2019 **Accepted:** 27.07.2020

Cite this article as: Ersöz MG, Hocaoğlu M, Sayman Muslubaş IB, Arf S, Karaçorlu M. Vitrectomy Due to Vitreous Hemorrhage and Tractional Retinal Detachment Secondary to Eales' Disease. Turk J Ophthalmol 2021;51:102-106

Performing early retinal photocoagulation on non-perfused areas has a positive effect on visual outcomes.[3,8,9,10] Anti-vascular endothelial growth factor agents may be beneficial for the regression of cystoid macular edema, but they do not accelerate resolution of VH and can lead to the development of TRD and secondary RRD.[11,12,13] Vitreoretinal surgery is required in the presence of non-clearing VH and TRD affecting or threatening the macula.[14,15,16]

In this study, we aimed to investigate the visual and anatomical outcomes of vitreoretinal surgeries in patients with Eales' disease and the factors affecting final visual acuity.

Materials and Methods

Twenty-two eyes of 21 patients who underwent vitrectomy for VH or TRD due to Eales' disease between January 1997 and December 2015 and were followed up for at least 1 year were included in this retrospective study. The study protocol was designed in accordance with the Declaration of Helsinki and approved by the Şişli Memorial Hospital Ethics Committee. Medical history, systemic diseases, age, sex, previous ocular surgeries, surgical procedure, best corrected visual acuity (BCVA), intraocular pressure, preoperative and postoperative ophthalmic examination findings, and postoperative complication data were obtained by retrospective chart review. Eales' disease was diagnosed in the presence of occlusive periphlebitis in one or both eyes after ruling out diabetic retinopathy, hypertensive retinopathy, non-inflammatory retinal vein occlusion, sickle cell anemia, and infectious or inflammatory causes such as collagen tissue diseases, Behçet's disease, sarcoidosis, and syphilis. Indications for vitrectomy were BCVA of 0.52 logMAR or worse due to non-clearing VH persisting for at least 2 months, and presence of macula-involving/threatening TRD with or without RRD. Patients with less than 1 year of follow-up and those with previous vitrectomy for Eales' disease or any other reason were not included in the study.

Treatment

All surgical procedures were performed under general anesthesia by the same surgeon (M.K.). All patients underwent a 20-gauge or 23-gauge pars plana vitrectomy and panretinal laser photocoagulation. Posterior hyaloid dissection was performed by aspiration in all patients without posterior hyaloid detachment. In addition to these surgical procedures, tractional membrane removal, epimacular membrane peeling, internal limiting membrane peeling, pars plana lensectomy, phacoemulsification and intraocular lens (IOL) implantation, dislocated IOL removal, retinotomy/retinectomy (relaxing), and circumferential scleral buckling (style 287) were performed according to disease severity. Air, sulfur hexafluoride (SF_6), perfluoropropane (C_3F_8), or silicone oil tamponade was used when needed.

Postoperatively, all patients were prescribed topical antibiotic and corticosteroid drops 4 times a day for 1 month. The antibiotic drops were discontinued after 1 month and the corticosteroid drops were tapered and discontinued within 2 weeks. Patients who developed cystoid macular edema received intravitreal triamcinolone (4 mg/0.1 mL) or bevacizumab (1.25 mg/0.1 mL) injections.

Statistical Analysis

All statistical analyses were performed using the SPSS software package (version 21, IBM Corp, Armonk, NY, USA). A p value less than 0.05 was considered statistically significant. Paired samples t-test was used to compare preoperative and postoperative data. Factors affecting final visual acuity were investigated by multivariate linear regression analysis.

Results

Nineteen (90.5%) of the patients were men and 2 (9.5%) were women. The mean age was 34.6±10.8 (range, 19-65) years. Of the 21 patients, 16 (76.2%) had bilateral involvement. The mean time from symptom onset to surgery was 34.5±10.8 (range, 2-180) months. The mean postoperative follow-up time was 67.8±78.8 (range, 12-240) months.

Preoperative and intraoperative findings and surgical procedures are summarized in Table 1. None of the eyes had active periphlebitis during surgery. Ten (45.5%) of the 22 eyes had previously undergone laser photocoagulation. Additional laser was applied to these eyes and 360° laser photocoagulation was applied to the remaining eyes (54.5%) to achieve panretinal photocoagulation.

Revision surgery was required once in 3 eyes (13.6%) and twice in 1 eye (4.6%) due to recurrent/new retinal detachment. At last examination, retinal reattachment without tamponade was achieved in 3 (13.6%) of these eyes, while 1 eye (4.6%) developed grade C proliferative vitreoretinopathy (PVR-C) followed by phthisis bulbi. Other than the eyes that underwent revision surgery, 1 eye (4.6%) developed total retinal detachment that was considered inoperable after the first surgery. PVR-C was observed in this eye during the first surgery. Peroperative or postoperative PVR-C was detected in a total of 3 patients. In the third eye with PVR-C, a single revision surgery resulted in retinal attachment without tamponade and visual acuity of 1.0 logMAR. Final anatomic success was achieved in 20 eyes (90.9%). In one eye (4.6%), the epimacular membrane that developed after the first operation was peeled. During the first surgery, phacoemulsification and IOL implantation were performed in 1 eye (4.6%) and pars plana lensectomy was performed in 3 eyes (13.6%). One of the eyes that had pars plana lensectomy later underwent scleral-fixated IOL implantation. Three eyes that underwent pars plana lensectomy and 1 eye that underwent dislocated IOL removal were aphakic at final examination. Postoperative complications and final examination findings are summarized in Table 2.

The mean BCVA was significantly higher at final examination (0.6±0.9 logMAR) compared to the preoperative period (1.8±1.1 logMAR) ($p<0.001$). After surgery, BCVA remained stable (≤1 Snellen line change) in 4 eyes (18.2%), increased in 16 eyes (72.7%), and decreased in 2 eyes (9.1%). There was no significant difference in intraocular pressure

between preoperative (14.9±6.3 mmHg) and final examination (13.6±4 mmHg) (p=0.5).

When surgical indications were grouped as VH and TRD ± RRD, the mean final BCVA was better in the VH group (0.3±0.34 logMAR) than in the TRD ± RRD group (0.9±1.1 logMAR), but the difference was not statistically significant (p=0.1). In the multivariate linear regression analysis, presence of preoperative or postoperative PVR-C, macular detachment, postoperative neovascular glaucoma, and longer preoperative disease duration were negatively associated with postoperative visual acuity, while preoperative visual acuity was positively correlated with postoperative visual acuity (Table 3). Final BCVA was not associated with presence of preoperative NVE, NVD, rubeosis iridis, or total posterior hyaloid detachment; preoperative laser application; surgical indication (VH, TRD, TRD ± RRD), sclerotomy diameter (20-gauge/23-gauge); preoperative lens status; and presence of preoperative or postoperative epimacular membrane, perioperative iatrogenic retinal tear, and postoperative hypotony, cystoid macular edema, and new or recurrent retinal detachment.

Table 1. Preoperative and intraoperative findings and primary surgical procedure

Findings and surgical procedure	n=22
Findings	
BCVA	
LogMAR (mean ± SD)	1.8±1.1
Snellen (mean)	20/1262
Intraocular pressure, mmHg (mean ± SD)	14.9±6.3
Preoperative laser photocoagulation, n (%)	10 (45.4)
Total posterior hyaloid detachment, n (%)	2 (9.1)
NVE, n (%)	14 (63.6)
NVD, n (%)	1 (4.6)
NVE + NVD, n (%)	1 (4.6)
Rubeosis iridis, n (%)	1 (4.6)
Lens status, n (%)	
Clear lens	19 (86.4)
Cataract	2 (9.1)
Pseudophakic	1 (4.6)
Epimacular membrane, n (%)	4 (18.2)
Iatrogenic retinal tear, n (%)	5 (22.7)
PVR grade C, n (%)	1 (4.6)
Macula-involving detachment, n (%)	5 (22.7)
Surgical indications	
Isolated VH, n (%)	10 (45.4)
TRD, n (%)	9 (40.1)
TRD + RRD, n (%)	3 (13.6)
Surgical procedure	
23 gauge/20 gauge	4/18
PPV + retinal laser photocoagulation, n (%)	22 (100)
Phacoemulsification and IOL implantation, n (%)	1 (4.6)
Pars plana lensectomy, n (%)	3 (13.6)
Dislocated IOL removal, n (%)	1 (4.6)
Epimacular membrane peeling, n (%)	4 (18.2)
Internal limiting membrane peeling, n (%)	5 (22.7)
Retinotomy/retinectomy, n (%)	3 (13.6)
Circumferential scleral band	2 (9.1)
Tamponade, n (%)	
None	4 (18.2)
Air	10 (45.4)
SF_6	2 (9.1)
C_3F_8	1 (4.6)
Silicone oil	5 (22.7)

BCVA: Best corrected visual acuity, IOL: Intraocular lens, NVD: Disc neovascularization, NVE: Retinal neovascularization, PPV: Pars plana vitrectomy, PVR: Proliferative vitreoretinopathy, RRD: Rhegmatogenous retinal detachment, TRD: Tractional retinal detachment, VH: Vitreous hemorrhage, SD: Standard deviation

Discussion

Among patients with Eales' disease, the proportion of males has been reported as 71-100% and the prevalence of bilateral involvement as 72-90%.[1,2,3,9,17] The rates of male patients and bilateral involvement in our study were consistent with the literature. The prevalence rates of NVE, NVD, and NVD + NVE have been reported as 33-73%, 1-4%, and 1-3%, respectively, in Eales' disease.[1,2,3] Consistent with the literature, these rates in the present study were 63.6%, 4.6%, and 4.6%, respectively. Recurrent VH attacks can be caused by these neovascular vessels, or may also be associated with necrosis in the vascular wall and leakage from the peripheral capillaries due to severe vasculitis.[18] Early vitrectomy results in better visual outcome in eyes with persistent VH.[14,19] Poor visual results have been observed in eyes that developed TRD, combined TRD + RRD, and neovascular glaucoma.[2] Shukla et al.[15] found that the mean final BCVA of eyes operated due to VH was higher than that of eyes operated due to retinal detachment, but the difference was not statistically significant. Similarly, although the visual outcome was better in the isolated VH group compared to the TRD ± RRD group in the present study, this difference was not significant. In addition, the presence of preoperative VH, TRD, and TRD ± RRD was not associated with final visual acuity in our study. The presence of PVR-C, macular detachment, postoperative neovascular glaucoma, preoperative low visual acuity, and longer preoperative disease duration were found to be associated with poor visual outcome.

There are marked differences among publications in the literature regarding post-vitrectomy visual results in Eales' disease. The proportion of eyes with decreased BCVA after vitrectomy was reported as 47% by Atmaca et al.[1], whereas Khanduja et al.[16] reported this rate to be 5%. Shukla et al.[15] determined that 60.6% of eyes had a final BCVA of 20/40

Table 2. Postoperative findings	
Findings	**n=22**
Follow-up time, months (mean ± SD, minimum-maximum)	67.8±78.8 (12-240)
Visual acuity	
LogMAR (mean ± SD)	0.6±0.9
Snellen (mean)	20/88
≥20/40, n (%)	12 (54.5)
≥20/200, n (%)	20 (90.9)
Light perception to 20/400, n (%)	2 (9.1)
Primary anatomical success, n (%)	18 (81.8)
Final anatomical success, n (%)	20 (90.9)
Intraocular pressure, mmHg (mean ± SD)	13.6±4
Recurrent/new VH, n (%)	0
Recurrent/new retinal detachment, n (%)	4 (18.2)
PVR grade C, n (%)	3 (13.6)
Epimacular membrane, n (%)	2 (9.1)
Cystoid macular edema, n (%)	5 (22.7)
Hypotension, n (%)	2 (9.1)
Neovascular glaucoma, n (%)	1 (4.6)
Cataract development, n (%) (Of 19 preoperatively phakic eyes)	7 (36.8)
Lens status, n (%)	
Clear lens	9 (40.9)
Pseudophakic	9 (40.9)
Aphakic	4 (18.2)
PVR: Proliferative vitreoretinopathy, VH: Vitreous hemorrhage, SD: Standard deviation	

Table 3. Multivariate linear regression analysis of factors affecting final BCVA			
	B	**P**	**95% CI**
PVR grade C	0.58	<0.001	1.11, 1.79
Macula-involving detachment	0.42	<0.001	0.62, 1.09
Preoperative BCVA	0.28	<0.001	0.13, 0.32
Postoperative neovascular glaucoma	0.29	<0.001	0.65, 1.79
Preoperative disease duration	0.14	0.02	0.001, 0.006
B: Regression coefficient, BCVA: Best corrected visual acuity, PVR: Proliferative vitreoretinopathy, CI: Confidence interval *As BCVA was analyzed as logMAR, positive B values indicate a negative relationship. In the preoperative BCVA and final BCVA relationship, positive B values indicate a positive relationship since they are both logMAR.			

or better, while this rate was 26% in a study by El-Asar and Al-Kharashi.[19] Khanduja et al.[16] reported that 77.6% of eyes had a final BCVA of 6/9 or better. The proportion of eyes with final BCVA worse than 20/200 was 6.7% in the study by Al-Astrar and Al-Kharashi[19] and 22.5% in the study by Shukla et al.[15] Postoperative vision was increased in 72% of the eyes in our study and decreased in 9.1%. Final BCVA reached 20/40 or higher in 54.5% of the eyes and was lower than 20/200 in 9.1% of the eyes. This discrepancy between studies may be due to differences in disease severity. The proportion of patients operated for retinal detachment was 10.6% in the study by Khanduja et al.[16], 31% in the study by Shukla et al.[15], and 53.7% in our study.

As with visual results, there are also differences between studies in terms of anatomic results. The development of VH and retinal detachment after the first surgery was reported in 9.2% and 2.6% of cases in the study by Khanduja et al.[16] and in 7% and 9.8% of cases in the study by Shukla et al.[15], respectively. Shukla et al.[15] performed revision surgery on 18.3% of the eyes and the surgical failure rate was 15.5%. Khanduja et al.[16] reported a surgical failure rate of 6.5%. In our study, none of the patients developed VH after surgery. The prevalence of new or recurrent retinal detachment was 18.2%. Only these patients were reoperated, and the surgical failure rate was 9.1%. Considering that a larger proportion of eyes were operated for TRD ± RRD compared to other studies, these rates are comparable to those in the literature. Cataract development was reported at rates of 24-37% in similar studies.[15,16] Consistent with these studies, this rate was 36.8% in the present study.

Another difference among studies investigating vitrectomy results in Eales' disease is the presence of total posterior hyaloid detachment, which has been reported in previous studies at rates ranging between 11.5% and 85%.[14,15,16] Although Shukla et al.[15] determined the absence of total posterior hyaloid detachment to be a poor prognostic factor, it was not found to be associated with visual outcome in our study.

Study Limitations

Limitations of the study include the small number of patients, the retrospective design, and the long study period. Prospective studies including larger samples may elucidate controversial issues.

Conclusion

In Eales' disease, good visual results can be achieved with timely surgery if detachment does not involve the macula and PVR-C does not develop pre- or postoperatively. Performing 20-gauge or 23-gauge vitrectomy is not associated with visual outcome.

Ethics

Ethics Committee Approval: The study protocol was designed in accordance with the Declaration of Helsinki and approved by the Şişli Memorial Hospital Ethics Committee.

Informed Consent: Retrospective study.

Peer-review: Externally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: M.K., Concept: M.G.E., M.K., S.A., Design: M.G.E., M.K., S.A., Data Collection or Processing: M.G.E., M.H., I.B.S.M., Analysis or Interpretation: M.G.E., M.K., S.A., Literature Search: M.G.E., M.H., I.B.S.M., Writing: M.G.E.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Atmaca LS, Batioglu F, Atmaca Sonmez P. A long-term follow-up of Eales' disease. Ocul Immunol Inflamm. 2002;10:213-221.
2. Saxena S, Kumar D. New classification system-based visual outcome in Eales' disease. Indian J Ophthalmol. 2007;55:267-269.
3. Biswas J, K R R, Pal B, Gondhale HP, Kharel Sitaula R. Long-Term Outcomes of a Large Cohort of Patients with Eales' Disease. Ocul Immunol Inflamm. 2018;26:870-876.
4. Kharel Sitaula R, Iyer V, Noronha V, Dutta Majumder P, Biswas J. Role of high-resolution computerized tomography chest in identifying tubercular etiology in patients diagnosed as Eales' disease. J Ophthalmic Inflamm Infect. 2017;7:4.
5. Singh R, Toor P, Parchand S, Sharma K, Gupta V, Gupta A. Quantitative polymerase chain reaction for Mycobacterium tuberculosis in so-called Eales' disease. Ocul Immunol Inflamm. 2012;20:153-157.
6. Agrawal S, Agrawal J, Agrawal TP. Intravitreal triamcinolone acetonide in Eales disease. Retina. 2006;26:227-229.
7. Ishaq M, Feroze AH, Shahid M, Baig MA, Ameen SS, Feroze SH, Chishti RA. Intravitreal steroids may facilitate treatment of Eales' disease (idiopathic retinal vasculitis): an interventional case series. Eye (Lond). 2007;21:1403-1405.
8. Banaz A, Bürümcek E, Karaçorlu S, Mudun B, Ünal Ş, Arslan MO. Treatment of Eales' Disease with Laser Photocoagulation. Turk J Ophthalmol. 2002;32:276-280.
9. Özelce R, Esgin H. Eales hastalığında tedavinin etkinliği. Ret-Vit. 2014;22:189-193.
10. Ünlü N, Acar MA, Kocaoğlan H, Sargın M, Aslan BS, Duman S. Eales hastalığında görsel prognoz. Ret-Vit. 2001;9:253-258.
11. Gupta SR, Flaxel CJ. The use of a vascular endothelial growth factor inhibitor (ranibizumab) in macular edema due to eales disease. Retin Cases Brief Rep. 2012;6:122-124.
12. Patwardhan SD, Azad R, Shah BM, Sharma Y. Role of intravitreal bevacizumab in Eales disease with dense vitreous hemorrhage: a prospective randomized control study. Retina. 2011;31:866-870.
13. Kumar A, Sehra SV, Thirumalesh MB, Gogia V. Secondary rhegmatogenous retinal detachment following intravitreal bevacizumab in patients with vitreous hemorrhage or tractional retinal detachment secondary to Eales' disease. Graefes Arch Clin Exp Ophthalmol. 2012;250:685-690.
14. Kumar A, Tiwari HK, Singh RP, Verma L, Prasad N. Comparative evaluation of early vs. deferred vitrectomy in Eales' disease. Acta Ophthalmol Scand. 2000;78:77-78.
15. Shukla D, Kanungo S, Prasad NM, Kim R. Surgical outcomes for vitrectomy in Eales' disease. Eye (Lond). 2008;22:900-904.
16. Khanduja S, Gupta S, Sinha S, Venkatesh P, Vohra R, Garg S. Surgical outcomes of minimally invasive vitrectomy surgery in Eales' disease. Nepal J Ophthalmol. 2013;5:182-189.
17. Das T, Biswas J, Kumar A, Nagpal PN, Namperumalsamy P, Patnaik B, Tewari HK. Eales' disease. Indian J Ophthalmol. 1994;42:3-18.
18. Gadkari SS, Kamdar PA, Jehangir RP, Shah NA, Adrianwala SD. Pars plana vitrectomy in vitreous haemorrhage due to Eales' disease. Indian J Ophthalmol. 1992;40:35-37.
19. El-Asrar AM, Al-Kharashi SA. Full panretinal photocoagulation and early vitrectomy improve prognosis of retinal vasculitis associated with tuberculoprotein hypersensitivity (Eales' disease). Br J Ophthalmol. 2002;86:1248-1251.

DOI: 10.4274/tjo.galenos.2020.08377
Turk J Ophthalmol 2021;51:107-113

Review

Congenital Cataract and Its Genetics: The Era of Next-Generation Sequencing

Hande Taylan Şekeroğlu*, Gülen Eda Utine**

*Hacettepe University Faculty of Medicine, Department of Ophthalmology, Ankara, Turkey
**Hacettepe University Faculty of Medicine, Department of Pediatrics, Department of Pediatric Genetics, Ankara, Turkey

Abstract

Congenital cataract is a challenging ophthalmological disorder which can cause severe visual loss. It can be diagnosed at birth or during the first year of life. Early diagnosis and treatment are crucial for the visual prognosis. It can be associated with various ocular and systemic abnormalities. Determining whether congenital cataract is isolated or associated with other pathology is an indispensable step for the prediction of potential vision as well as early diagnosis and treatment of conditions that can cause morbidity or mortality. Many genes have been identified in the molecular etiology of congenital cataract. Most mutations have been reported in the crystallin genes. Determination of the genetic cause may not only enable individualized genetic counseling but also help to identify concomitant ocular and/or systemic disorders depending on the characteristics of the genetic test used. Recently, next-generation sequencing in particular has become an evolving technology for determining the molecular etiology of congenital cataract and furthering our knowledge of the disease.

Keywords: Genetics, congenital cataract, crystallin, lens, next-generation sequencing

Introduction

Congenital cataract is lens opacity that presents at birth or early in the postnatal period. It may be unilateral or bilateral. Because it occurs during early vision development, it causes serious vision loss and, more importantly, severe amblyopia. Follow-up and treatment are long-term and important, and an etiology cannot be identified for a substantial proportion of patients.[1] For this reason, one of the main objectives of the Vision 2020: Right to Sight, a global initiative to eliminate preventable blindness worldwide, was to prevent causes of childhood blindness, including congenital cataract.[2]

Epidemiology and Etiology

In their systematic review and meta-analysis, Wu et al.[3] reported that congenital cataract had the highest incidence in Asia (7.43/10,000) and was usually diagnosed after 1 year of age. They also reported that congenital cataracts were more frequently bilateral and the most common type was total cataract.[3] Although most cases of congenital cataract were idiopathic (62.2%), the prevalence of inherited cataract was reported to be 22.3%.[3]

In their systematic review, Sheeladevi et al.[4] determined overall prevalence rates of 0.32-22.9 in 10,000 for childhood cataracts and 0.63-9.74 in 10,000 for congenital cataracts.

Factors such as the dynamic genetic infrastructure of societies, socioeconomic and cultural characteristics, access to health services, and the presence of early screening programs may cause major differences in the prevalence of congenital cataracts as well as associated morbidities between populations. This is an important consideration when evaluating statistics.

In congenital cataract, anterior segment structures other than the lens were also shown to differ from noncataractous eyes due to their simultaneous development and mutual interaction

Address for Correspondence: Hande Taylan Şekeroğlu, Hacettepe University Faculty of Medicine, Department of Ophthalmology, Ankara, Turkey
E-mail: h_taylan@yahoo.com **ORCID-ID:** orcid.org/0000-0002-4783-522X
Received: 13.05.2020 **Accepted:** 27.08.2020

Cite this article as: Taylan Şekeroğlu H, Utine GE. Congenital Cataract and Its Genetics: The Era of Next-Generation Sequencing. Turk J Ophthalmol 2021;51:107-113

during the embryological period.[5] Congenital cataract may be associated with ocular anomalies such as microcornea, microphthalmia, persistent fetal vascularization, glaucoma, and retinal dystrophies. Twenty-nine percent of congenital cataract cases may be linked to genetic causes, while unilateral cases are more likely to be idiopathic.[6]

In the Vision 2020 global initiative to fight preventable blindness, vitamin A deficiency, measles, neonatal conjunctivitis, and retinopathy of prematurity were also shown to be among the causes of childhood blindness along with congenital cataract.[2]

Congenital cataract accounts for 7.4-15.5% of all childhood blindness.[7] Early diagnosis and treatment are very important in terms of visual prognosis. Therefore, one of the most critical steps is recognizing congenital cataract at an early age through postnatal eye screening. The red reflex test is a simple screening test that is important in the detection of many ocular pathologies, especially congenital cataract. Neonatal eye screening has been implemented as routine practice in our country, and the detection of pathologies that disrupt the red reflex test in these examinations and their referral to ophthalmologists enables the recognition of many eye diseases that require early diagnosis and treatment, including congenital cataracts. Despite early surgery and early rehabilitation, visual outcomes of congenital cataract may be limited due to ocular diseases such as glaucoma, nystagmus, or concomitant systemic/neurological anomalies.[8]

Pediatric cataracts can be classified into two main groups, hereditary and nonhereditary.

1. Hereditary pediatric cataracts may be:[9]

a) Isolated

b) Associated with metabolic diseases (e.g., galactosemia, Wilson's disease, diabetes, cerebrotendinous xanthomatosis, Fabry disease, mannosidosis, Refsum disease)

c) Associated with renal diseases (e.g., Alport syndrome, Lowe syndrome)

d) Associated with musculoskeletal diseases (e.g., myotonic dystrophy, chondrodysplasia puncta)

e) Associated with dermatological diseases (e.g., incontinentia pigmenti, Cockayne syndrome, Rothmund-Thomson syndrome)

f) Associated with craniofacial anomalies (e.g., Hallerman-Streiff syndrome, Rubinstein-Taybi syndrome, Smith-Lemli-Optitz syndrome, cerebro-oculo-facial-skeletal syndrome)

g) Associated with genetic anomalies (e.g., trisomy 13, 18, 21; 5p deletion, 11p deletion, Norrie disease, Nance-Horan syndrome)

2. Non-hereditary pediatric cataracts:

May occur due to trauma, congenital infections such as TORCH (toxoplasma, rubella, cytomegalovirus, herpes simplex), drugs such as steroids, radiation, or teratogen exposure.

Classification:

Although congenital cataract can be classified according to the timing of development, etiology, location of opacity, or morphological features, morphological classification is most commonly used in clinical practice:[9]

1) Anterior cataract: This group includes anterior polar, anterior pyramidal, and anterior subcapsular cataracts.

2) Central cataract: This group includes nuclear, sutural, lamellar (zonular), cerulean, Christmas tree, pulverulent, aculeiform, polymorphic, crown-shaped, cuneiform, and coralliform cataracts.

3) Posterior cataract: This group includes posterior lenticonus, posterior subcapsular, posterior polar, and oil droplet cataracts, persistent hyperplastic primary vitreous, and Mittendorf dots.

4) Total cataract: This type of cataract involves the entire lens. It is often not possible to identify the morphology at the onset in the absence of additional ocular findings. Congenital Morgagnian and membranous cataract can also be considered in this group.

Perucho-Martinez et al.[10] reported that nuclear cataract was the most common congenital cataract morphology in their study.

The Genetics of Congenital Cataract

Determining the molecular etiology of congenital cataract is essential both to identify and better understand the pathways involved in its pathogenesis and to provide individualized genetic counseling. It has been shown that 47% of unilateral congenital cataracts and 61% of bilateral congenital cataracts are isolated, and the frequency of association with systemic diseases is 6% in unilateral and 25% in bilateral cases.[11] In addition, approximately half of congenital cataracts have a genetic etiology.[12] Congenital cataract is characterized by genetic heterogeneity and variable inheritance patterns.[13] Although the inheritance of congenital cataract is usually autosomal dominant, in rare cases it may be autosomal recessive or X-linked. The etiology of isolated congenital cataract is unknown in 50% of cases, but up to 30% are monogenic and generally have autosomal dominant inheritance.[14]

Determining the genetic etiology of congenital cataract in a family member enables a molecular diagnosis to be established and opens the possibility of prenatal diagnosis in pregnancies to be planned in the same or following generations. Non-invasive prenatal testing now makes it possible to collect blood from the mother and diagnose fetal chromosomal aneuploidy through extracellular fetal DNA circulating in the peripheral blood.[15] In addition, knowing the molecular etiology of a hereditary ocular disease in the family may also allow preimplantation genetic diagnosis.[16]

Mutations Associated with Congenital Cataract

Some genes that have been associated with congenital cataracts and the mutations demonstrated in these genes are shown in **Table 1**. Mutations that cause congenital cataracts are categorized into four basic groups:

1) Crystallin mutations

Crystallins comprise over 90% of the lens proteins and have the most fundamental place in the lens structure.[17] Crystallins can be divided into the α, β, and γ groups, although β and γ crystallins can also be considered a single family. α, β, and γ crystallins are water-soluble proteins that

account for the majority of lens proteins. They are found not only in the eye but also in extraocular tissues. Crystallins are essential for maintaining lens stability and transparency due to their antiapoptotic, antidegradation, and antioxidant effects.[18] Crystallin mutations have been associated with congenital cataracts of varying phenotype.[12]

Mutations in crystallin genes account for approximately 50% of autosomal dominant cataracts.[19] Numerous mutations have been detected in various crystallin genes, including *CRYAA*, *CRYAB*, *CRYBB1*, *CRYBB2*, *CRYBB3*, *CRYBA1*, *CRYGC*, *CRYGD*, and *CRYGS*.[13,20,21]

2) Lens membrane protein mutations

This group includes connexins, aquaporins, and other cell membrane proteins that enable intercellular communication. Congenital cataracts have also been reported in mutations affecting major intrinsic protein, connexin 46 and 50, and LIM-2 proteins.[12] It is known that 25% of mutations associated with congenital cataract are in connexin genes.[22]

3) Mutations of lens cytoskeletal elements

CP49 and filensin, which form beaded filaments, are the cytoskeletal elements. Mutations in the *BFSP-2* (beaded filament structural protein 2) gene encoding CP49 have been associated with cataract.[12]

4) Other mutations

Congenital cataract can also be observed in mutations of the developmental regulatory genes *PITX3* (paired-like homeodomain 3), *PAX6* (paired box 6), and *HSF-4* (heat shock protein factor-4).[12] Narumi et al.[23] described congenital cataract with microcornea and/or iris coloboma in some members of a Japanese family who had a c.908A>C mutation in the *MAF* (MAF bZIP transcription factor) gene.

Congenital cataract can also occur due to physical and environmental factors such as infections and teratogens. Many factors, including socio-cultural-economic background, race-specific genetic traits, the frequency of consanguineous marriage, and differences in vaccination and screening programs, result in population-specific patterns of congenital cataract prevalence and molecular etiology.

Hansen et al.[14] identified mutations in 20 of 28 Danish families with hereditary congenital cataract. They determined that 36% of these mutations were in crystallin genes, 22% in connexin genes, and 15% in the transcription factor genes *HSF4* and *MAF*.

Devi et al.[24] showed that crystallin gene mutations (*CRYAA*, *CRYAB*, *CRYBA1*, *CRYBB2*, *CRYGC*, *CRYGD*, *CRYGS*) were responsible for 16.6% of cases of hereditary pediatric cataract cases in 60 Indian families.

Chen et al.[25] conducted molecular genetic analysis in a homozygosity mapping study of Pakistani families with autosomal recessive congenital cataract and found that mutations were most commonly in the *FYCO1* (FYVE and coiled-coil domain autophagy adaptor 1) gene, followed by the *CRYBB3, GALK1* (*galactokinase 1*), and *EPHA2* (EPH receptor A2) genes.

Li et al.[26] investigated the molecular etiology in 74 patients with sporadic congenital cataracts in a Han Chinese population and reported the most common mutations in the *CRYBB3* gene, followed by the *EPHA2, NHS* (*NHS actin remodeling regulator*), and *WDR36* (WD repeat domain 36) genes.

Investigating the Molecular Etiology of Congenital Cataract

For a patient with bilateral congenital cataract, family history and pedigree tracing are followed by TORCH screening for intrauterine infections, as well as analysis of urine and blood amino acid analysis and reducing substances in the urine. Apart from these, specific genetic tests can be performed if a particular genetic etiology is suspected, and special organic acid analyses can also be performed if a metabolic disease other than galactosemia is suspected. For example, cerebrotendinous xanthomatosis is the result of a *CYP27A1* (cytochrome P450 family 27 subfamily A member 1) gene mutation that causes a cholesterol metabolism disorder. It causes juvenile cataract, and xanthomas and cognitive/neurological disorders later in life. If diagnosed early, initiating oral chenodeoxycholic acid therapy can prevent later symptoms of the disease. Another example is galactosemia, which is also seen in our country. With early diagnosis and a special diet, it may be possible to slow the progression of the cataract to a certain degree.

Various techniques can be used for the evaluation of a patient with congenital cataract:[27]

1) Conventional cytogenetic methods, especially standard karyotyping, may be preferred in the presence of developmental delay/mental disability, other malformations, growth retardation, and dysmorphic findings, which suggest that the cataract may be a component of a genetic etiology due to structural or numerical abnormalities at the chromosome level (large deletion, duplication, translocation).

2) Molecular cytogenetic methods such as fluorescence in situ hybridization is applicable if the cataract is believed to show a specific phenotypic pattern associated with a genetic etiology involving submicroscopic deletion/duplication.

3) Methods such as multiplex ligation-dependent probe amplification can be used if the cataract is suspected to occur as a result of a genetic alteration associated with a copy number change in a more specific and smaller region.

4) Methods such as array comparative genomic hybridization (array CGH) are preferable if the cataract is believed to be a component of genetic etiologies associated with copy number changes but are not clinically identifiable (e.g., mental disability spectrum).

5) Whole exome sequencing (WES) or whole genome sequencing (WGS) with confirmation by Sanger sequencing is an option if the etiology of the cataract is genetically heterogeneous and specifically associated with indistinguishable clinical presentations.

Table 1. Certain genes associated with congenital cataracts and some mutations/nucleotide changes demonstrated in these genes*

Gene name	Locus	Inheritance	Encoded protein	Nucleotide change
CRYAA	21q22.3	AD/AR	Crystallin, alpha-A	c.61C>T[37] c.34C>T[14, 38] c.155C>T[14] c.337G>A[14]
CRYBA1/A3	17q11.2	AD	Crystallin, beta-A1/A3	c.279-281delGGA[39] c.272-274delGAG[40] c.590-591delAG[41] IVS3+1 G>A[42] c.215+1G>A[43] IVS3+2 T>G[44]
CRYBA2	2q35	AD	Crystallin, beta-A2	c.148G>A[38]
CRYBB1	22q12.1	AD/AR	Crystallin, beta-B1	c.286G>T[38]
CRYBB2	22q11.23	AD	Crystallin, beta-B2	c.563G>A[17] c.498C>A[14] c.[433C>T;440A>G;449C>T][14]
CRYBB3	22q11.23	AD/AR	Crystallin, beta-B3	c.581T>A[38] c.493G>C[45] c.224G>A[16]
CRYGC	2q33.3	AD	Crystallin, gamma-C	c.124delT[37] c.157_161 dupGC GGC[38] c.417C>G[38] c.143G>A[46]
CRYGD	2q33.3	AD	Crystallin, gamma-D	c.418C>T[38] c.70C>A[47] c.418C>A[14]
GJA3	13q12.11	AD	Gap junction protein alpha 3	c.32T>C[14] c.176C>T[14] c.227G>A[14]
GJA8	1q21.2	AD	Gap junction protein alpha 8	c.200A>G[38] c.226C>T[38] c.218C>T[14] c.565C>T[14] c.836C>A[14]
HSF4	16q22.1	AD	Heat shock transcription factor 4	c.341T>C[14] c.355C>T[14]
MIP	12q13.3	AD	Major intrinsic protein of lens fiber	c.605G>A[38]
EYA1	8q13.3	AD	EYA transcriptional coactivator and phosphatase 1	c.121G>A[38]
MAF	16q23.2	AD	MAF bZIP transcription factor	c.895C>A[14] c.958A>G[14]

AD: Autosomal dominant, AR: Autosomal recessive

*Information about genes/variants involved in the molecular etiology of congenital cataract is constantly being updated. The table presents a portion of the available information to the reader. However, current platforms such as those mentioned in the text should be monitored for emerging data.

6) Sanger sequencing of a particular gene may be preferred if there is a strong and specific suspicion that the cataract is of genetic etiology and the suspect gene is known.

With all of these options, the key step is a thorough description of the phenotype, detailed evaluation of associated systemic anomalies/diseases, and identification of a preliminary clinical diagnosis.

Next-Generation Sequencing to Determine the Molecular Etiology of Congenital Cataract

Over the years, there has been a shift from genetic tests to genomic tests for many diseases with complex inheritance and genotypes, especially rare pediatric diseases. Genome-wide tests include aCGH, gene panels, and next-generation sequencing technologies. Traditional genetic tests include high-resolution single-gene tests (e.g., Sanger sequencing) that can identify diseases with a very specific phenotype which are caused by

mutations in one or a few genes, and genome-based low-resolution cytogenetic analyses.[28] Modern genetic tests, on the other hand, involve next-generation sequencing technologies that enable rapid and simultaneous sequencing of a large number of genes.[28]

Encoding regions of gene are called exons and noncoding regions are called introns. All of the exons in the human genome are referred to as the exome. Although the exome represents approximately 2% of the human genome, it contains 85% of variants known to cause disease.[29] Next-generation sequencing technologies are called whole exome and whole genome sequencing, although these techniques can also be targeted to a specific region of the exome or genome instead of the whole.

Whole exome sequencing is especially important in identifying mutations in Mendelian diseases with genetic heterogeneity. The main speed-limiting step in these technologies is the evaluation, interpretation, and validation of the data, which is difficult to review due to its scale. When the first genome/exome information is obtained from the patient, it is compared with the reference genome/exome to detect deviations/variants; in other words, variants are called. The next step is variant filtering by evaluating the variants' frequency in the population and their likely relationship and effect on phenotype and inheritance. After this process, some variants are prioritized.[30] The clinical presentation and variant are evaluated together and deep phenotyping is performed if necessary; i.e., additional clinical/laboratory/imaging examinations are requested.[30] This is followed by Sanger sequencing to validate the likely causative variant and segregation analysis based on demonstrating its presence in other affected family members.

Variants are classified as pathogenic, likely pathogenic, of unknown significance, likely benign, and benign according to the data in different platforms (e.g., Varsome, Genome Data Viewer, Ensemble, The 1000 Genomes Browsers, Variation Viewer, gnomAD).[31,32]

Next-generation sequencing is advantageous over other technologies in that it does not require the time-consuming and error-prone steps of older systems, DNA fragments are reproduced with special systems, and millions of sequences can simultaneously be read base by base (massive parallel sequencing) by various methods.[33] As a result, technology has gained speed, increased the reading length, and significantly reduced the frequency of errors over time.

With the technological capacity to screen the entire genome, incidental findings and/or variants of unknown significance can also be detected. These analyses produce extraordinary amounts of data, but major ethical and social issues may arise in reporting the results, especially in clinical conditions related to children.[34] In this case, providing genetic counseling can also become more complicated.

Although next-generation sequencing technology, WES or WGS, enables evaluation by comparing with the reference genome/exome, the large data burden poses a substantial challenge in the interpretation phase, especially with WGS. Deviations from the reference genome/exome do not always mean disease; they may need to be classified as normal variants or variants of unknown significance. In addition, it should be kept in mind that the continuing development and widespread use of this technology will increase global knowledge and experience, and as more data is obtained using this technology, earlier data will be updated and new information may emerge that results in laboratory results changing in significance and classification over time. A variant classified as unknown may later be included in the pathogenic or benign group, or a variant classified as benign may be moved to the pathogenic group. Therefore, considering that new generation technologies are a living system that are constantly evolving, it is extremely important before the test to inform the family in detail and clarify how the results could change the life of the individual and his/her family now and in the future.

A more practical implementation of next-generation sequencing technology in clinical use, which involved contacting the genetics department and informing the patient and family shortly after the patient was seen in the ophthalmology clinic, sample collection and rapid transfer to the laboratory for next-generation sequencing, was reported to increase the rate of children with congenital cataracts who received a diagnosis within 6 months from 26% to 71%.[35] The reduction in turnaround time was achieved by accelerating the steps that delay the workflow between clinic and laboratory and facilitating collaboration between clinicians and geneticists.[35]

In a research project-based study, it was reported that 70% of patients with congenital cataract could be diagnosed with next-generation sequencing technology.[36] This high rate may not always be possible in clinical practice, but appropriate selection of patients for genetic testing and the test to perform will increase the diagnosis rate. In addition, in cases where WES is insufficient, the diagnosis rate may be increased by the use of WGS methods, which are just now becoming widespread and still have some limitations in terms of data burden and interpretation.

Although some genes/mutations have been reported in conjunction with certain types of congenital cataracts, there is not yet a direct relationship with which to establish a valid and common genotype-phenotype correlation. One of the main reasons for this is that people diagnosed with congenital cataracts often present for investigation of the molecular etiology after surgery, and the cataract morphology cannot be determined because they are pseudophakic.

In conclusion, congenital cataract is rare but causes severe morbidity, and its diagnosis and treatment are a race against time. Molecular diagnosis will provide a better understanding of the pathogenesis of the disease and enable more detailed and individualized genetic counseling, including prenatal diagnosis. Next-generation sequencing technologies are a useful and reliable method for detecting and evaluating the underlying molecular etiology of this heterogeneous genetic disease, and seem likely to continue to provide more data in the future.

Ethics

Peer-review: Externally peer reviewed.

Authorship Contributions

Concept: H.T.Ş., G.E.U., Design: H.T.Ş., G.E.U., Data Collection or Processing: H.T.Ş., Analysis or Interpretation: H.T.Ş., G.E.U., Literature Search: H.T.Ş., Writing: H.T.Ş., G.E.U.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Lambert SR, Drack AV. Infantile cataracts. Surv Ophthalmol. 1996;40:427-458.
2. Thylefors B. A global initiative for the elimination of avoidable blindness. Community Eye Health. 1998;11:1-3.
3. Wu X, Long E, Lin H, Liu Y. Prevalence and epidemiological characteristics of congenital cataract: a systematic review and meta-analysis. Sci Rep. 2016;6:28564.
4. Sheeladevi S, Lawrenson JG, Fielder AR, Suttle CM. Global prevalence of childhood cataract: a systematic review. Eye (Lond). 2016;30:1160-1169.
5. Lin H, Lin D, Liu Z, Long E, Wu X, Cao Q, Chen J, Lin Z, Li X, Zhang L, Chen H, Zhang X, Li J, Chen W, Liu Y. A Novel Congenital Cataract Category System Based on Lens Opacity Locations and Relevant Anterior Segment Characteristics. Invest Ophthalmol Vis Sci. 2016;57:6389-6395.
6. Haargaard B, Wohlfahrt J, Fledelius HC, Rosenberg T, Melbye M. A nationwide Danish study of 1027 cases of congenital/infantile cataracts: etiological and clinical classifications. Ophthalmology. 2004;111:2292-2298.
7. Gilbert CE, Canovas R, Hagan M, Rao S, Foster A. Causes of childhood blindness: results from west Africa, south India and Chile. Eye (Lond). 1993;7:184-188.
8. Gasper C, Trivedi RH, Wilson ME. Complications of Pediatric Cataract Surgery. Dev Ophthalmol. 2016;57:69-84.
9. Vander Veen DK. Pediatric cataracts and other lens abnormalities. In: Wright KW, Strube YNJ, eds. Pediatric Ophthalmology and Strabismus (3rd ed). New York; Oxford; 2012:762-797.
10. Perucho-Martinez S, De-la-Cruz-Bertolo J, Tejada-Palacios P. [Pediatric cataracts: epidemiology and diagnosis. Retrospective review of 79 cases]. Arch Soc Esp Oftalmol. 2007;82:37-42.
11. Rahi JS, Dezateux C. Congenital and infantile cataract in the United Kingdom: underlying or associated factors. British Congenital Cataract Interest Group. Invest Ophthalmol Vis Sci. 2000;41:2108-2114.
12. Francis PJ, Moore AT. Genetics of childhood cataract. Curr Opin Ophthalmol. 2004;15:10-15.
13. Reis LM, Semina EV. Genetic landscape of isolated pediatric cataracts: extreme heterogeneity and variable inheritance patterns within genes. Hum Genet. 2019;138:847-863.
14. Hansen L, Mikkelsen A, Nürnberg P, Nürnberg G, Anjum I, Eiberg H, Rosenberg T. Comprehensive mutational screening in a cohort of Danish families with hereditary congenital cataract. Invest Ophthalmol Vis Sci. 2009;50:3291-3303.
15. Pös O, Budis J, Szemes T. Recent trends in prenatal genetic screening and testing. F1000Res. 2019;8:1000.
16. Yahalom C, Macarov M, Lazer-Derbeko G, Altarescu G, Imbar T, Hyman JH, Eldar-Geva T, Blumenfeld A. Preimplantation genetic diagnosis as a strategy to prevent having a child born with an heritable eye disease. Ophthalmic Genet. 2018;39:450-456.
17. Weisschuh N, Aisenbrey S, Wissinger B, Riess A. Identification of a novel CRYBB2 missense mutation causing congenital autosomal dominant cataract. Mol Vis. 2012;18:174-180.
18. Forrester JV, Dick AD, McMenamin PG, Roberts F. Biochemistry and cell biology. In: Forrester JV, Dick AD, McMenamin PG, Roberts F, eds. The Eye: Basic Sciences in Practice (3rd ed). Philadelphia; Elsevier; 2008:171-261.
19. Li J, Xia CH, Wang E, Yao K, Gong X. Screening, Genetics, Risk Factors, and Treatment of Neonatal Cataracts. Birth Defects Res. 2017;109:734-743.
20. Shiels A, Hejtmancik JF. Molecular Genetics of Cataract. Prog Mol Biol Transl Sci. 2015;134:203-218.
21. Shiels A, Hejtmancik JF. Mutations and mechanisms in congenital and age-related cataracts. Exp Eye Res. 2017;156:95-102.
22. Hejtmancik JF. Congenital cataracts and their molecular genetics. Semin Cell Dev Biol. 2008;19:134-149.
23. Narumi Y, Nishina S, Tokimitsu M, Aoki Y, Kosaki R, Wakui K, Azuma N, Murata T, Takada F, Fukushima Y, Kosho T. Identification of a novel missense mutation of MAF in a Japanese family with congenital cataract by whole exome sequencing: a clinical report and review of literature. Am J Med Genet A. 2014;164:1272-1276.
24. Devi RR, Yao W, Vijayalakshmi P, Sergeev YV, Sundaresan P, Hejtmancik JF. Crystallin gene mutations in Indian families with inherited pediatric cataract. Mol Vis. 2008;14:1157-1170.
25. Chen J, Wang Q, Cabrera PE, Zhong Z, Sun W, Jiao X, Chen Y, Govindarajan G, Naeem MA, Khan SN, Ali MH, Assir MZ, Rahman FU, Qazi ZA, Riazuddin S, Akram J, Riazuddin SA, Hejtmancik JF. Molecular Genetic Analysis of Pakistani Families With Autosomal Recessive Congenital Cataracts by Homozygosity Screening. Invest Ophthalmol Vis Sci. 2017;58:2207-2217.
26. Li D, Wang S, Ye H, Tang Y, Qiu X, Fan Q, Rong X, Liu X, Chen Y, Yang J, Lu Y. Distribution of gene mutations in sporadic congenital cataract in a Han Chinese population. Mol Vis. 2016;22:589-598.
27. Taylan Sekeroglu H, Utine GE, Alikasifoglu M. A Baseline Algorithm for Molecular Diagnosis of Genetic Eye Diseases: Ophthalmologist's Perspective. Turk J Ophthalmol. 2016;46:299-300.
28. Wright CF, FitzPatrick DR, Firth HV. Paediatric genomics: diagnosing rare disease in children. Nat Rev Genet 2018;19:253-268.
29. Choi M, Scholl UI, Ji W, Liu T, Tikhonova IR, Zumbo P, Nayir A, Bakkaloğlu A, Ozen S, Sanjad S, Nelson-Williams C, Farhi A, Mane S, Lifton RP. Genetic diagnosis by whole exome capture and massively parallel DNA sequencing. Proc Natl Acad Sci U S A. 2009;106:19096-19101.
30. Seaby EG, Pengelly RJ, Ennis S. Exome sequencing explained: a practical guide to its clinical application. Brief Funct Genomics. 2016;15:374-384.
31. Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL; ACMG Laboratory Quality Assurance Committee. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17:405-424.
32. Nykamp K, Anderson M, Powers M, Garcia J, Herrera B, Ho YY, Kobayashi Y, Patil N, Thusberg J, Westbrook M; Invitae Clinical Genomics Group, Topper S. Sherloc: a comprehensive refinement of the ACMG-AMP variant classification criteria. Genet Med. 2017;19:1105-1117.
33. van Dijk EL, Auger H, Jaszczyszyn Y, Thermes C. Ten years of next-generation sequencing technology. Trends Genet. 2014;30:418-426.
34. Burke K, Clarke A. The challenge of consent in clinical genome-wide testing. Arch Dis Child. 2016;101:1048-1052.
35. Musleh M, Ashworth J, Black G, Hall G. Improving diagnosis for congenital cataract by introducing NGS genetic testing. BMJ Qual Improv Rep. 2016;5:211094.
36. Gillespie RL, O'Sullivan J, Ashworth J, Bhaskar S, Williams S, Biswas S, Kehdi E, Ramsden SC, Clayton-Smith J, Black GC, Lloyd IC. Personalized diagnosis and management of congenital cataract by next-generation sequencing. Ophthalmology. 2014;121:2124-2137.
37. Kondo Y, Saitsu H, Miyamoto T, Lee BJ, Nishiyama K, Nakashima M, Tsurusaki Y, Doi H, Miyake N, Kim JH, Yu YS, Matsumoto N. Pathogenic mutations in two families with congenital cataract identified with whole-exome sequencing. Mol Vis. 2013;19:384-389.

38. Reis LM, Tyler RC, Muheisen S, Raggio V, Salviati L, Han DP, Costakos D, Yonath H, Hall S, Power P, Semina EV. Whole exome sequencing in dominant cataract identifies a new causative factor, CRYBA2, and a variety of novel alleles in known genes. Hum Genet. 2013;132:761-770.
39. Wang KJ, Zha X, Chen DD, Zhu SQ. Mutation Analysis of Families with Autosomal Dominant Congenital Cataract: A Recurrent Mutation in the CRYBA1/A3 Gene Causing Congenital Nuclear Cataract. Curr Eye Res. 2018;43:304-307.
40. Mohebi M, Akbari A, Babaei N, Sadeghi A, Heidari M. Identification of a De Novo 3bp Deletion in CRYBA1/A3 Gene in Autosomal Dominant Congenital Cataract. Acta Med Iran. 2016;54:778-783.
41. Zhang J, Zhang Y, Fang F, Mu W, Zhang N, Xu T, Cao Q. Congenital cataracts due to a novel 2bp deletion in CRYBA1/A3. Mol Med Rep. 2014;10:1614-1618.
42. Zhu Y, Shentu X, Wang W, Li J, Jin C, Yao K. A Chinese family with progressive childhood cataracts and IVS3+1G>A CRYBA3/A1 mutations. Mol Vis. 2010;16:2347-2353.
43. Yu Y, Li J, Xu J, Wang Q, Yu Y, Yao K. Congenital polymorphic cataract associated with a G to A splice site mutation in the human beta-crystallin gene CRYbetaA3/A1. Mol Vis. 2012;18:2213-2220.
44. Yang Z, Su D, Li Q, Yang F, Ma Z, Zhu S, Ma X. A novel T-->G splice site mutation of CRYBA1/A3 associated with autosomal dominant nuclear cataracts in a Chinese family. Mol Vis. 2012;18:1283-1288.
45. Jiao X, Kabir F, Irum B, Khan AO, Wang Q, Li D, Khan AA, Husnain T, Akram J, Riazuddin S, Hejtmancik JF, Riazuddin SA. A Common Ancestral Mutation in CRYBB3 Identified in Multiple Consanguineous Families with Congenital Cataracts. PloS One. 2016;11:e0157005.
46. Gonzalez-Huerta LM, Messina-Baas O, Urueta H, Toral-Lopez J, Cuevas-Covarrubias SA. A CRYGC gene mutation associated with autosomal dominant pulverulent cataract. Gene. 2013;529:181-185.
47. Vanita V, Singh D. A missense mutation in CRYGD linked with autosomal dominant congenital cataract of aculeiform type. Mol Cell Biochem. 2012;368:167-172.

DOI: 10.4274/tjo.galenos.2020.99248
Turk J Ophthalmol 2021;51:114-117

Case Report

Cytarabine-Induced Corneal Toxicity: Clinical Features and Relief of Symptoms with Loteprednol Etabonate 0.5% in Two Patients

Gökçen Özcan*, Ömür Özlenen Uçakhan**

*Ahi Evran University Training and Research Hospital, Clinic of Ophthalmology, Kırşehir, Turkey
**Ankara University Faculty of Medicine, Department of Ophthalmology, Ankara, Turkey

Abstract

We report two patients who developed toxic keratopathy following high-dose cytarabine chemotherapy and whose symptoms resolved following topical loteprednol etabonate 0.5% treatment. A 25-year-old woman and a 26-year-old man with acute myeloid leukemia were referred to our department with symptoms of ocular discomfort, photophobia, and blurred vision after consolidation chemotherapy. Central corneal epithelial microcysts were observed bilaterally in both patients, and *in vivo* confocal microscopy showed highly reflective disseminated granular and irregular intraepithelial opacities, mainly in the basal epithelial layers. Loteprednol etabonate 0.5% relieved both patients' symptoms in less than a week, and the microcysts disappeared in 2 to 3 weeks of treatment. Although there is no standardized treatment protocol for cytarabine-induced corneal toxicity, dexamethasone 0.1% and prednisolone phosphate 1.0% were reported to be effective in the resolution of discomfort and symptoms. In the two patients we report herein, loteprednol etabonate 0.5% four times daily was also effective in suppressing the symptoms.

Keywords: Acute myeloid leukemia, cytarabine, cytarabine-induced corneal toxicity, corneal microcysts, loteprednol etabonate, *in vivo* confocal microscopy

Introduction

Cytarabine is an anti-metabolite used mainly in the treatment of acute non-lymphoblastic leukemia. Corneal toxicity related to cytarabine treatment is dependent on the concentration and duration of treatment and is encountered in patients receiving high-dose intravenous treatment, particularly for consolidation therapy in acute myeloid leukemia (AML).[1,2] Following intravenous infusion, the drug penetrates the blood-brain barrier and reaches the cornea via both the aqueous and tears.[1] Cytarabine-induced corneal toxicity is characterized by corneal epithelial microcyst formation. The corneal toxic keratopathy is reversible without permanent damage or scarring, and vision usually returns to baseline. The resolution of symptoms is within 10 to 14 days and follows the desquamation of the affected cell line. Although uncommon, cytarabine-induced corneal toxicity has also been reported with low-dose treatment regimens.[3] While there is no standard treatment protocol for cytarabine-induced corneal toxicity, dexamethasone and prednisolone drops have been reported effective in treatment.[1,4,5] In this report we want to emphasize that loteprednol etabonate, a topical soft steroid, is also as effective as dexamethasone and prednisolone in the treatment of cytarabine-induced corneal toxicity.

Case Reports

Case 1

A 25-year-old woman with a diagnosis of acute myelomonocytic leukemia (AML-M4) presented with a 2-day history of foreign body sensation and photophobia following

Address for Correspondence: Gökçen Özcan, Ahi Evran University Training and Research Hospital, Clinic of Ophthalmology, Kırşehir, Turkey
E-mail: drgokcencondu@gmail.com **ORCID-ID:** orcid.org/0000-0002-2616-5941
Received: 16.07.2020 **Accepted:** 05.12.2020

Cite this article as: Özcan G, Özlenen Uçakhan Ö. Cytarabine-Induced Corneal Toxicity: Clinical Features and Relief of Symptoms with Loteprednol Etabonate 0.5% in Two Patients. Turk J Ophthalmol 2021;51:114-117

the last dose of consolidation chemotherapy with cytarabine. She had 3 doses of 6 g/m^2/day cytarabine treatment at 2-day intervals and did not use topical corticosteroid prophylaxis. She complained of ocular discomfort, photophobia, and best-corrected visual acuity was 20/20 in both eyes. Slit-lamp biomicroscopy examination revealed bilateral grade 3 staining in the inferior conjunctiva and corneal epithelial microcysts distributed more densely in the central cornea (Figures 1A and 1E). *In vivo* confocal microscopy (IVCM) showed highly reflective, disseminated granular and irregular intraepithelial opacities 8 to 20 µm in diameter, mainly in the epithelial basal cell layers (Figures 1B and 1F). The epithelial wing cell layers had less numerous intraepithelial opacities compared to the epithelial basal cell layers (Figures 1C and 1G). Loteprednol etabonate 0.5% 4 times daily and artificial preservative-free eye drops were prescribed. Four days after treatment, the patient's complaints wholly subsided. After 3 weeks of treatment, microcysts disappeared completely, and IVCM revealed a few hyperreflective elements mainly in the more superficial rather than the basal epithelial layers (Figures 1D and 1H). The loteprednol eye drop was subsequently tapered and stopped in the following weeks.

Case 2

A 26-year-old man with acute monocytic leukemia (AML-M5) presented with a 4-day history of blurred vision and ocular discomfort following the last dose of consolidation chemotherapy with cytarabine. He received 6 g/m^2/day cytarabine treatment 3 times at 2-day intervals. Although he was advised to use prophylactic topical prednisolone phosphate 1% eye drops starting the day before initiation of chemotherapy, he failed to do so regularly. Best-corrected visual acuities were 20/25 and 20/20 in the right and left eyes respectively. On slit-lamp biomicroscopy examination, bilateral corneal epithelial microcysts were noted (Figures 2A and 2D). There was no staining on the corneal or conjunctival surface. IVCM showed highly reflective disseminated granular irregular intraepithelial opacities 9 to 18 µm in size, again particularly in the epithelial basal cell layers (Figures 2B and 2E) rather than the epithelial wing cell layers (Figures 2C and 2F). The patient's complaints subsided in 5 days, and the microcysts disappeared in 2 weeks with loteprednol etabonate 0.5% 4 times daily and non-preserved artificial tear drops. The loteprednol eye drop was subsequently tapered and stopped in the following weeks.

Discussion

Cytarabine-based consolidation chemotherapy was proven mandatory in preventing relapses after achieving complete remission in AML patients.[6] A high-dose (3 doses of 6 g/m^2 daily) cytarabine regimen was reported to be superior to low-dose cytarabine regimens (5 doses of 0.4 g/m^2 or 0.1 g/m^2) for consolidation.[7] Ocular symptoms develop within 1 week after the initiation of cytarabine treatment and can be prevented with the use of topical corticosteroids. Patients usually complain of tearing, photophobia, foreign body sensation, and sometimes reduced visual acuity. At slit-lamp biomicroscopy, conjunctival hyperemia, superficial punctate keratopathy, and corneal epithelial microcysts with or without conjunctival punctate staining can be noted.

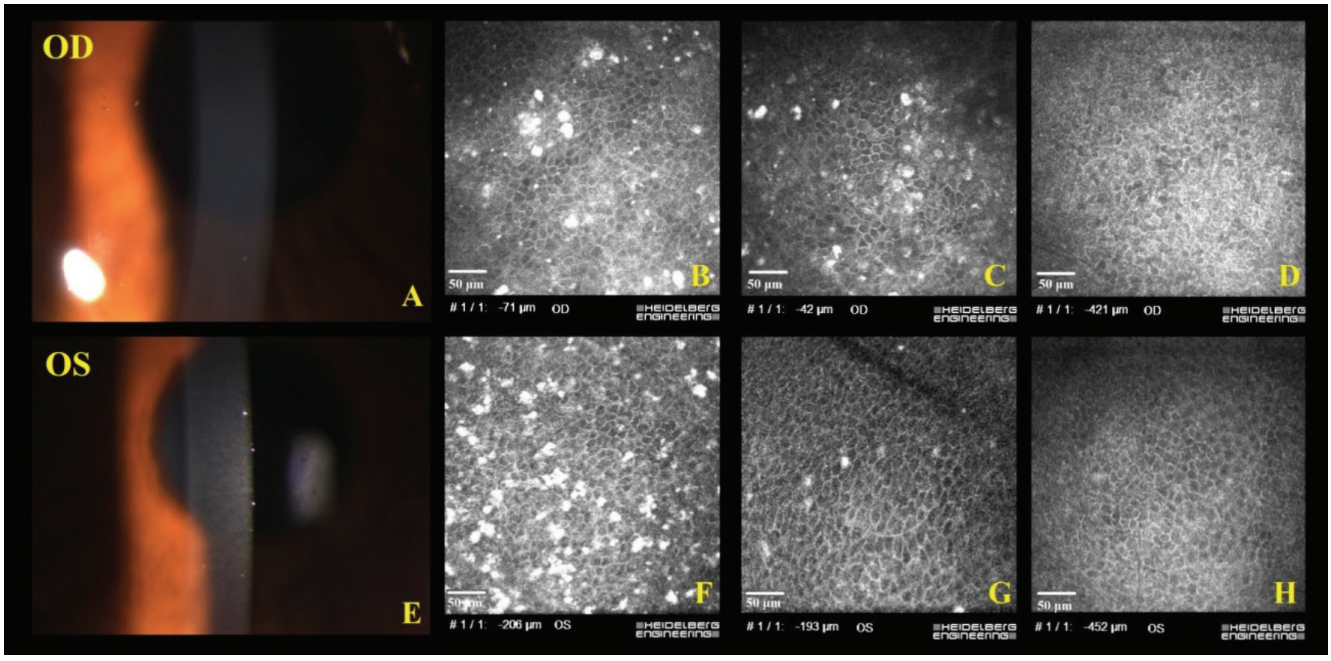

Figure 1. Patient 1, right eye (top row) and left eye (bottom row): Slit-lamp biomicroscopy and in-vivo confocal microscopy (IVCM) findings before and after loteprednol etabonate 0.5% treatment. Before treatment, corneal epithelial microcysts were visible on slit-lamp biomicroscopy (A, E) and IVCM revealed hyperreflective opacities that were mainly in the basal epithelial cell layers (B, F) and less numerous in the epithelial wing cell layers (C, G). Two weeks after initiation of treatment, the basal epithelial cell layer was observed to be almost clear of hyperreflective opacities (D, H)

The exact mechanism of corneal microcyst formation is unknown. Since cytarabine inhibits DNA polymerase during the S-phase of cell division, daughter transient amplifying cells that migrate centripetally to populate the basal layer of the corneal epithelium are expected to be more vulnerable to cytarabine toxicity. Since the peripheral epithelial stem cells have a longer cell cycle time compared to the central basal cells, they may not be equally sensitive to the toxic effect of cytarabine; thus, the peripheral cornea typically remains clear, and there remains a clear corneal zone free from microcysts at the corneal periphery.[1] Basal cells are displaced to more superficial layers of the cornea and are desquamated with dynamic turnover and sustained proliferation, hence the resolution of symptoms occurs. In the first few symptomatic days, IVCM shows hyperreflective opacities 8 to 20 µm in size in the basal cell layer. In the following 4 to 9 days, these hyperreflective opacities move to the superficial layers, also affecting the wing-cells and the apical cells. Guthoff et al.[8] also showed intraepithelial highly reflective elements were visualized only in the basal layer in IVCM on first symptomatic day, but at days 9 to 14 they mainly presented in more superficial layers. Histologically, these opacities were shown to represent degenerate cells with pyknotic nuclei intermixed with cytoplasmic debris.[9]

The incidence of cytarabine-induced corneal toxicity was reported to be around 85-92% without topical corticosteroid prophylaxis.[10] In this case, topical steroids are started 1 day before initiation of treatment and are continued throughout the therapy. Topical corticosteroid eye drops have been reported to reduce the incidence to 8-16%.[2,10] Although the mechanism of action is unknown, corticosteroid eye drops were hypothesized to render the corneal epithelial cells less susceptible to the effects of cytarabine by inducing a partial reduction in DNA replication.[2] In a randomized, double-masked trial that compared placebo to prophylactic steroid use, corticosteroids prevented the development of conjunctival hyperemia and visual reduction, and significantly reduced the degree of microcyst formation.[2] Additionally, prophylactic topical corticosteroid use certainly relieves the symptoms of cytarabine-induced corneal toxicity, such as tearing, photophobia, and foreign body sensation. Betamethasone sodium phosphate 0.1%, dexamethasone 0.1%, and prednisolone phosphate 1% eye drops have been recommended for prophylaxis against cytarabine-induced corneal toxicity.[1,2] In our two patients, loteprednol etabonate 0.5% eye drops were also quite effective in suppressing the patients' symptoms and relieving photophobia. Since these patients are already immunosuppressed, loteprednol etabonate 0.5% use may reduce the risk of secondary infection at the ocular surface, as well as minimizing the risk of short-term topical corticosteroid-induced side effects such as intraocular pressure elevation.

The use of topical 2-deoxycytidine, a competitive inhibitor of cytarabine, has also been shown to be effective in the management of the dose-related corneal toxicity of systemic cytarabine. However, this drug is not commercially available.[11] Artificial tear drops, on the other hand, can help relieve symptoms by diluting cytarabine in tears; therefore, the addition of topical lubricants to topical corticosteroid prophylaxis is usually recommended.[4]

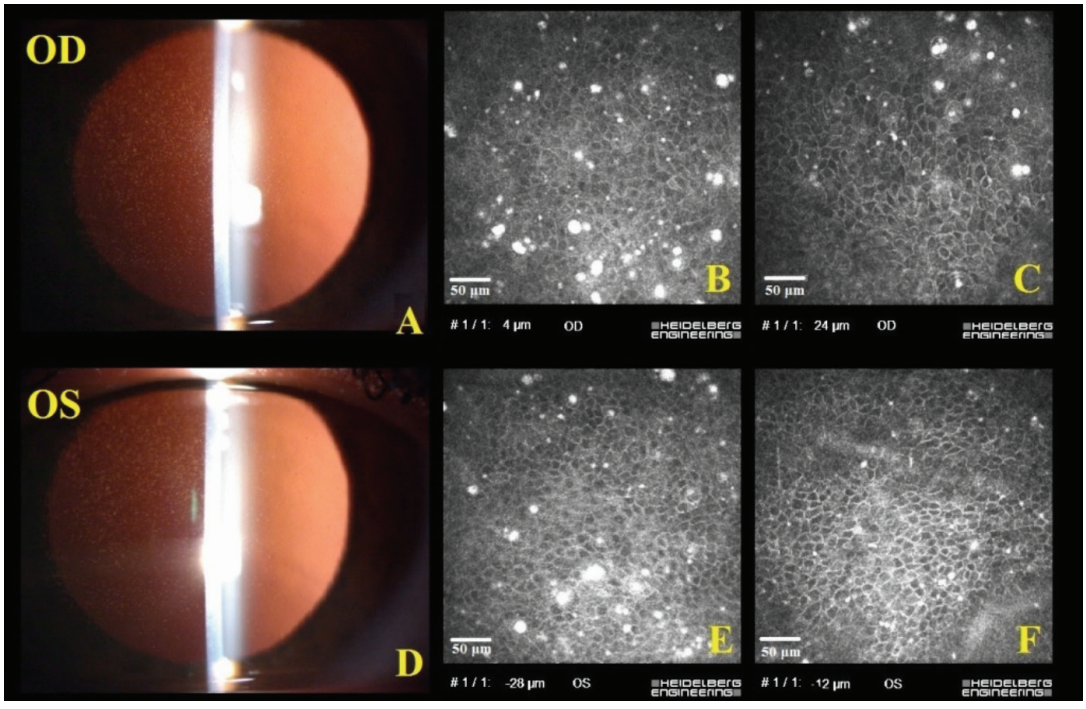

Figure 2. Patient 2, right eye (top row) and left eye (bottom row): Before initiation of loteprednol etabonate 0.5% treatment, slit-lamp biomicroscopy with retroillumination revealed numerous central corneal epithelial microcysts bilaterally (A, D). *In vivo* confocal microscopy (IVCM) revealed irregular hyperreflective opacities mainly in the basal epithelial cell layer (B, E) rather than in the epithelial wing cell layer (C, F). Post-treatment IVCM measurements could not be obtained from this patient

Acute anterior uveitis and optic neuropathy are the other rare complications of high dose cytarabine treatment.[12] High dose cytarabine treatment used in conjunction with total-body irradiation in the setting of induction for hematopoietic cell transplantation can rarely induce retinal microvascular damage with capillary nonperfusion, neovascularization, vitreous hemorrhage, and macular edema.[13]

In summary, ophthalmologists should be aware of the signs and symptoms of cytarabine-induced ocular toxicity, whereas oncologists need to know the importance of seeking ophthalmology consultation for initiation of topical corticosteroid treatment together with frequent lubrication in patients who need to receive high-dose chemotherapy regimens with cytarabine. Once cytarabine-induced keratopathy is diagnosed, topical soft steroids such as loteprednol etabonate 0.5% eye drops and frequent lubrication may also be as effective as topical dexamethasone and prednisolone eye drops in relieving ocular discomfort, photophobia, and foreign body sensation.

Ethics

Informed Consent: Obtained.

Peer-review: Externally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: Ö.Ö.U., G.Ö., Concept: Ö.Ö.U., G.Ö., Design: Ö.Ö.U., G.Ö., Data Collection or Processing: G.Ö., Ö.Ö.U., Analysis or Interpretation: G.Ö., Ö.Ö.U., Literature Search: G.Ö., Ö.Ö.U., Writing: G.Ö., Ö.Ö.U.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: This study was supported in part by a grant from Ankara University.

References

1. Lochhead J, Salmon JF, Bron AJ. Cytarabine induced corneal toxicity. Eye (Lond). 2003;17:677-678.
2. Lass JH, Lazarus HM, Reed MD, Herzig RH. Topical corticosteroid therapy for corneal toxicity from systemically administered cytarabine. Am J Ophthalmol. 1982;94:617-621.
3. Kumar L, Dua H, Agarwal S, Singh S, Kochupillai V. Ocular toxicity of low dose cytosar. N Z Med J. 1987;100:361.
4. Higa GM, Gockerman JP, Hunt AL, Jones MR, Horne BJ. The use of prophylactic eye drops during high-dose cytosine arabinoside therapy. Cancer. 1991;68:1691-1693.
5. Dhillon VK, Faraj LA, Elalfy MS, Bhatt U, Said DG, Dua HS. Corneal microcysts. Br J Ophthalmol. 2014;98:147-148.
6. Mayer RJ, Davis RB, Schiffer CA, Berg DT, Powell BL, Schulman P, Omura GA, Moore JO, McIntyre OR, Frei E 3rd. Intensive postremission chemotherapy in adults with acute myeloid leukemia. N Engl J Med. 1994;331:896-903.
7. Magina KN, Pregartner G, Zebisch A, Wölfler A, Neumeister P, Greinix HT, Berghold A, Sill H. Cytarabine dose in the consolidation treatment of AML: A systematic review and meta-analysis. Blood. 2004;130:946-948.
8. Guthoff T, Tietze B, Meinhardt B, Becher J, Guthoff R. Cytosine-arabinoside-induced keratopathy: A model of corneal proliferation kinetics keratopathy. Ophthalmologica. 2010;224:308-311.
9. Hopen G, Mondino BJ, Johnson BL, Chervenick PA. Corneal toxicity with systemic cytarabine. Am J Ophthalmol. 1981;91:500-504.
10. Herzig RH, Wolff SN, Lazarus HM, Phillips GL, Karanes C, Herzig GP. High-dose cytosine arabinoside therapy for refractory leukemia. Blood. 1983;62:361-369.
11. Lazarus HM, Hartnett ME, Reed MD, Murphy BF, Lass JH. Comparison of the prophylactic effects of 2-deoxycytidine and prednisolone for high-dose intravenous cytarabine-induced keratitis. Am J Ophthalmol. 1987;104:476-480.
12. Hoffman DL, Howard JR, Sarma R, Riggs JE. Encephalopathy, myelopathy, optic neuropathy, and anosmia associated with intravenous cytosine arabinoside. Clin Neuropharmacol. 1993;16:258-262.
13. Vogler WR, Winton EF, Heffner LT, Gordon DS, Sternberg P, Crocker I, Reynolds R, Dobbs CK. Ophthalmological and other toxicities related to cytosine arabinoside and total body irradiation as preparative regimen for bone marrow transplantation. Bone Marrow Transplant. 1990;6:405-409.

DOI: 10.4274/tjo.galenos.2020.04641
Turk J Ophthalmol 2021;51:118-122

Case Report

Utility of the Glabellar Flap in the Reconstruction of Medial Canthal Tumors after Mohs Surgery

Ricardo Andres Diaz Cespedes*, Leticia Ortega Evangelio**, Anca Oprisan***, Alvaro Olate Perez****

*Hospital de Manises, Department of Oculoplastics, Valencia, Spain
**Fisabio-oftalmología Médica Department of Oculoplastics, Valencia, Spain
***Universitary and Politechnic Hospital la Fe, Department of Radiology, Valencia, Spain
****Clinic and Provincial Hospital of Barcelona, Department of Ophthalmology, Barcelona, Spain

Abstract

The goals of periorbital region reconstruction are to obtain both functional and esthetic results. Medial canthus is the second most common periorbital location for basal cell carcinoma. If left untreated, it is locally destructive but rarely metastasizes. Incompletely resected medial canthal tumors recur or penetrate along the lacrimal path and expand to wider lesions. A safety margin is necessary to ensure a complete lesion resection. Since it was introduced in 1941, Mohs surgery has been promoted as an efficient method of dealing with infiltrative periorbital skin tumors. It has been shown to have high rates of complete cancer removal during surgery, minimizing the amount of normal tissue loss and securing better functional and cosmetic outcomes. Due to its concave contour and convergence of skin units with variable thickness, texture and mobility, reconstruction of the medial canthal region (MCR) remains challenging. Reconstructive methods such as free full-thickness skin grafts and glabellar flaps have been used alone or in combination with other techniques. The concavity of the canthus must be achieved, but the maintenance of the normal contour and symmetry of the surrounding tissue is critical. The glabellar flap (GF) is a triangular advancement flap that adequately restores the volume in deeper defects, guaranteeing sufficient vascular support without complex or undesirable scars. We present two cases of basal cell carcinoma affecting the MCR that was successfully reconstructed using a GF alone in one case and together with a cheek advancement flap in the second one. In both cases, tumor excision was performed using Mohs surgery.

Keywords: Basal cell carcinoma, glabellar flap, medial canthus, Mohs surgery

Introduction

Periocular malignancies constitute 5-10% of the total number of cutaneous malignancies.[1] The therapeutic approach to such tumors is predominately surgical and depends on the tumor characteristics, histological subtype, and the patient's facial features.[2] After excision, reconstructive surgery is frequently needed to obtain the best functional and cosmetic results, avoiding undesirable changes in blink dynamics. The reconstruction of the medial canthus can prove challenging due to the anatomic complexity of the region, which involves a concave contour and the convergence of skin units with variable texture, thickness, and mobility. Mohs micrographic surgery (MMS) is a very useful technique since it ensures complete cancer removal and decreases the amount of healthy tissue that is excised.[3] In the medial canthal region (MCR), reconstructive methods are selected depending on the size and location of the defect and morbidity of the donor site. When deeper defects straddle, skin flaps are the best choice. Although

Address for Correspondence: Ricardo Andres Diaz Cespedes, Hospital de Manises, Department of Oculoplastics, Valencia, Spain
E-mail: riediaz@gmail.com **ORCID-ID:** orcid.org/0000-0002-0789-0961
Received: 25.05.2020 **Accepted:** 07.12.2020

Cite this article as: Cespedes RAD, Evangelio LO, Oprisan A, Perez AO. Utility of the Glabellar Flap in the Reconstruction of Medial Canthal Tumors after Mohs Surgery. Turk J Ophthalmol 2021;51:118-122

bilobed flaps,[4,5] rhomboid flaps[6] and advancement flaps[7] are among the most commonly used procedures, the glabellar flap (GF) alone or in combination with other techniques remains useful in selected patients.[8,9]

We present two cases of basal cell carcinoma (BCC) involving a large soft-tissue defect of the MCR, one extending onto the nasal sidewall and the other one extending also onto the cheek. In the first case, a GF was sufficient to cover the defect. In the second case, a combination of GF and cheek lateral rotational flap (CLRF) was used to cover the defect. In both cases, good esthetic and functional results were obtained.

Case Reports

Case 1

A 75-year-old woman presented to our hospital oculoplastic department complaining of a growing mass in the inner corner of her right eye for 5 months. No ocular symptoms were reported. On clinical examination, a pink-colored lesion with pearly edges and telangiectasia was seen in the right MCR extending onto the nasal sidewall. Ulceration, peripheral keratosis and bleeding were also present. Punch biopsy was performed and the pathology report indicated an infiltrating BCC. In both cases, the lesions were excised by the same surgeon in the operating room under local anesthesia and intravenous sedation. The tumor was removed using MMS until completely tumor-free margins were achieved. A GF was designed and elevated to close the defect maintaining the esthetic subunits and concavity of the eyelid canthus and the nasal sidewall. The lacrimal system was inspected by probing and no defects were noted in the canaliculi. After surgery, no distortion of the surrounding tissues was observed, the eyebrow spacing was minimal, and overall good symmetry was obtained (Figure1a, b).

Case 2

A 52-year-old woman was referred from our hospital's dermatology department for evaluation of recurrent BCC near her left eye. She reported two previous local excisions of the lesions without margin checks. The first surgery was performed 3 years prior and the second one 4 months prior, with recurrence of the cutaneous lesion on both occasions. On clinical examination, a discolored plaque-like lesion with telangiectasia, raised pale borders, and a waxy appearance was seen in the left MCR extending onto the nasal sidewall. As in case 1, an MMS was proposed, so an immediate reconstruction with a maximal assurance of tumor ablation could be performed. The resultant soft-tissue defect affected a bigger area below the medial canthal tendon than the one seen in case 1. A GF was elevated, but it was insufficient to complete a tension-free closure of the defect. To avoid unnecessary facial distortion, a CLRF was designed and mobilized to meet the inferior edge of the GF taking advantage of laxity in the cheek. After surgery, the patient was pleased with the esthetic and functional results (Figure 1c, d).

Surgical Technique

In both cases, local examination revealed the tumors involving the MCR (Figure 2a, b). Their limits (inner margin) were first demarcated with a blue marker and the outermost margin was used to define the surgical margin (initially 2 mm) (Figure 2c, d).

Local anesthesia (xylocaine 20 mg/mL with adrenaline 0.0005 mg/mL) was injected, first in the MCR and after the flap was designed, in the glabellar region. Intravenous sedation was administered by the anesthetist.

In the first stage of MMS, a debulking of the central tumor was performed. The first Mohs layer of 2 mm was then taken with the incision beveled at 45°. This was immediately mapped maintaining orientation with anatomical landmarks in the eyelid (Figure 3a, b). Further Mohs stages were performed at the positive areas only and the same process was repeated until tumor-free margins were obtained (Figure 3a, b).

In case 1, using the caudal side as a pedicle, an inverted V-shaped advancement flap was designed over the area of maximal skin laxity in the glabellar region (Figure 4a). A periosteal attachment with a 5/0 polyglactin 910 suture was placed to tack the flap and maintain the normal concavity of the canthus (Figure 4b). The flap was raised in the subcutaneous plane with conservative elevation to preserve the blood supply and then rotated to cover the defect. In the donor area, a blunt dissection in the subgaleal plane at each side of the forehead was made, allowing the wound to be closed primarily. In both cases the defect was smaller than the flap and a small amount of redundant tissue was trimmed from the tip of the flap (Figure 4c). The periosteal attachment suture was passed through the flap and secured with a bolster to achieve direct contact with the wound bed (Figure 4d).

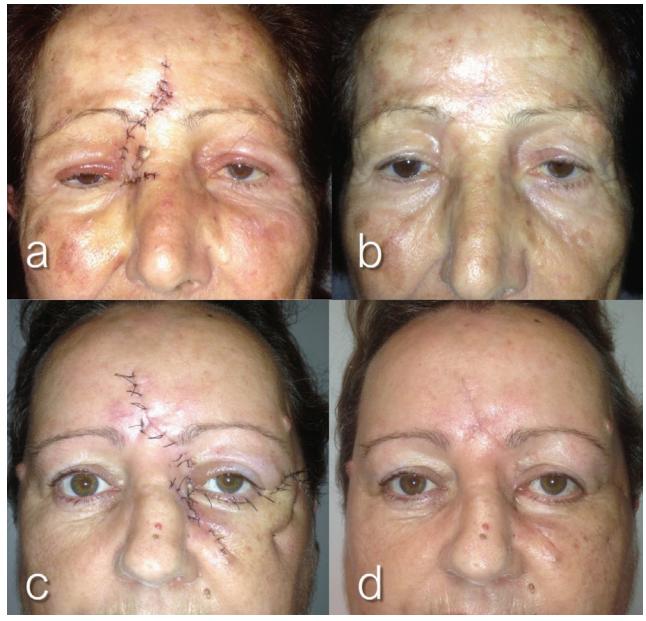

Figure 1. Postoperative aspect at 3 days and 1 month after the surgery in patient 1 (a, b) and patient 2 (c, d)

In case 2, a GF and CLRF were designed (Figure 5a). The GF was performed as described in case 1. A subciliary incision was then extended from the lateral border of the defect to beyond the lateral canthus. Dissection was performed between the orbicularis muscle and orbital septum above the orbital rim, and in the subcutaneous fat plane bellow the orbital rim (Figure 5b). The lower eyelid was stable so no lateral tarsal strip was needed. The CLRF was rotated medially to cover the inferior portion of the defect (Figure 5c). The posterior surface was fixated deep to periosteal attachments to relieve tension from the skin edges with 5/0 polyglactin 910 suture (Figure 5d). In both cases, skin incisions were closed in two planes with a 5/0 polyglactin 910 and 6/0 silk interrupted sutures (Figure 4d, 5d).

Discussion

Tumors of the periorbital region present unique assessment, diagnostic, and therapeutic challenges.[1,3] The most prevalent malignant lesion in the eyelids is BCC (80-92.2%)[10] followed by squamous cell carcinoma, sebaceous gland carcinoma, and cutaneous melanoma.[1] BCC most frequently affects the lower lid and medial canthus or extends to involve both areas. Although usually a slow-growing tumor, some may grow rapidly and invade adjacent tissues including the medial canthal tendon, lacrimal duct, or neurovascular structures. Metastasis of BCC is extremely uncommon, with an estimated rate ranging from 0.003% to 0.55%.[1] In these disorders, the goal of the surgical treatment is to obtain a precise ablation of the entire carcinoma using an accurate histological control.[3]

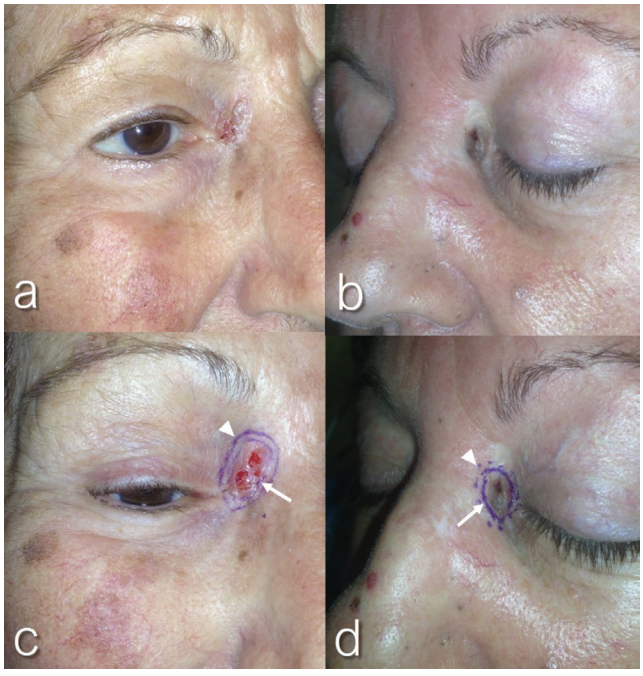

Figure 2. Preoperative aspect of patient 1 (a) and patient 2 (b). Demarcation of the lesion margins (arrow) and the surgical margins (arrowhead) in patient 1 (c) and patient 2 (d)

The MCR is crucial to the appearance and shape of the eye; thus, an accurate reconstruction after skin cancer resection is essential to avoid noticeable asymmetry.[11] The complexity of the region's structural anatomy is due to the confluence of different skin colors, textures, and thicknesses. It has a characteristic depression in the center, a thin subcutaneous tissue, and the least skin excess compared with the surrounding structures. If the tumor resection extends to the nasal sidewall, the upper and lower eyelids, or invades deeper tissues, reconstruction may become more difficult and a combination of different reconstructive techniques may be needed.[12] Inaccurate reconstructive techniques can lead to complications such as epiphora, telecanthus, visibly unnatural appearance, undesirable scarring, and lowered self-esteem.[11]

Conservation of the normal tissue is especially important with eyelid tumor removal because of the limited amount

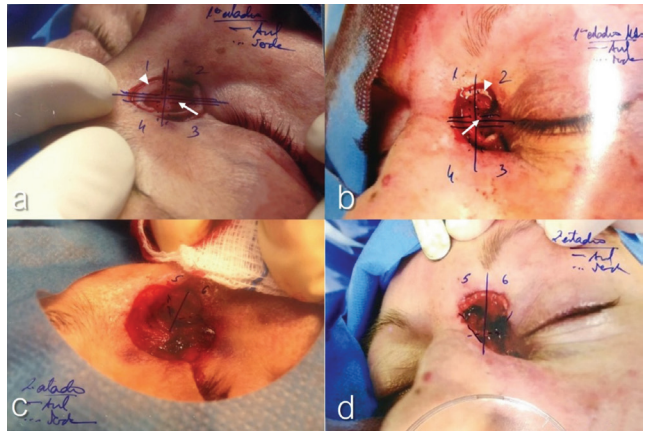

Figure 3. Mohs Micrographic Surgery stages. Debulking (arrow) of the lesion was performed. The first Mohs layer of 2 mm (arrowhead) was taken and immediately mapped in patient 1 (a) and patient 2 (b). Further Mohs stages were performed to the positive areas in patient 1 (c) and patient 2 (d)

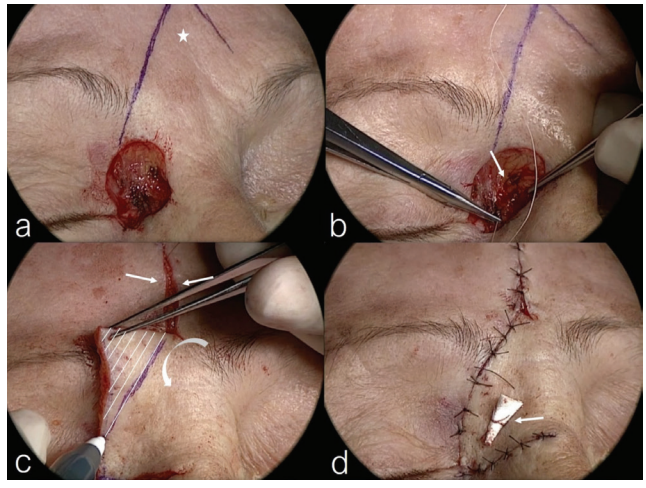

Figure 4. Case 1 surgery. (a) A glabellar flap (star) was designed. (b) Periosteal attachment suture (arrow). (c) Rotation of the glabellar flap to cover the defect (round arrow) and primarily closing of the donor area (arrows). Redundant tissue was trimmed from the tip of the flap (continuous lines). (d) Postoperative aspect at the end of the surgery with the bolster (arrow)

of tissue available to achieve acceptable cosmetic results and preserve normal eyelid function.[13] As described by Huggins et al.[3], MMS is regarded as the gold standard for treatment of BCC with deep tissue invasion in the MCR. It has the benefit of sampling and examining small quadrants of anatomically localized tissue, allowing the surgeon to return to the positive tumor margin and remove tissue only in that small designated area. Thus, MMS ensures a complete cancer removal with the maximum preservation of the normal tissue.[13,14] For primary BCC and squamous cell carcinoma, MMS has an overall 5-year cure rate of 97-99%.[3]

Reconstructive surgical planning in the MCR is tempered by several factors including the depth and size of the defect, the availability and integrity of surrounding tissues, and the surgeon's preferences. If the defect is small and restricted to the anterior lamella, spontaneous granulation and direct closure have been described as good alternatives.[15] A full-thickness skin graft obtained from a donor area with similar characteristics can also be employed for MCR reconstruction; however, graft revascularization is determined by the characteristics of the recipient area, and this can cause graft complications such as necrosis, retraction, or changes in color and texture.[8] For larger anterior defects, or those lacking a vascular bed, various transposition or advancement flaps such as the glabellar, forehead, finger, or orbicularis oculi muscle flaps had been used. A flap has the advantage of having its own intrinsic blood supply, allowing it to be transferred to another area with much less reliance upon the surrounding tissue bed. These aspects make it more predictable in its evolution.[8,9]

The GF described by McCord and Wesley[16] is a flap based on the subdermal plexus and the supratrochlear vessels.[17] It involves an inverted "V" created in the glabellar region and converted into a "Y" to allow the flap to be rotated to provide tissue for the anterior lamella repair. The midpoint of the triangle is midline. It may extend a few centimeters above the superior border of the eyebrow and the midpoint of the triangle may be readjusted more superiorly as needed for flap rotation. It is a relatively quick technique that provides appropriate filling of the resulting defect after MCR lesion removal, including those defects that extend to the bone, as the glabellar skin is thick and provides a good blood supply.[18] The GF offers several advantages, including similarity in color and texture to the recipient site and minimal prevalence of the donor site morbidity. It is obtained from a natural frown line and obviates the need for a second-time surgery or other donor site deformities.[17] One drawback is that it tends to draw the eyebrows together. A bulky nasal bridge and loss of the MCR concavity can also be seen. This can be overcome by avoiding too broad a base to the flap between the eyebrows and performing a meticulous thinning of the flap if needed.[8,19]

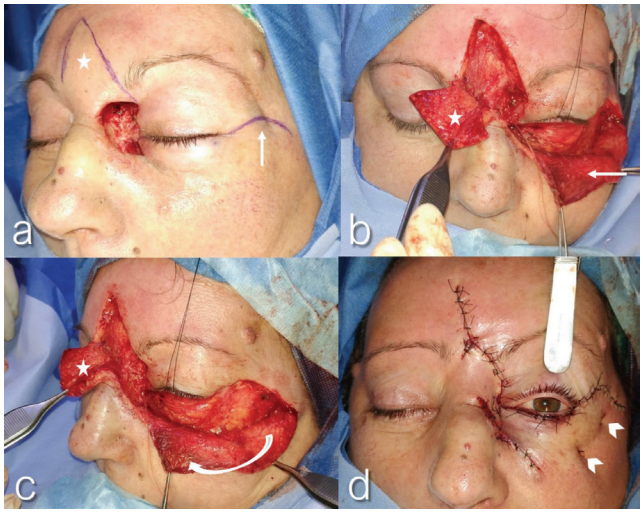

Figure 5. Case 2 surgery. a) A glabellar flap (GF) (star) and cheek lateral rotational flap (CLRF) (arrow) were designed. b) Dissection of the GF (star) and the CLRF (arrow). c) The CLRF was rotated medially (round arrow) to cover the inferior portion of the defect. d) Periosteal attachments were placed (arrowhead) and skin incisions were closed

In the cases presented, a GF was performed because of the defect depth after tumor excision. In these situations, a GF can result in a better cosmetic outcome than that obtained with a free skin graft.[20,21] In some cases, as described in the first patient, a GF alone was enough to successfully reconstruct the MCR as demonstrated by Meadows and Manners[18] or Turgut et al.[17] In cases of larger medial canthal defects involving upper and lower eyelid, simultaneous use of two flaps[22,23,24,25] or a combination of three local flaps[26,27,28] has also been reported. The procedure used in the second patient included two flaps, a GF and a CLRF. Even though cheek flap harvesting is associated with extensive undermining and prolonged operative time,[22] we considered the reconstructive technique highly successful, achieving similar postoperative results as obtained by other authors.[15,29,30]

In conclusion, the MCR can be successfully reconstructed with a GF alone or in combination with other surgical techniques depending on the characteristics of the defect resulting after tumor excision. The MMS has high rates of complete cancer removal during surgery, minimizing the amount of normal tissue loss, as demonstrated in the cases presented. In our experience, the GF is a versatile, simple, and highly reproducible flap. Its vascular pedicle allows reliable flap viability and minimal postoperative flap shrinkage. It provides tissue of adequate thickness and texture for the reconstruction of the MCR after cancer removal. In our practice, we have found that this flap provides an excellent color match and good esthetic and functional results.

Ethics

Informed Consent: Obtained.

Peer-review: Externally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: R.A.D.C., Analysis or Interpretation: R.A.D.C., L.O.E., A.O., A.O.P., Literature Search: R.A.D.C., L.O.E., A.O., A.O.P., Writing: R.A.D.C., L.O.E., A.O., A.O.P.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Slutsky JB, Jones EC. Periocular Cutaneous Malignancies: A Review of the Literature. Dermatol Surg. 2012;38:552-569.
2. Shi Y, Jia R, Fan X. Ocular basal cell carcinoma: a brief literature review of clinical diagnosis and treatment. OncoTargets Ther. 2017;10:2483-2489.
3. Huggins AB, Latting MW, Marx DP, Giacometti JN. Ocular Adnexal Reconstruction for Cutaneous Periocular Malignancies. Semin Plast Surg. 2017;31:22-30.
4. Mehta JS. Infraglabellar Transnasal Bilobed Flap in the Reconstruction of Medial Canthal Defects. Arch Ophthalmol. 2006;124:111-115.
5. Sullivan TJ, Bray LC. The bilobed flap in medial canthal reconstruction. Aust N Z J Ophthalmol. 1995;23:42-48.
6. Chasmar LR. The versatile rhomboid (Limberg) flap. Can J Plast Surg. 2007;15:67-71.
7. Lee BJ, Elner SG, Douglas RS, Elner VM. Island Pedicle and Horizontal Advancement Cheek Flaps for Medial Canthal Reconstruction. Ophthal Plast Reconstr Surg. 2011;27:376-379.
8. Bertelmann E, Rieck P, Guthoff R. Medial Canthal Reconstruction by a Modified Glabellar Flap. Ophthalmologica. 2006;220:368-371.
9. Russo F, Linares M, Iglesias ME, Martínez-Amo JL, Cabo F, Sánchez JT, Vieira RC, Pastrana TT, Rodenas JM. Técnicas reconstructivas de elección por unidades estéticas faciales. Actas Dermo-Sifiliográficas. 2017;108:729-737.
10. Cook BE, Bartley GB. Epidemiologic characteristics and clinical course of patients with malignant eyelid tumors in an incidence cohort in Olmsted County, Minnesota. Ophthalmology 1999;106:746-750.
11. Han J, Kwon ST, Kim SW, Jeong EC. Medial and Lateral Canthal Reconstruction with an Orbicularis Oculi Myocutaneous Island Flap. Arch Plast Surg. 2015;42:40-45.
12. Ogino A, Onishi K, Okada E, Nakamichi M. Medial canthal reconstruction with multiple local flaps. JPRAS Open. 2018;15:4-9.
13. Carter KD, Nerad JA, Whitaker DC. Clinical factors influencing periocular surgical defects after Mohs micrographic surgery. Ophthal Plast Reconstr Surg. 1999;15:83-91.
14. Mohs FE. Micrographic surgery for the microscopically controlled excision of eyelid cancers. Arch Ophthalmol. 1986;104:901-909.
15. Czyz CN, Cahill KV, Foster JA, Michels KS, Clark CM, Rich NE. Reconstructive options for the medial canthus and eyelids following tumor excision. Saudi J Ophthalmol. 2011;25:67-74.
16. McCord C, Wesley R. Reconstruction of the upper eyelid and medial canthus. In: McCord CD, Tannenbaum M, eds. Oculoplastic Surgery (2nd ed). New York; Raven Press; 1987:73-91.
17. Turgut G, Ozcan A, Yeşiloğlu N, Baş L. A new glabellar flap modification for the reconstruction of medial canthal and nasal dorsal defects: 'flap in flap' technique. J Craniofac Surg. 2009;20:198-200.
18. Meadows AER, Manners RM. A simple modification of the glabellar flap in medial canthal reconstruction. Ophthal Plast Reconstr Surg. 2003;19:313-315.
19. Emsen IM, Benlier E. The use of the superthinned inferior pedicled glabellar flap in reconstruction of small to large medial canthal defect. J Craniofac Surg. 2008;19:500-504.
20. Alghoul M, Pacella SJ, McClellan WT, Codner MA. Eyelid Reconstruction. Plast Reconstr Surg. 2013;132:288–302.
21. Leibovitch I, Huilgol SC, Hsuan JD, Selva D. Incidence of host site complications in periocular full thickness skin grafts. Br J Ophthalmol. 2005;89:219-222.
22. Motomura H, Taniguchi T, Harada T, Muraoka M. A combined flap reconstruction for full-thickness defects of the medial canthal region. J Plast Reconstr Aesthet Surg. 2006;59:747-751.
23. Chao Y, Xin X, Jiangping C. Medial canthal reconstruction with combined glabellar and orbicularis oculi myocutaneous advancement flaps. J Plast Reconstr Aesthet Surg. 2010;63:1624-1928.
24. Jelks GW, Glat PM, Jelks EB, Longaker MT. Medial canthal reconstruction using a medially based upper eyelid myocutaneous flap. Plast Reconstr Surg. 2002;110:1636-1643.
25. Yildirim S, Aköz T, Akan M, Çakir B. The Use of Combined Nasolabial V-Y Advancement and Glabellar Flaps for Large Medial Canthal Defects. Dermatol Surg. 2001;27:215-218.
26. Berry MG, Fernandes AEL. Triple-flap medial canthal reconstruction. Can J Plast Surg. 2008;16:170-172.
27. Ayhan S, Ozmen S, Sarigüney Y, Latifoğlu O, Atabay K. Reconstruction of the medial canthal region with the 'triple-flap' technique. Ann Plast Surg. 2001;47:354-355.
28. Lykoudis EG, Lykoudis GE, Alexiou GA. "Pickaxe" Double Flap: A Useful "Tool" for Reconstruction of Deep Large Medial Canthal Defects-5-Year Experience and Brief Literature Review. Aesthetic Plast Surg. 2015;39:410-413.
29. Chahal HS, Allen RC. Combination Lateral Rotational and Glabellar Flaps for Medial Canthal Defects. JAMA Facial Plast Surg. 2016;18:491-492.
30. Yan J, Liu L, Qian J. Reconstruction of upper eyelid and medial canthus following basal cell carcinoma resection: a successful one-stage repair with three local flaps. Int J Dermatol. 2013;52:611-613.

DOI: 10.4274/tjo.galenos.2020.66909
Turk J Ophthalmol 2021;51:123-126

Case Report

A Case of Multiple Optic Disc Pits: 21-Year Follow-up

Osman Melih Ceylan, Alper Can Yılmaz, Ali Hakan Durukan, Mehmet Talay Köylü, Fatih Mehmet Mutlu

University of Health Sciences Turkey Gülhane Faculty of Medicine, Department of Ophthalmology, Ankara, Turkey

Abstract

Optic disc pits (ODP) are an uncommon congenital abnormality. Patients remain asymptomatic unless they develop maculopathy. The use of optic coherence tomography has critical benefits in the follow-up of patients who are at the amblyogenic age. The aim of this study is to present a case of double ODP in the right eye and single ODP in the left eye in a partially accommodative esotropia patient followed for 21 years. To our knowledge, multiple ODP has never been described in a patient with partially accommodative esotropia.
Keywords: Accommodative esotropia, optic disc pit, optical coherence tomography, multifocal electroretinography

Introduction

An optic disc pit (ODP) is a rare congenital defect that usually presents as an ovoid, grey-white excavation in the lamina cribrosa of the optic disc.[1] It is seen in 1 per 11,000 population and equally in both sexes, occurring singly and unilaterally in 85-90% of cases and bilaterally in 10-15% of cases.[1,2] Serous macular detachment is estimated to affect 25-75% of patients with ODP.[2] Vitreomacular traction and vitreous strands over the optic disc were reported by Theodossiadis et al.[3] in eyes with ODP-related maculopathy. However, there are very few studies showing that this rare, sight-threatening anomaly can sometimes be multiple. Only 12 cases of double ODP have been reported in the literature to date.[4,5,6]

The aim of this study was to present a case of double ODP in the right eye (RE) and single ODP in the left eye (LE) of a patient with partially accommodative esotropia who was followed-up for 21 years.

Case Report

A 25-year-old female was followed-up for partially accommodative esotropia from the age of 4 years. She underwent strabismus surgery at 6 years of age for residual esotropia at distance and near with full cycloplegic refraction. Bilateral ODP was found at her first visit. Her best-corrected visual acuity (BCVA) was 20/20 (Snellen chart) in both eyes. Anterior segment examination was unremarkable bilaterally. Intraocular pressure was 16 mmHg in both eyes. Cycloplegic refraction was +2.50 (+1.00x100) in the RE and +2.00 (+0.50x90) in the LE. Dilated fundoscopy revealed a double ODP in temporal and nasal rims of the right optic disc (Figure 1A) and single ODP in nasal rim of left optic disc (Figure 1B). The ODPs were also clearly visible in red-free fundus photography (Figure 1C, 1D).

Spectral-domain optical coherence tomography (SD-OCT) (Heidelberg Engineering, Heidelberg, Germany) showed subfoveal deposits in the RE (Figure 2A). This accumulation

Address for Correspondence: Osman Melih Ceylan, University of Health Sciences Turkey Gülhane Faculty of Medicine, Department of Ophthalmology, Ankara, Turkey
E-mail: drmelihceylan@yahoo.com.tr **ORCID-ID:** orcid.org/0000-0002-8832-8013
Received: 08.09.2020 **Accepted:** 24.11.2020

Cite this article as: Ceylan OM, Yılmaz AC, Durukan AH, Köylü MT, Mutlu FM. A Case of Multiple Optic Disc Pits: 21-Year Follow-up. Turk J Ophthalmol 2021;51:123-126

probably occured after subretinal fluid resorption and spontaneously regressed (Figure 2B). The macula was stable in the LE. Swept-source OCT (Topcon Corp, Japan) through the optic disc showed two distinct hyporeflective areas in the RE suggestive of ODPs, one each in the temporal and nasal quadrants, as well as fluid accumulation under the optic nerve head and intrapapillary septum structure (Figure 2C). In the LE, a shallow ODP located nasally and associated vitreous fibers were seen (Figure 2D).

The patient's 30/2 visual field analysis (Humphrey field analyzer, Carl Zeiss Meditec, Dublin, CA) demonstrated an enlarged blind spot in the RE (Figure 3A) and no visual field defect in the LE (Figure 3B). Multifocal electroretinography (mfERG) (Vision Monitor, Monpack 3, Metrovision, France) revealed low amplitudes correlated with 2° of macula in the RE (Figure 3C) and normal results in the LE (Figure 3D). However, despite the pathological findings in the tests, the patient had no complaints. The patient was followed up annually by ophthalmic examination and OCT evaluation. Her BCVA remained stable (20/20) 21 years after the initial diagnosis.

Discussion

ODPs have typically been an incidental finding on routine dilated fundus exam. To our knowledge, multiple ODP has never been described in a patient with partially accommodative esotropia.

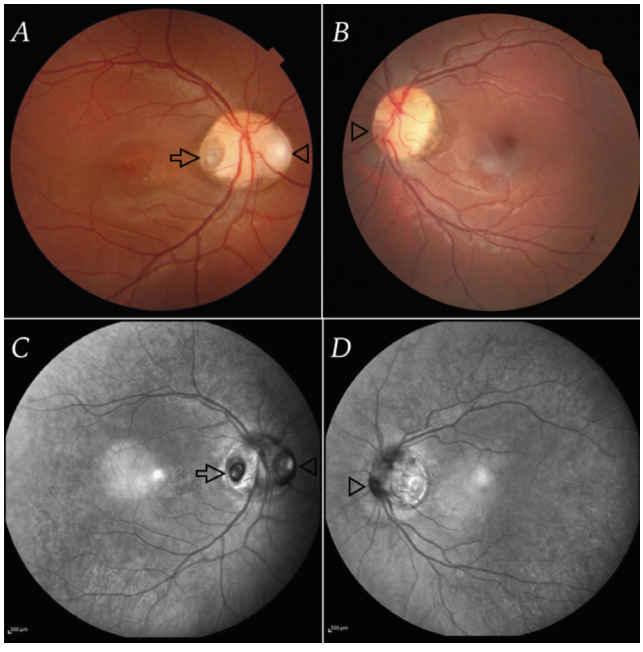

Figure 1. Color fundus and red-free photographs of the right and left eye. A, B) Two optic disc pits located temporally (arrow) and nasally (arrowhead) in the right eye and one optic disc pit located nasally (arrowhead) in the left eye. C, D) The double optic disc pit in the right eye and single optic disc pit in the left eye are clearly observed

In differential diagnosis, congenital optic disc anomalies (such as optic nerve hypoplasia, megalopapilla, morning glory syndrome, and coloboma), and acquired ODP (as in glaucoma, high myopia) should be eliminated.[7,8] In the differential diagnosis, it is easy to distinguish congenital and acquired ODP from optic disc coloboma. Optic disc coloboma typically affects the inferior nasal rim of the optic nerve while ODP most commonly affects the inferotemporal quadrant of the optic disc.[1] Patients often remain asymptomatic until macular changes are present. Interestingly, we diagnosed this case in the first decade, and the patient was asymptomatic despite findings of maculopathy in long-term follow-up. Despite attenuated amplitudes on mfERG, her BCVA was not affected. In our opinion, her BCVA may have been preserved as a result of self-healing serous retinal detachment attacks. Although spontaneous resolution with good visual acuity was reported in about 25% of cases, pediatric patients often develop maculopathy due to traction from the formed vitreous in younger eyes.[9]

Maculopathy secondary to ODP is treated with juxtapapillary laser photocoagulation (JLP), pars plana vitrectomy (PPV), or combined treatments, but there is no consensus on the optimal surgical technique. It has been reported that the combination of PPV, gas tamponade, and JLP is more effective than PPV and gas.[10] Recent studies have reported no additional benefit from JLP in long-term success rates.[11,12] Avci et al.[13] stated that PPV gives the best functional results in ODP maculopathy. They also emphasized that JLP may not be necessary for the success of PPV. Although there are studies showing that gas tamponade removes retinal and subretinal fluid from the macula,[14,15] there are also studies reporting that it does not significantly contribute to the final success rate.[10,16]

OCT is an non-invasive test to interpret the macular status, however it shows the relationship of ODP with vitreous and retina as well.[3,17] In some cases, a hyporeflective area within the optic disc excavation is visible, which may reflect accumulated fluid underneath the optic nerve head.[9] Other important OCT findings are intrapapillary cavities, intrapapillary proliferations, septum-like structures, and subretinal precipitates which can be detected as a marker for chronicity of maculopathy.[18,19] In our patient, one eye had fluid accumulation under the optic nerve head and an intrapapillary septum structure (Figure 2C).

Although macular and optic nerve head-related findings can be easily detected with OCT, the use of mfERG may be beneficial in patients who are uncooperative and at the amblyogenic age.

To the best of our knowledge, a total of 3 ODPs with bilateral involvement has never been described in association with partially accommodative esotropia. Therefore, in order to prevent amblyopia, patients should be closely followed from childhood. OCT and mfERG are useful tests for detecting retinal changes.

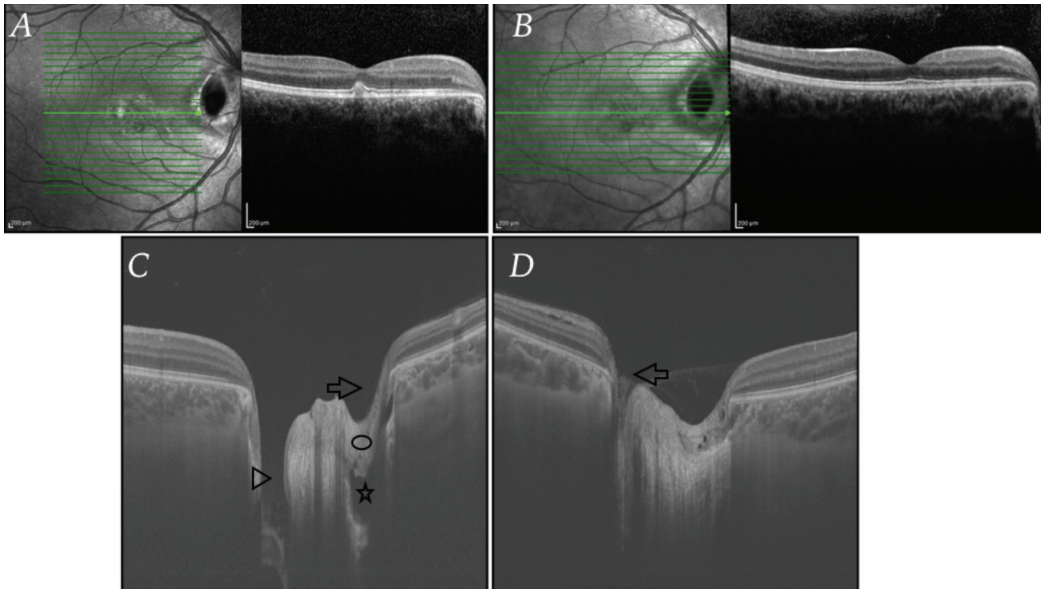

Figure 2. A) Spectral domain optical coherence tomography (SD-OCT) shows subfoveal deposits at age 19. B) Subfoveal deposits are not seen on SD-OCT at final follow-up 6 years later. C) Swept-source OCT (SS-OCT) of the right eye shows the temporal (arrowhead) and nasal (arrow) optic disc pits. Fluid under the optic nerve head appears as a hyporeflective area (star) and an intrapapillary septum structure is seen between the accumulation of fluid under the optic nerve head and the optic disc pit (circle). D) SS-OCT of the left eye shows a shallow optic disc pit (arrow) located nasally and associated vitreous fibers

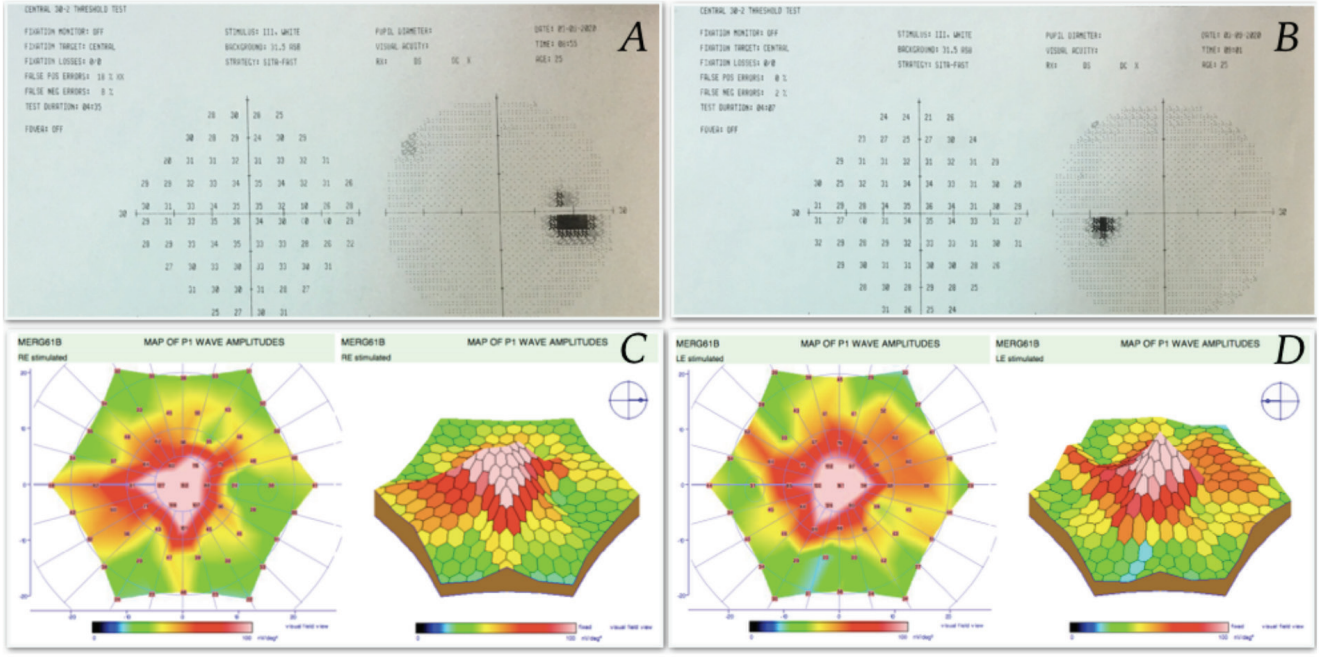

Figure 3. A) In the visual field, blind spot enlargement is observed in the right eye. B) No visual field defect is seen in the left eye. C) Multifocal electroretinography (mfERG) revealed low amplitudes correlated with 2° of the macula in the right eye. D) mfERG is normal in the left eye

Ethics

Informed Consent: The authors certify that they have obtained all appropriate patient consent forms. The patient consented to the reporting of clinical information and images under the condition of anonymity.

Peer-review: Externally and internally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: O.M.C., Concept: O.M.C., F.M.M., A.H.D., Design: O.M.C., F.M.M., A.H.D., Data Collection or Processing: O.M.C., A.C.Y., M.T.K., Analysis

or Interpretation: O.M.C., A.C.Y., M.T.K., Literature Search: O.M.C., A.C.Y., M.T.K., Writing: O.M.C., F.M.M., A.H.D.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Kranenburg EW. Crater-like holes in the optic disc and central serous retinopathy. Arch Ophthalmol. 1960;64:912-924.
2. Georgalas I, Ladas I, Georgopoulos G, Petrou P. Optic disc pit: a review. Graefes Arch Clin Exp Ophthalmol. 2011;249:1113-1122.
3. Theodossiadis PG, Grigoropoulos VG, Emfietzoglou J, Theodossiadis GP. Vitreous findings in optic disc pit maculopathy based on optical coherence tomography. Graefes Arch Clin Exp Ophthalmol. 2007;245:1311-1318.
4. Pozza E, Postelmans L. Double optic pit and associated maculopathy. J Fr Ophtalmol. 2018;41:884 885.
5. Boese EA, Huang D, Tehrani S. Unilateral double optic nerve head pits. Ophthalmology. 2018;125:458.
6. Babu N, Baliga G, Kohli P, Ramasamy K. Management of double optic disc pit complicated by maculopathy. Indian J Ophthalmol. 2020;68:663-665.
7. You JY, Park SC, Su D, Teng CC, Liebmann JM, Ritch R. Focal lamina cribrosa defects associated with glaucomatous rim thinning and acquired pits. JAMA Ophtalmol. 2013;131:314-320.
8. Ohno-Matsui K, Akiba M, Moriyama M, Shimada N, Ishibashi T, Tokoro T, Spaide RF. Acquired optic nerve and peripapillary pits in pathologic myopia. Ophtalmology. 2012;119:1685-1692.
9. Yuen CH, Kaye SB. Spontaneous resolution of serous maculopathy associated with optic disc pit in a child: a case report. J AAPOS. 2002;6:330-331.
10. Moisseiev E, Moisseiev J, Loewenstein A. Optic disc pit maculopathy: when and how to treat? A review of the pathogenesis and treatment options. Int J Retin Vitreous. 2015;1:13.
11. Steel DH, Williamson TH, Laidlaw DA, Sharma P, Matthews C, Rees J, Petrou P, Charteris DG, Charles SJ, Patel CK, Crama N, Herbert E, Jackson TL. Extent and location of intraretinal and subretinal fluid as prognostic factors for the outcome of patients with optic disk pit maculopathy. Retina. 2016;36:110-118.
12. Rayat JS, Rudnisky CJ, Waite C, Huang P, Sheidow TG, Kherani A, Tennant MT. Long-Term outcomes for optic disk pit maculopathy after vitrectomy. Retina. 2015;35:2011-2017.
13. Avci R, Kapran Z, Ozdek Ş, Teke MY, Oz O, Guven D, Yilmaz S, Kaderli B, Durukan AH, Sobaci G, Unver YB, Akduman L, Kaynak S, Dogan I, Inan UU. Multicenter study of pars plana vitrectomy for optic disc pit maculopathy: MACPIT study. Eye (Lond). 2017;31:1266-1273.
14. Lincoff H, Yannuzzi L, Singerman L, Kreissig I, Fisher Y. Improvement in visual function after displacement of the retinal elevations emanating from optic pits. Arch Ophthalmol. 1993;111:1071-1079.
15. Johnson TM, Johnson MW. Pathogenic implications of subretinal gas migration through pits and atypical colobomas of the optic nerve. Arch Ophthalmol. 2004;122:1793-1800.
16. Teke MY, Citirik M. 23 Gauge vitrectomy, endolaser, and gas tamponade versus vitrectomy alone for serous macular detachment associated with optic disc pit. Am J Ophthalmol. 2015;160:779-785.
17. Tzu JH, Flynn HW Jr, Berrocal AM, Smiddy WE, Murray TG, Fisher YL. Clinical manifestations of optic pit maculopathy as demonstrated by spectral domain optical coherence tomography. Clin Ophthalmol. 2013;7:167-172.
18. Maertz J, Mohler KJ, Kolb JP, Kein T, Neubauer A, Kampik A, Priglinger S, Wieser W, Huber R, Wolf A. INTRAPAPILLARY PROLIFERATION IN OPTIC DISK PITS: Clinical Findings and Time-Related Changes.Retina. 2017;37:906-914.
19. Chatziralli I, Theodossiadis G, Brouzas D, Theodossiadis P. Incidence and Evolution of Subretinal Precipitates in Optic Disc Pit Maculopathy.Eur J Ophthalmol. 2017;27:769-773.

DOI: 10.4274/tjo.galenos.2020.95852
Turk J Ophthalmol 2021;51:127-130

Case Report

ANCA-Negative Churg-Strauss Syndrome Presenting as Bilateral Central Retinal Artery Occlusion: A Case Report

Malihe Nikandish*, Zeinab Saremi**

*Birjand University of Medical Sciences, Valiasr Hospital, Department of Ophthalmology, Birjand, Iran
**Birjand University of Medical Sciences Valiasr Hospital, Department of Internal Medicine, Birjand, Iran

Abstract

A 42-year-old man with undiagnosed Churg-Strauss syndrome (CSS) developed bilateral central retinal artery occlusion (CRAO). His medical history included bronchial asthma and irregular prednisolone usage but no atherosclerotic risk factors. At presentation, visual acuity (VA) was hand motion in the right eye and counting fingers in left eye. On fundoscopy, retinal whitening and a cherry red spot were observed in the right eye, while the fundus was normal in the left eye. After eyeball massage and systemic intraocular pressure lowering agents, his VA improved. On day 5 of treatment, he experienced right limb weakness and purpura on his right foot, and electromyography revealed mononeuritis multiplex. Laboratory tests indicated eosinophilia (52%). Based on the presence of hypereosinophilia, bronchial asthma, mononeuritis multiplex, vasculitis purpura, and sinusitis that was detected during etiological investigations, the patient was diagnosed as having CSS according to the American College of Rheumatology diagnostic criteria. Intravenous methylprednisolone 1 g/day was administrated for 3 consecutive days and 1 g cyclophosphamide was started and continued monthly for 6 months. Foot drop and vasculitic purpura improved after 7 days, but there was no further improvement in visual acuity. In conclusion, in the presence of bilateral CRAO and lack of atherosclerotic risk factors, CSS should be considered as a predisposing factor and investigations should be conducted accordingly.

Keywords: Central retinal artery occlusion, anti-neutrophil cytoplasmic antibodies, Churg-Strauss syndrome

Introduction

Central retinal artery occlusion (CRAO) is a devastating ocular emergency that usually occurs secondary to one or more serious systemic diseases such as carotid artery or cardiac valvular disease, hypercoagulability, atrial fibrillation, and autoimmune diseases.[1] According to pathophysiology, CRAO can be divided into two groups, arteritic and non-arteritic. The arteritic category comprises less than 5% of CRAO cases and is related to a vasculitic etiology.[2] Eosinophilic granulomatosis with polyangiitis (EGPA), also called Churg-Strauss syndrome (CSS), is known as a form of vasculitis characterized by inflammation of the blood vessels that can restrict blood flow and damage vital organs and tissues. Individuals diagnosed with EGPA usually have a history of asthma or allergies. Despite the presence of clear diagnostic criteria, the diagnosis of CSS can be delayed in the clinical setting. This is partly related to the sheer variety of clinical presentations of the disease.[3] Regarding anti-neutrophil cytoplasmic antibody (ANCA) status, CSS can be divided into two major subsets: the ANCA-positive patients, who demonstrate clinical and histopathologic features of vasculitis, and the ANCA-negative patients, who exhibit tissue eosinophilic infiltration.[4] Eosinophilic myocarditis[5], neuroendocrine carcinoma[6], eosinophilic vasculitic neuropathy[7], multiple oral ulcerations[8], and inflammatory pseudotumor of the anterior orbit[9] have been reported as initial presentations of CSS in the literature. Herein, we describe a patient with undiagnosed

Address for Correspondence: Zeinab Saremi, Birjand University of Medical Sciences Valiasr Hospital, Department of Internal Medicine, Birjand, Iran
E-mail: zsaremi@bums.ac.ir **ORCID-ID:** orcid.org/0000-0003-2317-6159
Received: 24.09.2020 **Accepted:** 26.11.2020

Cite this article as: Nikandish M, Saremi Z. ANCA-Negative Churg-Strauss Syndrome Presenting as Bilateral Central Retinal Artery Occlusion: A Case Report. Turk J Ophthalmol 2021;51:127-130

CSS who developed simultaneous bilateral CRAO. To the best of our knowledge, this is a rare case of CSS with this clinical presentation, which we recognized during CRAO workup. This case report is of great importance, as the first presentation of CSS might be purely ocular.

Case Report

A 42-year-old man presented to the hospital due to acute painless loss of vision in the right eye 12 hours before and in the left eye immediately before admission. He had a 6-month history of bronchial asthma and irregularly took prednisolone 10 mg/day. Ocular examination revealed that his visual acuity (VA) was hand motion in the right eye and counting fingers (CF) in the left eye. Slit-lamp examination showed bilateral posterior subcapsular cataract that was more severe in the right eye. Fundus photograph showed a significant retinal whitening and cherry red spot in the right eye (Figure 1A), and varying degrees of retinal whitening and soft exudates in the left eye at the presentation (Figure 1B).

Eyeball massage was performed as the initial treatment for both eyes, followed by systemic intraocular pressure lowering medication. The patient refused fluorescein angiography in the acute phase of CRAO. Therefore, the diagnosis of CRAO was made according to fundus appearance. Two hours after the initial treatment, retinal perfusion improved in both eyes, and VA was CF in the right eye and 3/10 in the left eye. The patient underwent a thorough systemic work-up including assessment for diabetes, hypertension, hyperlipidemia, carotid stenosis, and cardiovascular diseases in an effort to identify undiagnosed risk factors, but the results were negative.

Neurologic, respiratory, and dermatologic examinations were unremarkable on the day of admission. Laboratory data showed leukocytosis (11,900/mm^3) and eosinophilia (8%). C-reactive protein (CRP) level was 21 mg/dL (normal range: <5 mg/dL) and erythrocyte sedimentation rate (ESR) was 43 mm/h. Hepatic and renal laboratory tests were normal. Lupus anti-coagulant, anti-cardiolipin, and anti-B2 glycoprotein levels were within normal ranges. Transthoracic echocardiography was normal and there were no abnormal findings in chest X-ray or brain computed tomography (CT). Because of the elevated ESR and CRP and lack of atherosclerotic risk factors, there was a high suspicion of vasculitis as the etiology and oral prednisolone 60 mg/day was administered. However, there was no further improvement in his vision.

On day 5 of treatment, the patient experienced right limb weakness and purpura on his right foot. Neurologic examination showed L5 neuropathy and foot drop. Electromyography and nerve conduction velocity were performed and mononeuritis multiplex was reported. Skin examination revealed palpable, non-blanchable purpuric rash on his right foot (Figure 2). Repeat complete blood count showed significant leukocytosis (17,400/mm^3) with 52% eosinophils. Perinuclear and cytoplasmic ANCA (p-ANCA and c-ANCA) were negative. ESR was 51 mm/h and CRP level was 32 mg/dL. Brain magnetic resonance imaging was normal (Figure 3A, B) but coronal and axial slices revealed paranasal sinusitis (Figure 3C, D). Therefore, CT scans were not performed to prevent radiation. Based on the presence of hypereosinophilia, bronchial asthma, mononeuritis multiplex, vasculitic purpura, and sinusitis, the patient met the classification criteria of the American College of Rheumatology (Table 1) and was diagnosed as having CSS.

Intravenous methylprednisolone 1 g/day for 3 consecutive days and 1 g cyclophosphamide was started and continued monthly for 6 months. Thereafter, oral prednisolone 50 mg/day was prescribed and tapered to 25 mg/day at 6 weeks. Foot drop and vasculitic purpura improved 7 days later; however, there was no further improvement in his visual acuity. Fundus photograph showed retinal exudate in the posterior pole and macular retinal pigment epithelial changes as well as pale disc due to optic atrophy in the right eye (Figure 4A) and normal fundus in the left eye (Figure 4B) at 2-month follow-up. As expected, CRAO led to optic atrophy in the right eye.

The patient provided written informed consent for publishing the images and details of the disease. Based on our university

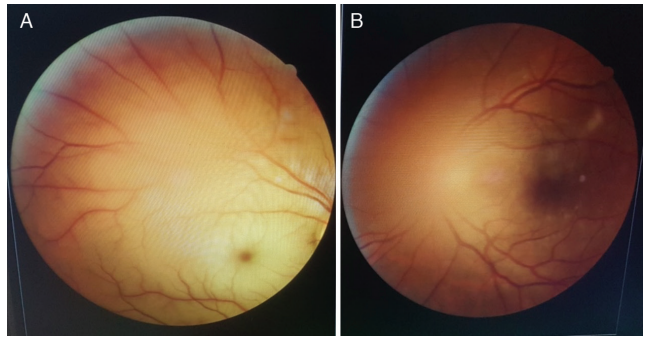

Figure 1. A) Color fundus photograph of the right eye showing a classical cherry-red spot in the macula. B) Retinal whitening and soft exudates in the left eye

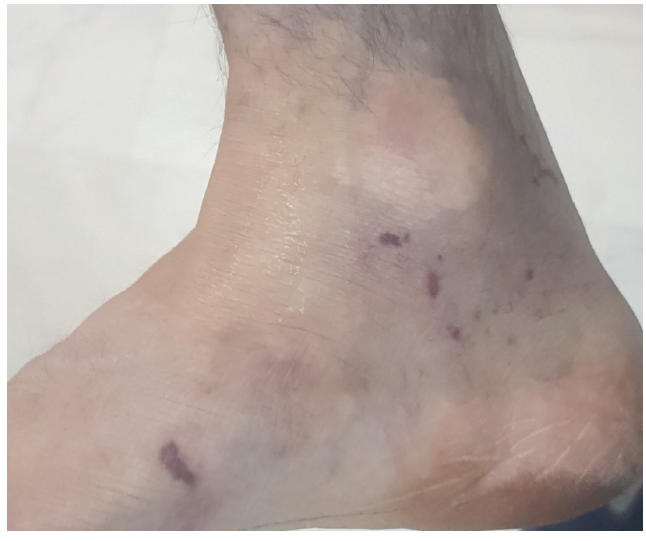

Figure 2. Palpable, non-blanchable purpuric rash on the patient's right foot

Table 1. Churg-Strauss syndrome: American College of Rheumatology classification criteria (4 of the 6 criteria should be present)[12]
Asthma
Eosinophilia >10%
Mononeuropathy or polyneuropathy
Non-fixed pulmonary infiltration
Paranasal sinus abnormalities
Extravascular eosinophils infiltration on biopsy finding

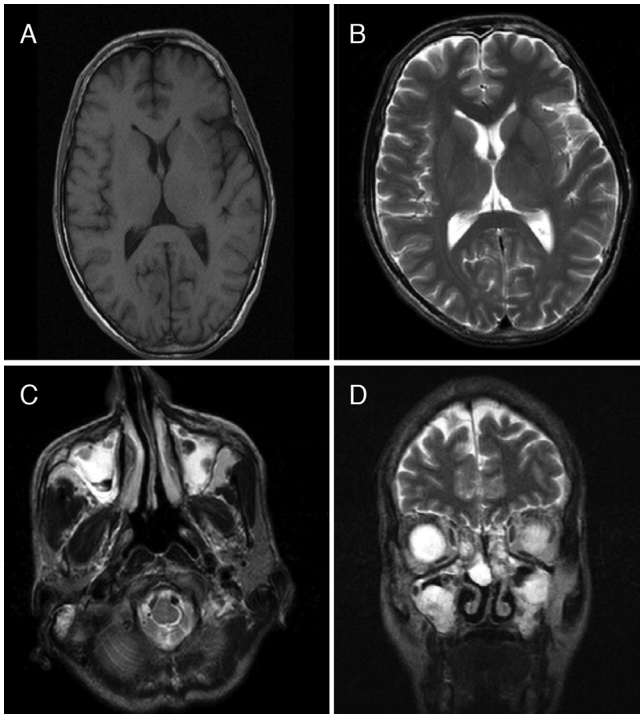

Figure 3. Magnetic resonance imaging (MRI) of the brain is normal (A, B). Coronal (C) and axial (D) slices show paranasal sinusitis

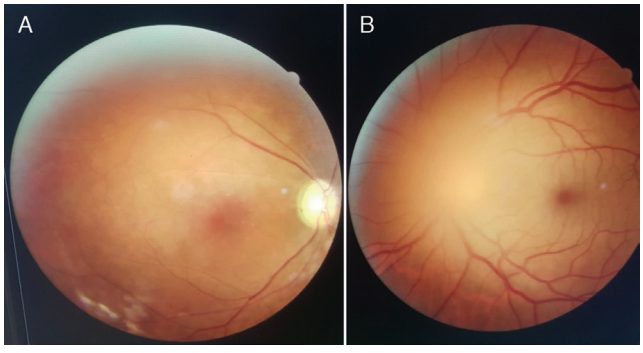

Figure 4. Color fundus photograph at 2-month follow-up: A) Retinal exudates in the posterior pole and macular retinal pigment epithelial changes as well as pale disc in the right eye. B) Normal fundus in the left eye

policy, institutional review board approval is not required for case reports.

Discussion

CSS is a rare disease with small vessel vasculitis characterized by eosinophilia and occurs almost exclusively in patients with asthma. The syndrome can vary in presentation and there is no pathognomonic ocular finding. Ocular presentations can be categorized into 2 groups, largely for prognostic explanations, as idiopathic orbital inflammation-type and ischemic vasculitis-type. Patients with ischemic vasculitis tend to be older than those with idiopathic orbital inflammation.[10] According to a report by Takanashi[11], ANCA-positive patients are more likely to present clinically with classical small-vessel vasculitis, which affects the disease progression and outcomes. However, this was not confirmed in a study by Akella et al.[10] that showed no statistically significant difference in ANCA positivity between the ischemic and inflammatory groups. In the literature, ischemic vasculitis presentations including retinal artery and vein occlusions have been reported in 12 patients. These presentations were mostly accrued in the known cases of CSS and were not the first presentations, and in two cases they were bilateral.[10] However, our patient was ANCA-negative with bilateral CRAO as the first presenting clinical sign, and steroid pulse therapy resulted in no improvement in visual acuity. This result is consistent with the Akella[10] study showing that ischemic vasculitis-type ophthalmic presentations have a less dramatic response to steroids. However, early diagnosis and timely treatment of CSS can prevent systemic life-threatening complications.

In the presence of bilateral CRAO and lack of atherosclerotic risk factors, it is important to rule out systemic vasculitis like CSS. Early diagnosis of the disease can be life-saving. However, the effect of systemic treatment on improving the patient's vision is still unclear.

Ethics

Acknowledgment: Special thanks to the patient for granting us permission to report his illness.

Informed Consent: Written informed consent was obtained from the patient for publishing the images and details of the disease.

Peer-review: Externally peer reviewed.

Authorship Contributions

Concept: M.N., Z.S, Design: M.N., Z.S, Data Collection or Processing: M.N., Z.S, Analysis or Interpretation: M.N., Z.S, Literature Search: M.N., Z.S, Writing: M.N., Z.S.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Youn TS, Lavin P, Patrylo M, Schindler J, Kirshner H, Greer DM, Schrag M. Current treatment of central retinal artery occlusion: a national survey. J Neurol. 2018;265:330-335.

2. Mehta N, Marco RD, Goldhardt R, Modi Y. Central Retinal Artery Occlusion: Acute Management and Treatment. Curr Ophthalmol Rep. 2017;5:149-159.
3. Katerenchuk IP, Tkachenko LA, Yarmola TI, Talash VV, Rustamyan ST, Pustovoyt AL, Kateren. Churg-strauss syndrome: clinical case and its feautures. Wiad Lek. 2019;72:723-726.
4. Psychogios K, Evmorfiadis I, Dragomanovits S, Stavridis A, Takis K, Kaklamanis L, Stathis P. ANCA-Negative Churg-Strauss Syndrome Presenting as Acute Multiple Cerebral Infarcts: A Case Report. J Stroke Cerebrovasc Dis. 2017;26:47-49.
5. Bluett R, McDonnell D, o'Dowling C, Vaughan C. Eosinophilic myocarditis as a first presentation of eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome). BMJ Case Rep. 2017;2017:2017221227.
6. Park D, Lee HJ, Lee KH, Kwon BS, Park JW, Nam KY, Lee KH. Diagnosis of Churg-Strauss syndrome presented with Neuroendocrine carcinoma: a case report. Ann Rehabil Med. 2017;41:493-497.
7. Devarapalli S, Thaisetthawatkul P, Zabad R, Dyck PJB. Eosinophilic Vasculitic Neuropathy As A Presentation Of Churg-Strauss Syndrome. AAN. 2018;90(15 Suppl):445.
8. Ivanoff CS, Ivanoff IK, Hottel TL. Multiple oral ulcerations: A very rare case of Churg-Strauss syndrome with renal disease. J Oral Maxillofac Surg Med Pathol. 2018;30:175-179.
9. Heine A, Beck R, Stropahl G, Unger K, Guthoff R. Inflammatory pseudotumor of the anterior orbit. A symptom in allergic granulomatous angiitis (Churg-Strauss syndrome). Ophthalmologe. 1995;92:870-873.
10. Akella SS, Schlachter DM, Black EH, Barmettler A. Ophthalmic Eosinophilic Granulomatosis With Polyangiitis (Churg–Strauss Syndrome): A Systematic Review of the Literature. Ophthalmic Plast Reconstr Surg. 2019;35:7-16.
11. Takanashi T, Uchida S, Arita M, Okada M, Kashii S. Orbital inflammatory pseudotumor and ischemic vasculitis in Churg-Strauss syndrome: report of two cases and review of the literature. Ophthalmology. 2001;108:1129-1133.

DOI: 10.4274/tjo.galenos.2020.83284
Turk J Ophthalmol 2021;51:131-133

Case Report

Solar Retinopathy Presenting with Outer Retinal Defects Among Habitants of High Altitude

Rajan Sharma*, Nagesha Chokkahalli Krishnappa **, Rakesh Gupta*, Ravinder Gupta*

*M.M. Medical College & Hospital, Himachal Pradesh, India
**B.W. Lions Eye Hospital, Bangalore, India

Abstract

Solar radiation causes acute foveal injury resulting in outer retinal defects. Symptoms often follow an event of unprotected gazing at a solar eclipse or directly viewing the sun. We encountered a series of cases during winter among habitants of high altitudes who complained of visual field scotomas. All of them had a typical history of prolonged sunbathing but denied gazing at the sun directly. Optical coherence tomography showed outer retinal defects involving the ellipsoid zone characteristic of solar retinopathy in all patients. In this case series, we would like to emphasize the role of geographical factors in the causation of solar retinopathy.
Keywords: Altitudinal retinopathy, outer retinal defects, photic retinopathy, solar retinopathy, UV radiation

Introduction

Outer retinal defects are defects in the ellipsoid zone which predominantly involve the foveal cones. They often present with acute central scotoma following unprotected solar eclipse or sun viewing. These defects can also be caused by trauma, acute posterior vitreous detachment, and unprotected welding exposure.[1] Eliciting a proper history can point towards the possible etiology and helps in formulating preventive measures. We encountered a series of patients with outer retinal defects who resided at high altitudes. They had no significant risk factors except for the history of prolonged sunbathing, which suggested solar retinopathy as a possible cause of the outer retinal defects.

Case Reports

Case 1

A 42-year-old farmer from the hilly regions of Himachal Pradesh presented with a 1-day history of visual scotoma. He denied a history of trauma, direct sun gazing, or use of medications. His best-corrected visual acuity (BCVA) was 6/9 in both eyes (BE) and BE had central scotoma on the Amsler grid chart. The anterior segment was normal with a clear lens. Indirect ophthalmoscopy showed grossly normal-looking fundus in BE. Spectral domain optical coherence tomography (OCT) through the fovea revealed a cube-shaped outer retinal defect at the fovea in BE (Figure 1a, b). Solar retinopathy was suspected but he denied a history of prolonged direct sun-gazing. On further interrogation, it was learned that he had engaged in long hours of sunbathing the previous 3 days, which was not a typical habit and he did to combat the severe cold.

Case 2

A 40-year-old woman from the hilltops was examined for decreased vision in her right eye for 4 days. She was a field supervisor on farmland and had the habit of sunbathing for long hours (lying supine with closed eyes directly under the sun). Her BCVA was 6/12 in the right eye (RE) and 6/6 in the left eye (LE). The anterior segment was normal in BE with clear lenses. Foveal

Address for Correspondence: Rajan Sharma, M.M. Medical College & Hospital, Himachal Pradesh, India
E-mail: rajansharma122@gmail.com **ORCID-ID:** orcid.org/0000-0002-2718-9689
Received: 18.05.2020 **Accepted:** 05.11.2020

Cite this article as: Sharma R, Chokkahalli Krishnappa N, Gupta R, Gupta Rav. Solar Retinopathy Presenting with Outer Retinal Defects Among Habitants of High Altitude. Turk J Ophthalmol 2021;51:131-133

reflex was dull in the RE and normal in the LE. OCT of the RE showed partial inner segment/outer segment (IS/OS) loss at the fovea with internal limiting membrane (ILM) draping (Figure 1c). The LE also showed an outer retinal defect smaller than that in the RE (Figure 1c, d).

Case 3

A 28-year-old man presented to our clinic with complaints of seeing a red spot in his LE for 2 months. He had a history of frequently sunbathing and more so during November and winter. His BCVA was 6/6 in the RE and 6/12 in the LE. The anterior segment was quiet with a clear lens in BE. The fundus was grossly normal in the RE, while the LE showed a dull foveal reflex. OCT of the RE revealed a minimal defect in the IS/OS line and the LE showed focal loss of the outer retinal layers at the fovea with decreased subfield thickness (RE: 236 µm, LE: 206 µm) (Figure 1e, f).

Discussion

Outer retinal defects can be secondary to intrinsic ocular factors like acute posterior vitreous detachment (PVD), macular telangiectasia, Stargardt's disease, and extrinsic factors like trauma, unprotected direct eclipse/sun-gazing, and welding arc exposure.[1,2] Thorough history-taking is paramount to ascertain the etiology, since ultra-structural retinal changes due to all the above causes appear similar on OCT.

Solar retinopathy is an acute injury to foveal structures resulting from staring at the sun during a solar eclipse or during normal daylight hours. Patients often correlate the onset of symptoms with the event of sun-gazing or viewing a solar eclipse without protective glasses. Ultraviolet (UV) light from solar radiation is toxic to photoreceptors as well as the RPE. The major component of damage to the retina by UV radiation is through the photochemical pathway. It causes lipid and protein peroxidation in RPE cells, leading to loss of lysosomal integrity and cell death. Various morphological presentations have been described in OCT secondary to solar retinopathy, namely inner retinal layer hyperreflectivity, outer layer hyperreflectivity, full-thickness retinal hyperreflectivity, outer layer retinal defects, and foveal thinning in long-standing cases.[3] In the present case series, all patients had outer retinal layer defects on OCT. None had predisposing factors or history of prolonged gazing at the sun. The common factor among them was repeated sunbathing for a few hours.

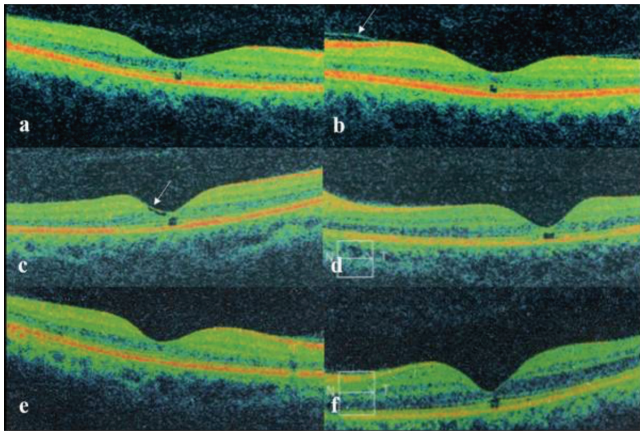

Figure 1. a, b) Optical coherence tomography (OCT) images show outer retinal defects in the right and left eyes of patient 1. Shallow vitreous detachment with normal interface contour is seen in the left eye (arrow). c, d) OCT images of patient 2. Internal limiting membrane draping over the temporal foveal slope is seen in the right eye (arrow). e, f) OCT images of patient 3 with partial discontinuity in the ellipsoid zone in the right eye and full-thickness defect in the outer retinal layers in the left eye

All of the patients resided in the Solan district of Himachal Pradesh, India. This area is at an altitude of approximately 1,300-1,500 m above sea level and often has snowfall in winters. It is well known that high altitudes above 1,350 m can cause deleterious health effects. The quantity of UV light increases with altitude at a rate of 4% for each 300 m ascent. A combination of high altitude and snow at 2,000 m results in twice the amount of UV light compared to sea level.[4]

UVB (280-340 nm) waves can cause a wide range of pathologies from snow blindness to skin cancer. UVB rays increase with high altitude, and high surface reflectivity (sand, watery snow, glass, metal) can increase the net solar irradiance.[5] Yannuzzi et al.[6] observed a similar series of cases with foveal pseudocyst presenting with an acute central scotoma. They had no history of prolonged sun gazing but had sunbathed and exercised under the sun for long hours. The author extensively analyzed the geophysical factors and attributed the occurrence of solar retinopathy to clear sky, exposure to solar noon, and possibly UVB radiation due to relatively lower ozone layers. Age-related lenticular changes reduce the transmission of radiant energy and protect the retina.[7,8] In this series, all had a clear lens and were emmetropic, putting them at risk of damage by UV radiation.

The impact of altitude on the retina is secondary to a hypoxic environment. They present with engorged retinal vessels, retinal hemorrhages, and disc edema.[9] The patients in this series were habitants of high altitudes. Though changes of altitudinal retinopathy were not seen, its deleterious effects might have added to the insult apart from sunbathing.

The other causes of outer retinal defects in this series were ruled out with good history taking and imaging. None of the patients' OCT images showed PVD (except patient 1, Figure 1b) or gross vitreoretinal anomalies. The second patient exhibited ILM drape sign (Figure 1a) but the fundus had no parafoveal telangiectatic vessel or grey hue reflex suggestive of macular telangiectasia. No history of any intraocular procedure, topical or systemic medication, or previous hospitalization ruled out other causes of outer retinal defects.

To conclude, the present case series documents the occurrence of outer retinal defects as a presenting feature of solar retinopathy in individuals living at high altitudes who reported prolonged sunbathing under the direct sun to combat the cold climate but denied direct sun-gazing. This series adds additional evidence to the existing literature about the harmful effects of prolonged unprotected sun exposure at high altitudes.

Ethics

Acknowledgment: We are grateful to Dr. Pratyusha Ganne (consultant, AIIMS Mangalagiri, India) for reviewing the manuscript for grammatical aspects.

Peer-review: Externally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: R.S., Concept: R.S., R.G., Rav. G., Design: R.S., N.C.K., Data Collection or Processing: R.S., N.C.K., Analysis or Interpretation: R.S., N.C.K., Literature Search:R.S., N.C.K., R.G., Rav.G., Writing: R.S., N.C.K., R.G., Rav.G.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Zambarakji HJ, Schlottmann P, Tanner V, Assi A, Gregor ZJ. Macular microholes: pathogenesis and natural history. Br J Ophthalmol. 2005;89:189-193.
2. Commander J, Gardiner M, Loewenstein J. High-resolution optical coherence tomography findings in solar maculopathy and the differential diagnosis of outer retinal holes. Am J Ophthalmol. 2011;152:413-419.
3. Begaj T, Schaal S. Sunlight and ultraviolet radiation-pertinent retinal implications and current management. Surv Ophthalmol. 2018;63:174-192.
4. Karaküçük S, Mirza GE. Ophthalmological effects of high altitude. Ophthalmic Res. 2000;32:30-40.
5. Taylor HR. The biological effects of UV-B on the eye. Photochem Photobiol. 1989;50:489-492.
6. Yannuzzi LA, Fisher YL, Slakter JS, Krueger A. Solar retinopathy: a photobiologic and geophysical analysis. 1989. Retina. 2012;32(Suppl 1):28-43.
7. Youssef PN, Sheibani N, Albert DM. Retinal light toxicity. Eye (Lond). 2011;25:1-14.
8. Cruickshanks KJ, Klein R, Klein BE. Sunlight and age-related macular degeneration. The Beaver Dam Eye Study. Arch Ophthalmol. 1993;111:514-518.
9. McFadden DM, Houston CS, Sutton JR, Powles AC, Gray GW, Roberts RS. High-altitude retinopathy. JAMA. 1981;245:581-586.