www.oftalmoloji.org

E-ISSN: 2149-8709

TURKISH JOURNAL OF OPHTHALMOLOGY

TURKISH JOURNAL OF OPHTHALMOLOGY TJO

galenos

July August 2021
51 Volume
Issue 4

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: August 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, 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 4 at a Glance:

Esteemed colleagues,

In our fourth issue of 2021, the *Turkish Journal of Ophthalmology* features 6 original studies, a review, 3 letters to the editor with 1 author response, and 2 case reports.

Burcu et al.'s clinical study titled "Donor cornea use in scleral surface reconstruction" emphasizes an important commonality between the sclera and cornea despite their different optic, vascular, and neural architectures. With their type I collagen-rich protein composition, both of these tissues can effectively complete each other anatomically, and this function was exemplified by the successful use of full-thickness and lamellar corneal tissue grafts to repair defects that compromised or threatened scleral integrity in 16 eyes of 16 patients.

Hashemi et al. from Tehran, the capital of Iran, compared 213 Down syndrome patients with 184 control subjects and showed that refractive errors, visual impairment, and amblyopia are more common in Down syndrome. The researchers also performed a vector analysis of astigmatism and determined the frequency of oblique astigmatism in Down syndrome.

Yalçındağ et al. analyzed data obtained in the Behçet Uveitis Screening Trial (BUST) and found that of 4,978 eyes of 3,363 patients in 33 centers, patients with Behçet disease had lower education level and socioeconomic status compared to those with other non-infectious uveitis. However, whether this difference in education and socioeconomic status is a cause or result of Behçet disease is a new subject that requires discussion.

External dacryocystorhinostomy is the gold standard for the treatment of nasolacrimal canal obstruction, and bicanalicular silicone tubes (BST) are frequently utilized in this procedure since their description by Gibbs in 1967. In their study, Özcan et al. investigated the relationship between BST removal time and microbiological analysis results and determined that later BST removal was associated with a higher number of bacterial strains isolated in culture and that *Haemophilus influenzae* was isolated more frequently in patients with recurrence, adding a new dimension to a classical treatment.

Er et al. evaluated 65 eyes of 65 patients who underwent pars plana vitrectomy and silicone endotamponade due to ruptured retinal detachment and reported that macular structural changes may differ according to the duration of silicone in the eye. This finding also represents a new dimension for a classical treatment method.

Özdek et al. evaluated the safety and effectiveness of simultaneous bilateral vitrectomy surgery for active, bilateral stage 4-5 retinopathy of prematurity (ROP) based on the experience of a single surgeon and suggested that simultaneous bilateral vitrectomy surgery can be considered as an option, but the risk of endophthalmitis should be weighed against the risks of disease progression and anesthesia-related complications.

Değirmenci et al. examined the use of immunomodulatory drugs, which are considered a risk factor during the COVID-19 pandemic, in terms of uveitis treatment and reported that uveitis treatment should be continued while maintaining strict follow-up criteria. Given the drastic change in conditions, they emphasized the need for new guidelines in the management of patients receiving immunomodulatory agents for the treatment of uveitis and made drug- and disease-specific recommendations that will serve as a reference.

Biçer et al. state in a case report titled "Systematized epidermal nevus syndrome involving the upper and lower eyelids bilaterally" that in such rare cases, patients should be examined for extraocular anomalies and their skin lesions should be monitored for possible malignant transformation.

Yabanoğlu et al. highlight familial predisposition in spheroidal corneal degeneration, an extremely rare disease with hereditary transmission, in their case report of two siblings.

Erdinest et al. briefly share the preliminary results of their own survey study which is similar to the survey study published in our journal in the article "Effects of the COVID-19 pandemic on Turkish ophthalmologists." They draw attention to the importance of a continually updated information approach as taken in Turkey and the UK while we navigate this uncharted territory in which correct practices have not been established.

In response to the same article, Gurnani and Kaur summarize the innovative ophthalmology practices they exemplified in India in their letter to the editor titled "Innovations in clinical ophthalmology during the COVID-19 pandemic." As many of these innovations are simple and modified clinical applications that our ophthalmologist colleagues in nearly every country can incorporate into their practice, this article will be an important reference as long as the pandemic continues.

TURKISH JOURNAL OF OPHTHALMOLOGY

TJO

www.oftalmoloji.org

EDITORIAL

In another letter to the editor, Gönül and Eker respond to an article by Kayıkçıoğlu et al. titled "Unintentional staining of the anterior vitreous with trypan blue during cataract surgery." They noted that as none of the patients had 20/20 vision postoperatively, they suspect that the inadvertent passage of trypan blue into the vitreous cavity may have caused retinal toxicity. Kayıkçıoğlu et al. considered this suspicion justified, as the patients were not evaluated using electrophysiological tests.

As the pandemic continues, our clinical practices are being reshaped, and this new environment also has an impact on the article titles in our journal. In this issue, 3 of the 13 articles were related to the pandemic. I hope that in subsequent issues, articles focusing primarily on pandemic damage, anxiety, and protection will be replaced by those reporting solutions and successful therapies.

Respectfully on behalf of the Editorial Board,

Sait Eğrilmez, MD

DOI: 10.4274/tjo.galenos.2020.27116
Turk J Ophthalmol 2021;51:192-198

Original Article

Donor Cornea Use in Scleral Surface Reconstruction

Ayşe Burcu, Züleyha Yalnız-Akkaya, Evin Şingar Özdemir, Selma Özbek-Uzman

University of Health Sciences Turkey Ankara Training and Research Hospital, Ankara, Turkey

Abstract

Objectives: To investigate the indications for and results of treating scleral surface problems with donor corneal grafts that are not used in keratoplasty surgery or are left over from keratoplasty.

Materials and Methods: The records of 16 patients in whom corneal tissue was used to repair a scleral tissue defect or cover an exposed glaucoma drainage implant were evaluated retrospectively. Partial-thickness grafts were prepared using a combined microkeratome system with artificial anterior chamber in 10 eyes and by manual dissection in 3 eyes. Full-thickness grafts were used in 3 eyes.

Results: There were 8 female and 8 male patients aged 5-79 years (mean: 39.37±24.68). Indications for the use of corneal tissue on the scleral surface were limbal dermoid excision (n=2), pterygium surgery (n=1), intraocular lens removal and scleral fixation intraocular lens (SFIOL) implantation (n=1), exposed SFIOL suture coverage (n=1), trauma (n=2), scleral tissue loss due to repeated glaucoma surgeries (n=5), and exposed glaucoma drainage implant (n=4). The patients were followed for 6-42 months (mean: 14.37±9.14). None of the patients had graft infection, thinning, immunological graft rejection, or vision loss during follow-up. Tectonic lamellar grafts did not adversely affect final visual acuity in any case. At final examination, a good combination of graft and recipient tissue, a smooth ocular surface, and a cosmetic appearance were achieved in all eyes.

Conclusion: Donor corneas that are not suitable for corneal transplantation or left over from the cornea transplant can be used in patients with scleral tissue loss due to various pathologies and in the treatment of glaucoma drainage implant erosion. In these cases, the use of corneal grafts provides a good ocular surface restoration and cosmetic appearance. The effectiveness and safety of this method should be investigated with large patient series and long follow-up times.

Keywords: Lamellar patch graft, scleral tissue loss, glaucoma drainage surgery

Introduction

Scleral tissue defects may occur due to ocular traumas, infectious or autoimmune scleral diseases, the removal of congenital or acquired tumoral masses in or adjacent to the sclera, and other anterior segment surgeries such as glaucoma, pterygium, and cataract surgery. Scleral tissue defects that develop for various reasons pose a risk for endophthalmitis.[1] Depending on their size, they may be cosmetically unattractive, as well as compromise the tectonic integrity of the globe.[2] Surgical repair of scleral tissue defects is necessary for tectonic and therapeutic purposes. The basic principle of surgical treatment is to restore the scleral defect with autologous or allogeneic grafts and prevent the development of infection. If infection is present, debridement of the infected tissue and additional anti-infective therapy are required.

Partial-thickness autologous sclera, Tenon, and conjunctival supports and numerous allogeneic patch graft materials are used to provide tectonic support to scleral defects.[3,4,5,6] Partial-thickness autologous scleral tissue grafts may cause damage and tectonic weakness at the graft preparation site. In large scleral defects, Tenon's capsule and conjunctiva may not provide

Address for Correspondence: Ayşe Burcu, University of Health Sciences Turkey Ankara Training and Research Hospital, Ankara, Turkey
E-mail: anurozler@yahoo.com.tr **ORCID-ID:** orcid.org/0000-0002-2345-0456
Received: 21.07.2020 **Accepted:** 12.10.2020

Cite this article as: Burcu A, Yalnız-Akkaya Z, Şingar Özdemir E, Özbek-Uzman S. Donor Cornea Use in Scleral Surface Reconstruction. Turk J Ophthalmol 2021;51:192-198

sufficient tectonic support, necessitating the use of allogeneic patch grafts.

Glaucoma drainage implants may erode the overlying tissue and become exposed over time. It occurs in 5-10% of cases.[7,8,9] Autologous conjunctivo-Tenonplasty is often inadequate, and the implant must be covered with allogeneic materials such as sclera, pericardium, dura mater, and donor cornea.

In this study, we present the indications and results of the use of donor corneal grafts that are not used in keratoplasty surgery or are left over from keratoplasty in the treatment of scleral surface problems.

Materials and Methods

The records of patients for whom donor cornea was used to treat scleral surface pathologies between May 2016 and June 2019 were analyzed retrospectively. The study was approved by the Clinical Research Ethics Committee of University of Health Sciences Turkey Ankara Training and Research Hospital (study e. kurul-E-20/307) and a preoperative informed consent form was obtained from each patient. Sixteen eyes of 8 female and 8 male patients were included in the study. The patients' demographic data, ophthalmic history, previous surgical procedures, systemic diseases, slit-lamp examination findings, operative details of corneal graft use, postoperative medications, initial and final visual acuity, complications, need for additional surgical treatment, follow-up time, and clinical outcomes were obtained from hospital records and surgical videos.

The operations were performed under local or general anesthesia by two surgeons (A.B. and Z.Y.A.). Depending on the size of the defect, the donor corneal margin remaining after keratoplasty surgery, the anterior stromal lamellae remaining after descemet stripping endothelial keratoplasty (DMEK), or seronegative donor corneas unsuitable for optical keratoplasty were used. As needed according to the depth of the defect, grafts were prepared at the desired thickness using a combined artificial anterior chamber and microkeratome system (ALTK System, Moria/Microtech Inc. Doylestown, PA, USA) or were prepared manually to partial thickness. The following were ensured during surgery:

- The graft epithelium was debrided in all cases.
- After the necrotic sclera was cleared, the size of the healthy scleral and choroidal bed was measured. Based on the size and depth of the defect, a full-thickness or lamellar graft approximately 0.5-1 mm larger than the area to be covered was prepared from the donor cornea.
- In the limbal region, care was taken to ensure that grafts were thick enough to avoid dellen formation and that the corneoscleral junction approximated a natural appearance.
- The graft was sutured to the scleral bed and limbal margins with 10/0 monofilament nylon sutures.
- In cases of glaucoma drainage implant exposure, care was taken to center the partial-thickness graft over the area of exposure and suture it in a watertight manner.
- In order to prevent postoperative graft melting and to ensure epithelialization, it was covered by freeing conjunctival and Tenon's tissue surrounding the donor corneal grafts or using amniotic membrane in cases where adequate Tenon-conjunctival flap could not be obtained.

Postoperatively, 1% prednisolone acetate was used at 2-hour intervals for the first week and then at a reduced dose for 3-6 months. Moxifloxacin 0.5% was administered 4-6 times a day for 2 weeks. Topical lubricants were used every 2-4 hours. Patients were followed up on day 1, 7, and 15, then once a month for the first 3 months, and every 3-6 months thereafter.

In the absence of loosening or vascularization, the sutures were removed at 9-12 months.

Results

The 8 female and 8 male patients were between 5 and 79 years of age (mean: 39.37±24.68). Indications for the use of corneal tissue on the scleral surface were limbal dermoid excision (n=2) (Figure 1a), scleral melting after pterygium surgery (n=1), intraocular lens (IOL) removal and scleral fixation intraocular lens (SFIOL) implantation (n=1), exposed SFIOL suture coverage (n=1), trauma (n=2), scleral tissue loss due to repeated glaucoma surgeries (n=5) (Figure 2a), and exposed glaucoma drainage implant (n=4) (Figure 3a). The demographic and clinical features of the patients are presented in Table 1.

Donor corneal rim remaining from keratoplasty was used in 5 eyes, stroma left over from DMEK was used in 1 eye, and donor corneas unsuitable for optical keratoplasty were used in 10 eyes. Partial-thickness grafts were prepared by manual dissection for 3 eyes and using an artificial anterior chamber and microkeratome system for 10 eyes.

Corneal grafting on the scleral surface was performed during primary surgery in only one case (patient 1, limbal dermoid); in all others, it was done during follow-up after primary surgery. Twelve patients underwent primary surgery in another center and were referred to our clinic for further treatment. As the time between primary surgery and the need for corneal grafting could not be determined reliably from the patients' history, we did not evaluate this in our study.

Eleven of the 16 eyes had undergone multiple surgical procedures on the scleral surface that could predispose to the need for corneal grafting. In 7 eyes, conjunctivo-Tenonplasty with or without amniotic membrane transplantation (AMT) performed before corneal grafting was unsuccessful.

There were no intraoperative complications in any of the eyes. The patients were followed for 6-42 months (mean: 14.37±9.14). Postoperatively, resuturation was necessary in 2 eyes (patients 1 and 2) due to suture loosening and AMT was needed to preserve the corneal graft until epithelialization was completed in 1 eye with a large scleral defect (patient 3). Graft infection, thinning, or immunological rejection and dellen formation were not observed and regrafting was not required in any of the eyes during follow-up. In all eyes, there was sufficient tissue thickness in the covered area and the graft

Table 1. Demographic and clinical characteristics of the patients

Patient #	Sex	Age (years)	Eye	Etiology	Previous surgeries	Lesion size (mm) HxV	Graft size (mm) HxV	Surgical procedure, Graft, Graft thickness (mm)	Preoperative BCVA (LogMAR)	Postoperative BCVA (LogMAR)	Follow-up (months)
1	M	16	Left	Limbal dermoid		8, disc	9, disc	Dermoid excision + 350 µm Microkeratome	0.30	0.30	42
2	F	5	Left	Limbal dermoid	- Dermoid excision - AMT + conjunctivo-tenonplasty	5.5x8.5	6.5x9.5	350 µm Microkeratome	0.10	0.10	21
3	M	63	Right	Scleral melting after MMC pterygium	- Pterygium surgery with MMC and autograft, - Conjunctivoplasty	3.5 and 4, two separate lesions	4 and 5, two separate grafts	300 µm Microkeratome	1.80	0.30	7
4	M	72	Right	Exposed SFIOL superonasal suture	- Cataract surgery - SFIOL, - Conjunctivo-tenonplasty		3x5	Donor corneal rim Partial-thickness	3.10	1.10	6
5	F	26	Left	Melting at the posterior edge of the scleral incision after SFIOL	- Phacoemulsification + sulcus IOL - IOL extraction, SFIOL - DALK	3x5	4x6	Donor corneal rim Partial-thickness	0.40	0.40	17
6	F	36	Left	Post-traumatic	- Primary suturing after trauma	6 disc	7 disc	300 µm Microkeratome	0.52	0.15	12
7	F	35	Right	Traumatic scleral rupture	- Primary suturation - Resuturation + conjunctivo-tenonplasty	2x8	5x10	200 µm Microkeratome	1.30	1.30	6
8	F	79	Right	Scleral melting after repeated glaucoma surgeries	- Trabeculectomy - GDI implantation, - GDI extraction - AMT + conjunctivo-tenonplasty	4.5x7.5	5.5x8.5	Donor corneal rim Full-thickness	1.10	1.10	24
9	M	5	Left	Scleral melting after repeated glaucoma surgeries	- GDI - GDI extraction + dura patch + conjunctivo-tenonplasty	8 disc	9 disc	350 µm Microkeratome	3.10	3.10	13
10	M	40	Right	Scleral defect after trabeculectomy	- Trabeculectomy	6x4.5	7x5	Donor cornea Full-thickness	1.80	1.80	12
11	M	34	Left	Scleral flap defect after trabeculectomy	- Trauma - SFIOL + pupilloplasty - DMEK (twice) - Trabeculectomy	2x1.5	3x2.5	Stroma left over from DMEK surgery, partial-thickness	1.00	1.00	15
12	F	18	Left	Scleral melting after glaucoma surgeries	- GDI - GDI extraction + conjunctivo-tenonplasty	8	7 disc	300 µm Microkeratome	0.10	0.10	13
13	F	55	Right	Exposed GDI	- GDI	2.5x4.5	4x6	300 µm Microkeratome	0.70	0.70	18
14	F	18	Right	Exposed GDI	- GDI	2.5 x4	5x7.5	Stroma left over from DMEK surgery, partial-thickness	0.52	0.52	9
15	F	78	Left	Exposed GDI	- Trabeculectomy - GDI - Phacoemulsification - DMEK	2.5x4	5x7.5	350 µm Microkeratome	3.10	3.10	8
16	F	50	Right	Exposed GDI	- Lensectomy (pediatric) - PKP - GDI	2.5x3	5x7	350 µm Microkeratome	0.70	0.70	7

MMC: Mitomycin C, IOL: Intraocular lens, SFIOL: Scleral fixation intraocular lens, GDI: Glaucoma drainage implant, AMT: Amniotic membrane transplantation, DALK: Deep anterior lamellar keratoplasty, DMEK: Descemet's membrane endothelial keratoplasty, PKP: Penetrating keratoplasty, HxV: Horizontal x vertical, BCVA: Best corrected visual acuity, LogMAR: Logarithmic value of the minimum resolution angle

showed good integration into the recipient tissue and was epithelialized.

The mean visual acuity was 1.22±0.60 logMAR preoperatively and 0.98±0.95 logMAR postoperatively. Tectonic lamellar grafts did not adversely affect final visual acuity in any case. Level of visual acuity did not change in 13 eyes, while an increase from hand movements to 1.10 logMAR was obtained in 1 eye, from 1.80 to 0.30 logMAR in 1 eye, and from 0.52 to 0.15 logMAR in 1 eye.

Discussion

Allogeneic patch grafts are used in cases of scleral tissue loss and exposed glaucoma drainage implants when autologous tissues provide insufficient coverage. When selecting allogeneic materials, desired features include biocompatibility, being immunologically safe, providing a favorable cosmetic appearance, and being easy to obtain, easy to use, and inexpensive. The most commonly used materials are preserved sclera, pericardium, dura mater, amniotic membrane, and donor cornea.[4,8,10,11,12,13,14,15,16] Many materials are expensive, difficult to obtain, or may not provide a cosmetically acceptable appearance. Amniotic membranes used in recent years reduce scleral melting and accelerate epithelialization but provide weak tectonic support in deep tissue loss.

With preserved sclera, there may be issues regarding sterility and variable quality; it is also thick and not cosmetically preferable. Pericardium tends to melt over extended follow-up. Moreover, pericardium and dura mater are expensive materials.[4] Corneal tissue is more compact than scleral tissue and is more resistant to recurrent melting and ectasia. In addition, the compact lamellae are more resistant to the spread of infection than sclera.[16] Its transparent structure enables monitoring of the glaucoma drainage implant and for possible complications.

Aside from these advantages, the higher curvature radius of the cornea compared to sclera may cause swelling when placed on a large scleral defect.[2] Partial-thickness corneal grafts prepared from donor corneas that are not suitable for corneal transplantation provide a more cosmetically satisfying appearance and prevent dellen formation by creating better wound apposition when used near the limbal margin. The transparency of corneal tissue causes the underlying choroidal tissue to appear dark in large and deep defects. Covering with a conjunctival flap and gradual opacification of the graft may improve this appearance.[2]

Glaucoma drainage implants are frequently used in the surgical treatment of glaucoma. The most important complication of this procedure is erosion of the overlying tissues and subsequent tube exposure. Glaucoma drainage implant exposure can lead to serious vision-threatening complications such as endophthalmitis and hypotony.[1] Therefore, it requires surgical repair or removal. Coverage with simple conjunctival flaps is often inadequate, and once tube erosion occurs, there is greater tendency for recurrent tube erosions.[6] For this reason, when placing glaucoma drainage implants, many surgeons prefer to cover the tube with various materials such as preserved sclera, dura mater, pericardium, and donor cornea. Allograft materials tend to erode the conjunctiva over time. Comparative studies and literature data on which of these materials is superior in terms of tube erosion in the long term are still not fully adequate. Favorable results have been reported regarding the use of donor cornea as a patch graft.[13,16,17,18] Technical variations include the use of glycerol-preserved cornea,[10] gamma-irradiated cornea (VisionGrafts, Tissue Banks International, Baltimore, MD, USA),[19] stromal lenticule obtained in SMILE surgery,[12] and riboflavin-ultraviolet cross-linking to increase resistance to collagenolysis in the long term.[9,20]

In our study, exposed glaucoma drainage implants were successfully covered with donor corneal grafts in 4 eyes. Because we observed from previous experience that simple conjunctivo-Tenonplasties are inadequate and repeated surgical procedures disrupt the anatomy of the surrounding Tenon's capsule and conjunctiva and lead to deterioration of tube function, no other surgical procedures to cover the glaucoma drainage implant was performed in these cases before using donor cornea.

In repeated glaucoma surgeries, scleral erosion has been reported in the early period or years after trabeculectomy in association with surgical trauma or mitomycin C.[11] Ischemia, inflammation, and apoptosis are factors that trigger scleral thinning and necrosis. Scleral defects that occurred after trabeculectomy in 2 eyes and after repeated glaucoma surgeries and/or glaucoma drainage implant removal in 3 eyes were successfully treated with full-thickness or lamellar corneal grafts, depending on defect size and depth (Figure 2b and 3b).

Scleromalacia is an important complication after pterygium surgery, manifesting with scleral thinning, melting, and necrosis. It can occur with all pterygium-related surgical techniques. With the bare sclera technique, it can occur even years after surgery. Although the pathogenesis is not completely clear, the main risk factor is chronic resistance to conjunctival growth over the bare scleral defect.[2] Changes in the distribution and content of the tear film layer predispose to scleral drying, melting, and secondary infections. Additional treatments such as β radiation, thiotepa, and mitomycin C increase the risk.[2] Scleral necrosis is observed in 0.2-4.5% of cases.[9,21,22] In particular, the risk increases with high concentrations and repeated applications of mitomycin C. In our study group, patient 3 underwent pterygium surgery with autograft and mitomycin C followed by cataract surgery 1 year later at another center, after which they developed conjunctival and scleral melting 1 month later. Despite applying conjunctival autografts twice from different parts of the same eye, the areas of scleral melting could not be closed, and the patient was referred to our clinic where he was successfully treated with a partial-thickness donor corneal graft and AMT.

Because limbal dermoids penetrate the cornea, conjunctiva, and scleral tissue, their removal causes tissue defects depending on their size and depth. Excision alone can cause scarring, corneal vascularization, pseudopterygium, and symblepharon.[23,24,25,26,27] Closing the defect with partial-thickness corneal grafts after

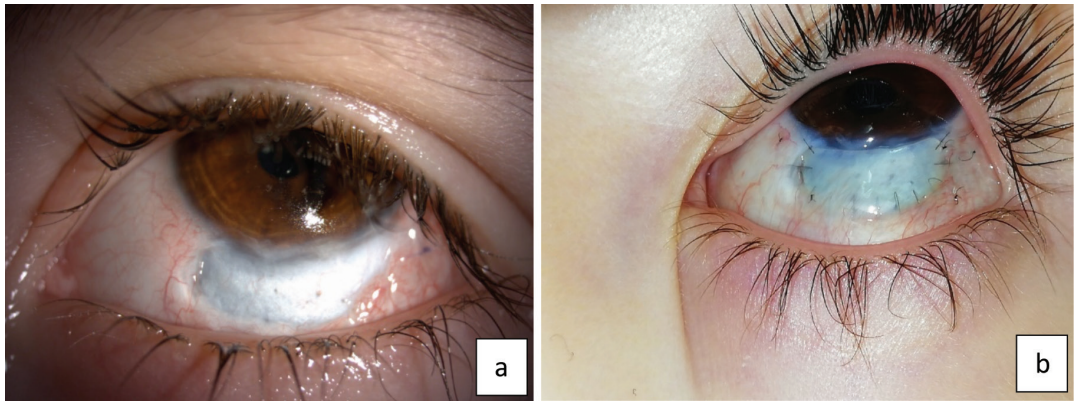

Figure 1. Patient 2, aged 5 years, underwent dermoid excision in another center 15 months earlier and developed scleral melting that could not be treated with conjunctivo-Tenonplasty and amniotic membrane transplantation; a) before corneal patch grafting, b) 6 months after patch grafting

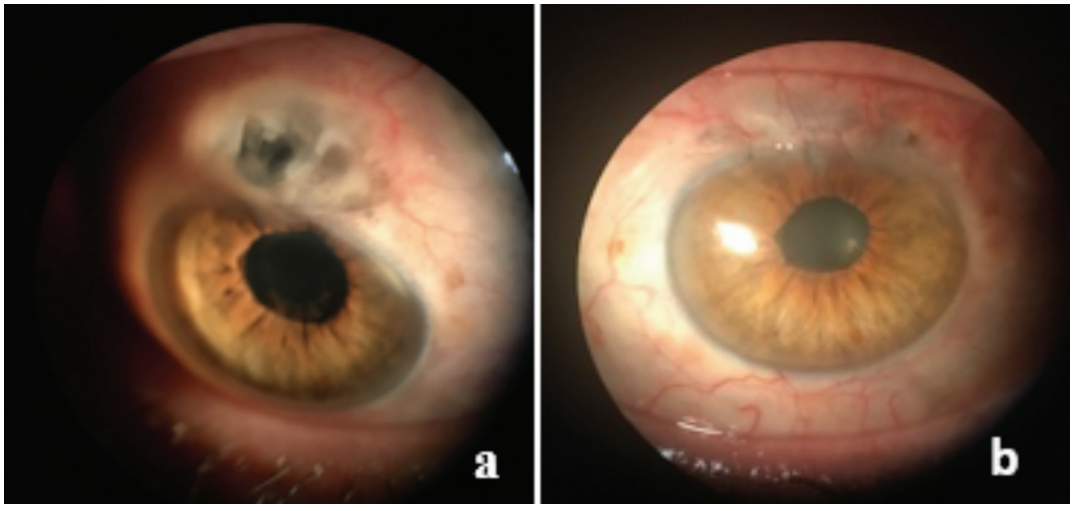

Figure 2. Patient 10, a 40-year-old man, referred from another center due to large scleral defect after glaucoma surgery; a) preoperative, b) postoperative, 3 months after defect closure with 7x5 mm full-thickness donor cornea

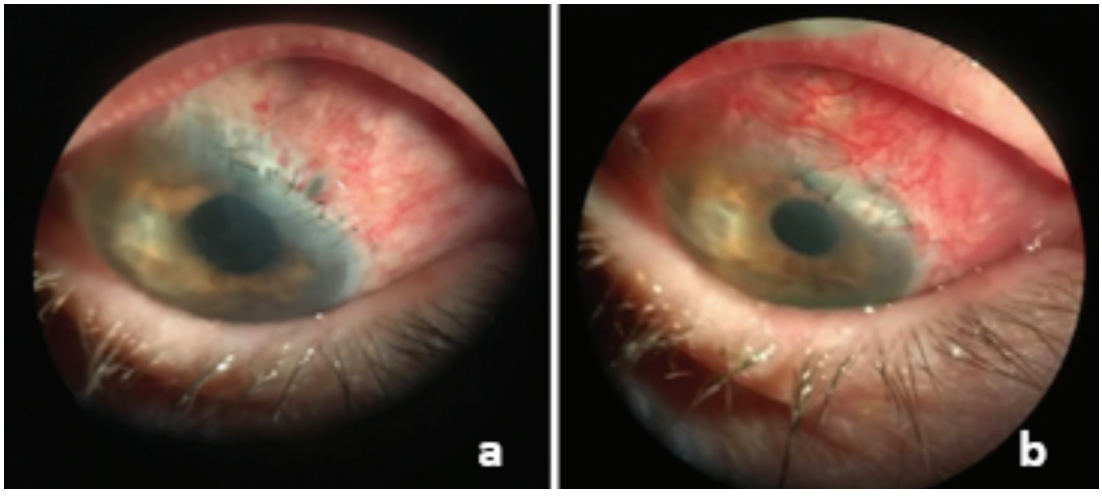

Figure 3. Patient 13, a 55-year-old woman, with exposed Ahmet glaucoma valve implant; a) insufficient conjunctivo-Tenonplasty before patch grafting, b) after grafting with a 300 µm patch graft prepared with Moria microkeratome

resection reduces the development of these complications and creates a more cosmetically pleasing appearance.[26,27] AMT and conjunctivo-Tenonplasty was performed in the same session as dermoid excision in patient 1 and approximately 15 months after dermoid excision performed in another center in an attempt to close the area of scleral melting in patient 2. When adequate results could not be obtained, the patients were referred to our center and underwent donor corneal grafting (Figure 1b).

In SFIOL implantations, inadequate suture coverage and suture exposure due to tissue erosion are the most important complications.[28,29] Microorganisms can enter the eye through the suture tract and cause endophthalmitis. Because fibrosis does not occur between the ciliary body and the haptic, removing the exposed suture is not recommended. If possible, the knot should be surgically repositioned, embedded under the sclera, or covered with scleral or corneal patch grafts.[29] Patient 4 in our study group underwent SFIOL surgery in another center 2 years earlier and the exposed SFIOL suture was closed with a partial-thickness donor corneal graft after failed conjunctivo-Tenonplasty.

In phacoemulsification surgery, corneal and scleral thermal damage can denature the collagen and the tissue opacifies and contracts, preventing adequate wound closure. The wound edges assume a "fish-mouth" appearance that leads to postoperative wound leakage.[30,31] Patient 5, who was also referred from another center, had undergone IOL removal via a corneoscleral incision, anterior vitrectomy, and SFIOL implantation. After deep anterior lamellar keratoplasty due to macular dystrophy 3 months later, a gradually increasing conjunctival bleb was noted during follow-up. Exploration of the conjunctiva at 10 months revealed melting of the posterior edge of the corneoscleral incision, and the incision site was covered with a watertight lamellar corneal graft. As ultrasonic energy was not used in this case, thermal damage was not considered the cause. There were no pathological findings in autoimmune investigations that could cause scleral melting.

To avoid the less favorable cosmetic appearance of full-thickness corneal grafts, prevent dellen formation in lesions near the limbus, and achieve a more natural corneoscleral limbal appearance, we preferred to use partial-thickness lamellar corneal grafts to cover the glaucoma drainage implant in cases close to the limbus. If a donor corneal rim or the remaining corneal stroma from DMEK was used, lamellar grafts were prepared manually to approximately half thickness and no cosmetic problems occurred in any case. Grafts prepared with the Moria ALTK system, which is an expensive system, were made at the desired thickness with a smooth surface cut. In addition, beveled edge of the grafts, similar to LASIK flaps, provided a smooth recipient-donor junction with no elevation, especially when used near the limbus. During the follow-up period, none of the lamellar grafts prepared manually or with the automated system or the full-thickness grafts used in deep tissue loss created a cosmetically unacceptable appearance or dellen formation.

In our cases with scleral tissue loss or glaucoma drainage implant erosion caused by various pathologies, the use of corneal grafts provided good ocular surface restoration and cosmetic appearance with a maximum follow-up period of 42 months. The use of partial- or full-thickness corneal grafts in scleral tissue loss due to various causes resulted in anatomically successful restoration of global integrity as well as good graft-recipient apposition and favorable cosmesis.

Study Limitations

Limitations of the study were that other patch graft materials could not be compared in long-term follow-up due to the small number of patients with scleral defects, many of which developed as complications. The strength of the study is that our evaluation of the use of left-over donor corneal tissues for scleral surface reconstructions associated with different etiologies and the transfer of surgical experience can shed light on other studies.

Conclusion

Donor corneal rims left over from keratoplasty, stromal grafts remaining after using the endothelium for DMEK, seronegative grafts not suitable for optical corneal transplantation, and corneal tissues removed during keratoplasty can be used for the reconstruction of scleral surface pathologies of varying etiology. Long-term graft viability should be investigated in large patient series with long follow-up periods to determine whether the method is effective and safe in terms of graft failure.

Ethics

Ethics Committee Approval: The study was approved by the Clinical Research Ethics Committee of University of Health Sciences Turkey Ankara Training and Research Hospital (study e. kurul-E-20/307).

Informed Consent: Obtained.

Peer-review: Externally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: A.B., Z.Y.A., Concept: A.B., Design: A.B., Data Collection or Processing: A.B., Z.Y.A., E.Ş.Ö., S.Ö.U., Analysis or Interpretation: A.B., Literature Search: A.B., Writing: A.B.

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. Gedde SJ, Scott IU, Tabandeh H, Luu KK, Budenz DL, Greenfield DS, Flaynn Jr HW. Late endophthalmitis associated with glaucoma drainage implants. Ophthalmology. 2001;108:1323-1327.
2. Ti SE, Tan DT. Tectonic Corneal Lamellar Grafting for Severe Scleral Melting After Pterygium Surgery. Ophthalmology. 2003;110:1126-1136.
3. Singh M, Chew PT, Tan D. Corneal patch graft repair of exposed glaucoma drainage implants. Cornea. 2008;27:1171-1173.
4. Smith MF, Doyle JW, Ticrney JW Jr. A comparison of glaucoma drainage implant tube coverage. J Glaucoma. 2002;11:143-147.
5. Lankaranian D, Reis R, Henderer JD, Choe S, Moster MR. Comparison of single thickness and double thickness processed pericardium patch graft in glaucoma drainage device surgery: a single surgeon comparison of outcome. J Glaucoma. 2008;17:48-51.

6. Tamcelik N, Ozkok A, Sarıcı AM, Atalay E, Yetik H, Gungor K. Tenon advancement and duplication technique to prevent postoperative Ahmed valve tube exposure in patients with refractory glaucoma. Jpn J Ophthalmol. 2013;57:359-364.
7. Lind JT, Shute TS, Sheybani A. Patch graft materials for glaucoma tube implants. Curr Opin Ophthalmol. 2017;28:194-198.
8. Zalta AH. Long-term experience of patch graft failure after ahmed glaucoma valve surgery using donor dura and sclera allografts. Ophthalmic Surg Lasers Imaging. 2012;43:408-415.
9. Stone DU, Craven ER, Ahmad SI, AlBeshri A, Owaidhah OA. Glaucoma Patch Graft Surgery Utilizing Corneas Augmented with Collagen Cross-linking. Middle East Afr J Ophthalmol. 2019;26:148-152.
10. Wigton E, C Swanner J, Joiner W, Feldman A, McGwin G Jr, Huisingh C, Curcio CA, Girkin CA. Outcomes of shunt tube coverage with glycerol preserved cornea versus pericardium. J Glaucoma. 2014;23:258-261.
11. Coutinho I, Silva D, Mota M, Lisboa M, Trancoso Vaz F, Prieto I. Reconstruction of delayed scleral flap melting with bovine pericardium after trabeculectomy with mitomycin C. GMS Ophthalmol Cases. 2017;7:15.
12. Song YJ, Kim S, Yoon GJ. Case series: Use of stromal lenticule as patch graft. Am J Ophthalmol Case Rep. 2018;12:79-82.
13. Ahmed SF, Schmutz M, Mosaed S. Case Series: Keratolimbal Allograft as a Patch Graft for Glaucoma Drainage Devices. J Glaucoma. 2017;26:205-209.
14. Wang Y, Li X, Huang W, Liu J, Xu Y, Chen M, Wang Q. Partial thickness cornea tissue from small incision lenticule extraction: A novel patch graft in glaucoma drainage implant surgery. Medicine (Baltimore) 2019;98:e14500.
15. Thakur S, Ichhpujani P, Kumar S. Grafts in Glaucoma Surgery: A Review of the Literature. Asia Pac J Ophthalmol (Phila). 2017;6:469-476.
16. Spierer O, Waisbourd M, Golan Y, Newman H, Rachmiel R. Partial thickness corneal tissue as a patch graft material for prevention of glaucoma drainage device exposure. BMC Ophthalmol. 2016;16:20.
17. Fukuchi T, Matsuda H, Ueda J, Yamada A, Suda K, Abe H. Corneal lamellar grafting to repair late complications of mitomycin C trabeculectomy. Clin Ophthalmol. 2010;4:197-202.
18. Bochmann F, Kaufmann C, Kipfer A, Thiel MA. Corneal patch graft for the repair of late-onset hypotony or filtering bleb leak after trabeculectomy: a new surgical technique. J Glaucoma. 2014;23:76-80.
19. Ekici F, Moster MR, Cvintal V, Hu WD, Waisbourd M. Tube shunt coverage with gamma-irradiated cornea allograft (VisionGraft). Clin Ophthalmol. 2015;9:751-755.
20. Arafat SN, Robert MC, Shukla AN, Dohlman CH, Chodosh J, Ciolino JB. UV cross-linking of donor corneas confers resistance to keratolysis. Cornea. 2014;33:955-959.
21. Tarr KH, Constable IJ. Late complications of pterygium treatment. Br J Ophthalmol.1980;64:496-505.
22. Sullivan LJ, Snibson G, Joseph C, Taylor HR. Scedosporium prolificans sclerokeratitis. Aust N Z J Ophthalmol. 1994;22:207-209.
23. Panton RW, Sugar J. Excision of limbal dermoids. Ophthalmic Surg. 1991;22:85-89.
24. Panda A, Ghose S, Khokhar S, Das H. Surgical outcomes of Epibulbar dermoids. J Pediatr Ophthalmol Strabismus. 2002;39:20-25.
25. Yao Y, Zhang MZ, Jhanji V. Surgical management of limbal dermoids: 10-year review. Acta Ophthalmol. 2017;95:517-518.
26. Spierer O, Gologorsky D, Adler E, Forster RK. Lamellar keratoplasty with corneoscleral graft for limbal dermoids. Int J Ophthalmol. 2018;11:512-515.
27. Zhou AX, Ambati BK. Sutureless Lamellar Corneoscleral Patch Graft With Fibrin Sealant for Limbal Dermoid Removal. J Pediatr Ophthalmol Strabismus. 2016;53:22-25.
28. Davies EC, Pineda R 2nd. Complications of Scleral-Fixated Intraocular Lenses. Semin Ophthalmol. 2018;33:23-28.
29. Bucci FA Jr, Holland EJ, Lindstrom RL. Corneal Autografts for External Knots in Transsclerally Sutured Posterior Chamber Lenses. Am J Ophthalmol. 1991;112:353-354.
30. Ernest P, Rhem M, McDermott M, Lavery K, Sensoli A. Phacoemulsification conditions resulting in thermal wound injury. J Cataract Refract Surg. 2001;27:1829-1839.
31. Sippel KC, Pineda R Jr. Phacoemulsification and thermal wound injury. Semin Ophthalmol. 2002;17:102-109.

DOI: 10.4274/tjo.galenos.2020.52959
Turk J Ophthalmol 2021;51:199-205

Original Article

Refractive and Vision Status in Down Syndrome: A Comparative Study

Hassan Hashemi*, Shiva Mehravaran**, Soheila Asgari***, Farzaneh Dehghanian Nasrabadi****

*Noor Eye Hospital, Noor Ophthalmology Research Center, Tehran, Iran
**Iran University of Medical Sciences, School of Rehabilitation, Department of Optometry, Tehran, Iran
***Morgan State University, Ascend Center for Biomedical Research, Baltimore, MD, USA
****Noor Eye Hospital, Noor Research Center for Ophthalmic Epidemiology, Tehran, Iran

Abstract

Objectives: To determine the prevalence of refractive errors and visual impairment in Down syndrome (DS) patients compared to normal controls.

Materials and Methods: Cycloplegic refraction was tested in 213 DS patients and 184 normal age- and gender-matched controls using autorefraction followed by retinoscopy. Data from the worse eye of each case were used in the analyses.

Results: In the DS and control groups, respectively, mean age was 17.2±4.8 and 17.2±4.4 years (p=0.993) and 53.0% and 49.5% were male (p=0.473). In the DS and control groups, respectively, mean spherical equivalent (SE) was -5.13±4.47 and -4.15±3.04 diopters (D) in myopics (p=0.050) and 2.47±1.64 and 2.36±2.04 D in hyperopics (p=0.482), mean cylinder error was -2.17±1.39 and -2.05±1.57 D (p=0.451), mean J0 was -0.03±0.89 and 0.12±0.76 D (p=0.086), and mean J45 was 0.11±1.02 and -0.13±1.03 D (p=0.024). The prevalence of oblique astigmatism was higher in the DS group (20.4% vs. 6.1%) while against-the-rule astigmatism was more prevalent in the control group (84.0% vs. 71.6%) (p<0.001). The prevalence of anisometropia was not significantly different between the groups (19.4% vs. 13.8%). Visual impairment was detected in 11.7% of the DS and 0.5% of the control group (p<0.001). The prevalence of amblyopia was 36.3% and 3.8% in the DS and control groups, respectively (p<0.001). Based on the multiple model, only absolute SE inversely correlated with age and differed between males and females (all p<0.05).

Conclusion: In DS patients, the prevalence rates of refractive errors, amblyopia, and visual impairment are higher than those in non-DS individuals, and emmetropization appears to be either defective or slow. Cylinder error is stable in this age range, but the rotation of astigmatism axis is different from normal samples.

Keywords: Refractive errors, visual impairment, amblyopia, emmetropization, Down syndrome, comparative study

Introduction

Refractive errors are one of the main items and the fifth priority of the 2020 Vision: Right to Sight Initiative.[1] In 2012, a systematic review of surveys in 39 countries showed that uncorrected refractive errors were the leading cause of visual impairment (43%).[2] A systematic review in 2018 reported the pooled prevalence of myopia, hyperopia, and astigmatism in children worldwide to be 11.7%, 4.6%, and 14.9% respectively, which are considerably high prevalence rates.[3] Studies have shown a significant correlation between refractive errors, socioeconomic status, and lifestyle.[4] In patients with Down syndrome (DS), quality of life is reduced due to medical conditions,[5] and declines further as they age.[6] Therefore, the identification and correction of refractive errors in this population deserves even higher priority than in normal populations.

Address for Correspondence: Hassan Hashemi, Noor Eye Hospital, Noor Ophthalmology Research Center, Tehran, Iran
E-mail: research@norc.ac.ir **ORCID-ID:** orcid.org/0000-0002-2109-0856
Received: 12.03.2020 **Accepted:** 06.09.2020

Cite this article as: Hashemi H, Mehravaran S, Asgari S, Nasrabadi FD. Refractive and Vision Status in Down Syndrome: A Comparative Study. Turk J Ophthalmol 2021;51:199-205

To date, several studies have been done on the prevalence and degree of refractive errors in patients with DS.[7,8,9,10,11] These studies were mostly carried out in age groups 10 years of age and younger, and one study reported non-cycloplegic refraction in a group with a mean age of 15 years (range, 4 to 60 years).[8,9,10,11]

The goal of this study was to determine the prevalence and distribution of refractive errors, type of astigmatism, visual impairment, and amblyopia in order to provide a comprehensive report on the refractive status in this particular population. We used cyclopentolate, as evidence showed that it is the gold standard for epidemiological studies of refraction and increases the reliability of findings.[12] The distribution of refraction in DS patients was compared to a group of age- and gender-matched normal controls.

Materials and Methods

Study Subjects

The sampling details have been described elsewhere.[13] This report is part of a larger comparative study in which 10- to 30-year-old DS patients recruited from the nation's special needs schools, the DS Society, and relevant non-governmental organizations were consecutively screened for eligibility and enrolled in the study (Table 1). Inclusion criteria were a diagnosis of DS and minimum age of 10 years. Exclusion criteria were any concomitant mental illnesses such as autism or Klinefelter syndrome. Of the 250 respondents, 16 were not eligible due to mental disabilities, Klinefelter syndrome, or autism. The remaining 234 underwent clinical and paraclinical examinations at Noor Eye Hospital. For a comparison group, 200 non-DS participants were consecutively selected from candidates for refractive surgery presenting for their first work-up session (87 cases) and individuals presenting for a vision check-up (113 cases) in Noor Eye Hospital. This group had no personal or family history of DS or other intellectual disabilities.

Ethical Consideration

Prior to enrollment, the goals and methods of the study were explained and written consent was obtained. For all cases in the DS group and those under 18 years of age in the control group, informed consent was obtained from their parents/guardians, and participants were asked for verbal assent before any procedure. This project was approved by the Ethics Committee of Tehran University of Medical Sciences (ID: 1397-091) and adhered to the Declaration of Helsinki at all stages.

Examinations

Visual acuity was evaluated with Snellen chart (SC-2000; Nidek Co., Tokyo, Japan) without correction (uncorrected distance visual acuity; UDVA) and with correction (corrected distance visual acuity [CDVA]). Manifest refraction was first evaluated using autorefraction (ARK-510A, NIDEK, Gamagory, Japan), followed by retinoscopy (ParaStop HEINE BETA 200; HEINE Optotechnik, Herrsching, Germany). Cycloplegic refraction was done in participants who, as determined by the physician, had no contraindication for cycloplegia and whose parents consented to the procedure. This was done 20 minutes after instilling 2 drops of cyclopentolate 10 mg/ml eye drops (Novartis, Barcelona, Spain) 10 minutes apart.

Definitions

Spherical equivalent (SE) was calculated as the spherical error plus half of the cylinder error. Myopia and hyperopia were defined as an SE ≤-0.5 diopter (D) and ≥0.5 D in the worse eye, respectively, and the prevalence of these conditions was determined. Myopia was categorized into 4 groups: mild (-0.51 to -3.0 D), moderate (-3.01 to -6.0 D), high (-6.01 to -9.0 D), and extreme (<-9.0 D), and hyperopia was categorized into 3 groups: mild (0.51 to 2.0 D), moderate (2.01 to 4.0 D), and high (>4.0 D). The worse eye was the one with higher absolute SE value, and if refractive error data were available for only one eye, it was considered the worse eye.

The definition and prevalence of astigmatism was based on a cylinder error <-0.5 D in the worse eye (higher absolute astigmatism). Astigmatism types were with-the-rule (WTR, steep axis 90°±30°), against-the-rule (ATR, steep axis 180°±30°), and oblique (other axes). If cylinder error data were available for only one eye, it was considered the worse eye. Pure astigmatism was defined as a spherical error of -0.5 to 0.5 D and a cylinder error higher than 0.5 D.

Thibos astigmatism vector analysis[14] was used to decompose cylinder error to J0 and J45. As such, $J0 = -C/2\cos 2\alpha$ and $J45 = -C/2\sin 2\alpha$, where C is the cylinder value and α is the cylinder axis. A positive value for J0 indicates WTR astigmatism and a negative value indicates ATR. J45 represents oblique astigmatism at 45° and 135°, and a positive value indicates + cylinder axis >90°.

Anisometropia was reported in terms of an interocular SE difference more than 1.0 D and visual impairment was based on a CDVA <20/60 in the worse eye. Amblyopia was defined as 2

Table 1. Summary of sources from which Down syndrome patients were recruited

Source	Geographic distribution	Number of cases enrolled in this study	Number of 10-30 Down cases covered
Special needs schools	All provinces throughout the nation	146 from 12 provinces	1650
Down Syndrome Society	Tehran province	36	640
National Angels Foundation - Wall 47	Tehran, Rasht, Zanjan, Sanandaj, Semnan, Kerman, Shiraz, Qom, Qazvin	22	500
Social media (5)	Mostly Tehran province	30	-

lines or greater interocular difference in CDVA in the absence of correctable pathology.[15]

Statistical Analysis

Prevalence was calculated as the ratio of cases with a given condition in at least one eye to the total number of people who were examined for the condition. Data of the worse eye were used in the analysis. Four age groups of 10-15, 16-20, 21-25, and 26-30 years of age were defined, and prevalence rates were determined for all age and gender subgroups. Multiple linear regression was used to examine the correlation of absolute refractive error with age (continuous variable), gender (female: 0 and male: 1), and group (normal: 0 and DS: 1). In addition, multinomial regression model (baseline: emmetropia) was used to test the correlation of the prevalence of refractive errors with age, gender, and group. The prevalence of anisometropia, visual impairment, and amblyopia was compared between the two groups using the chi-square test.

Results

After applying the inclusion criteria for this report (having cycloplegic refraction results, no ectasia, and no history of corneal surgery), of the 234 patients with DS and 200 normal controls enrolled into the study, data from 213 DS cases and 184 controls were used in the analyses.

In the DS and control groups, respectively, the mean age was 17.2±4.8 and 17.2±4.4 years (p=0.993), and 53.0% and 49.5% were male (p=0.473). In the DS and control groups, mean UDVA was 0.36±0.34 and 0.86±0.62 logMAR (p<0.001) and mean CDVA was 0.20±0.11 and 0.02±0.06 logMAR (p<0.001), respectively.

Distribution of Refractive Errors

Table 2 summarizes refractive indices in the two studied groups and in refractive error, age, and gender subgroups. Based on multiple analysis, absolute SE was significantly correlated with age (β=0.11, p=0.002), gender (β=0.853, p=0.007), and group (β=-0.81, p=0.010). Mean cylinder error, J0, and pure astigmatism were not correlated with these parameters (all p>0.05). J45 was higher in the DS group (β=0.24, p=0.022).

Prevalence of Refractive Errors, Visual Impairment, and Amblyopia

Table 3 presents the prevalence of emmetropia, myopia, hyperopia, and pure astigmatism in the DS and control groups and their age and gender subgroups. Figure 1 shows the subtypes of refractive errors in each group. Anisometropia >1.0 D was detected in 19.4% of the DS and 13.8% of the control group (p=0.136). Visual impairment was observed in 11.7% of the DS and 0.5% of the control group (p<0.001). The prevalence of amblyopia was 36.3% and 3.8% in the DS and control groups (p<0.001), respectively.

Based on multinomial analysis, the prevalence of myopia increased with age (odds ratio [OR]=1.11, p=0.004) and was higher in the control group (OR=7.95, p<0.001). The prevalence of hyperopia was age-independent and higher in the DS group (OR=2.36, p=0.049). The prevalence of pure astigmatism was age-independent and higher in the DS group (β=2.83, p<0.001). The prevalence of refractive errors and pure astigmatism did not correlate with gender.

The prevalence of oblique astigmatism was higher in DS patients (20.4% vs. 6.1%), while WTR (84.0% vs. 71.6%) and ATR (9.9% vs. 8.1%) astigmatism was more common in the control group (p<0.001). The multinomial regression model showed that the prevalence of WTR astigmatism decreased with age (OR=0.893, p=0.003) and was not significantly different between the two groups (p=0.940). Oblique astigmatism was age-independent and the prevalence was higher in the DS group (OR=4.24, p=0.003) (Figure 2). The prevalence rates of the three types of astigmatism orientation were not significantly different between genders (all p>0.05).

Age and gender were not significantly correlated with anisometropia (p=0.764 and p=0.136), visual impairment (p=0.133 and p=0.220), or amblyopia (p=0.482 and p=0.118, respectively).

Discussion

In this large comparative study, we showed the distribution and prevalence of myopia, hyperopia, astigmatism, amblyopia, and visual impairment in a sample of DS patients aged 10-30 years (when the incidence of refractive errors is highest) and compared the results to a group of age- and gender-matched controls. The strength of this study was selecting DS patients from different sources and creating a sample with diverse cases. Although several studies have been done on refractive errors in DS patients, they have often been studied in the 10-year-old age group[7,9,10,11] or a broad age range (3 months to 60 years) without cycloplegia.[8] As emmetropization has been suggested to be incomplete in DS patients even up to 17 years of age[16] and the prevalence of myopia tends to increase in non-DS individuals after the age of 9 years[17] and continue up to 30

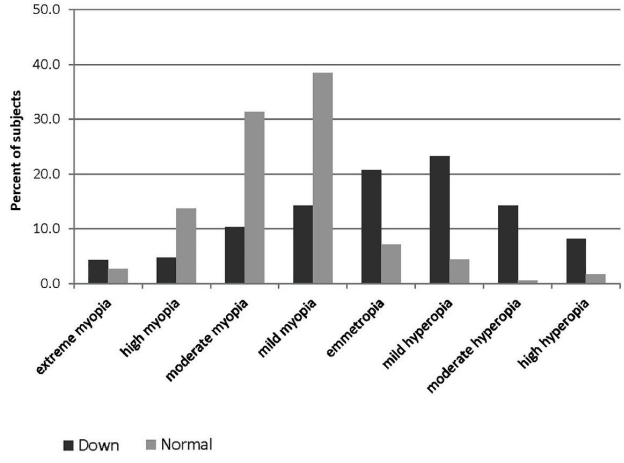

Figure 1. The subtypes of refractive errors in patients with Down syndrome patients and normal control group

Table 2. Distribution of refractive components by age and gender in 10- to 30-year-old Down syndrome patients and normal control group

			n	Spherical equivalent (D)	Sphere (D)	Cylinder (D)	J0 (D)	J45 (D)
Total		Down	213	-0.59±4.38	0.49±4.20	-2.17±1.39	-0.03±0.89	0.11±1.02
		Normal	184	-3.42±3.43	-2.37±3.47	-2.05±1.57	0.12±0.76	-0.13±1.03
Refractive error	Myopia	Down	72	-5.13±4.47	-3.87±4.41	-2.61±1.45	-0.22±1.06	-0.08±1.07
		Normal	159	-4.15±3.04	-3.15±3.05	-2.00±1.52	0.12±0.77	-0.14±0.98
	Hyperopia	Down	97	2.47±1.64	3.43±1.74	-1.96±1.03	-0.02±0.72	0.24±0.89
		Normal	12	2.36±2.04	3.44±2.10	-2.15±1.61	0.00±0.87	0.27±1.03
	Pure astigmatism	Down	43	-0.02±0.24	-2.13±1.26	-2.18±1.26 D	-0.26±0.85	-0.06±0.88
		Normal	15	0.05±0.38	-2.62±1.68	-2.62±1.68 D	0.07±0.89	-0.22±1.30
Age group (years)	10-15	Down	101	0.03±3.70	1.03±3.60	-2.01±1.15	0.02±0.85	0.13±0.89
		Normal	70	-2.57±3.81	-1.30±3.76	-2.43±1.65	0.24±0.87	-0.04±1.17
	16-20	Down	68	-0.87±4.00	0.28±3.78	-2.30±1.45	0.01±0.96	-0.06±0.96
		Normal	75	-4.27±2.90	-3.34±2.95	-1.86±1.46	0.05±0.67	-0.08±0.98
	21-25	Down	33	-1.61±5.69	-0.52±5.68	-2.17±1.09	-0.29±0.87	0.12±0.87
		Normal	35	-3.21±3.55	-2.37±3.60	-1.69±1.55	0.003±0.69	-0.35±0.85
	26-30	Down	11	-0.76±5.98	0.48±5.15	-2.50±2.61	0.09±0.80	0.64±1.58
		Normal	4	-3.84±1.74	-2.94±1.05	-1.81±1.54	0.11±0.69	-0.15±1.07
Gender	Female	Down	101	-1.08±5.07	-0.02±4.98	-2.13±1.29	-0.04±0.96	0.21±0.87
		Normal	93	-3.86±3.63	-1.79±3.09	-2.26±1.58	0.07±0.81	-0.17±1.10
	Male	Down	112	-0.15±3.62	0.95±3.30	-2.20±1.48	-0.02±0.82	0.02±1.13
		Normal	91	-2.96±3.17	-2.94±3.73	-1.84±1.54	0.16±0.70	-0.09±0.97

n: Number of individuals, D: Diopters

Table 3. Frequency (%) of refractive components by age and gender in 10- to 30-year-old Down syndrome patients and normal control group

			n	Emmetropia n, (%)	Myopia n, (%)	Hyperopia n, (%)	Pure astigmatism n, (%)
Total		Down	213	44 (20.7)	72 (33.6)	97 (45.6)	43 (20.3)
		Control	184	13 (7.1)	159 (86.3)	12 (6.6)	15 (8.2)
Age group	10-15	Down	101	23 (22.5)	27 (26.5)	52 (51.0)	23 (22.5)
		Control	70	9 (13.2)	52 (76.5)	7 (10.3)	12 (17.1)
	16-20	Down	68	16 (21.6)	26 (35.2)	32 (43.2)	14 (18.9)
		Control	75	3 (4.0)	69 (92.0)	3 (4.0)	2 (2.7)
	21-25	Down	33	8 (20.5)	17 (43.6)	14 (35.9)	8 (20.5)
		Control	35	1 (2.9)	32 (91.4)	2 (5.7)	1 (2.9)
	26-30	Down	11	1 (5.8)	8 (47.1)	8 (47.1)	2 (11.8)
		Control	4	0 (0.0)	4 (100.0)	0 (0.0)	0 (0.0)
Gender	Female	Down	101	18 (16.4)	43 (39.1)	49 (44.5)	17 (15.5)
		Control	93	8 (8.6)	80 (86.0)	5 (5.4)	6 (6.5)
	Male	Down	112	30 (24.6)	35 (28.7)	57 (46.7)	30 (24.6)
		Control	91	5 (5.6)	77 (86.5)	7 (7.9)	9 (9.9)

n: Number of individuals; Prevalence of refractive errors and pure astigmatism were statistically different between Down syndrome and control groups (all $p<0.001$)

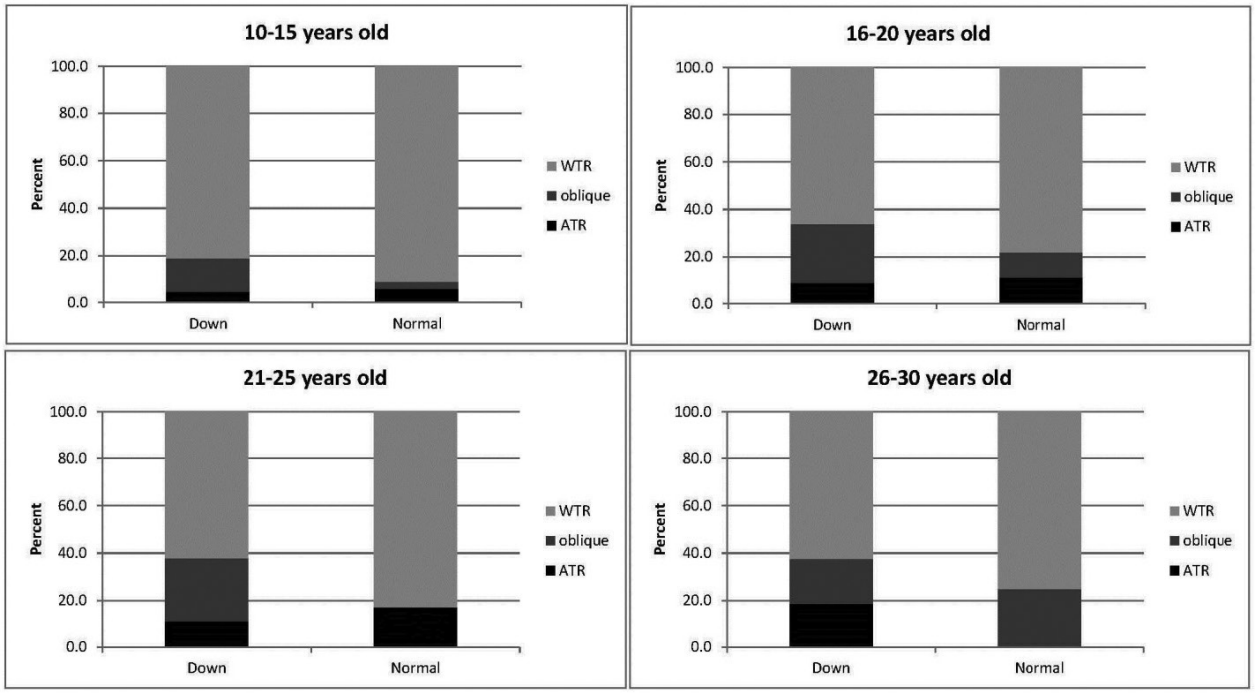

Figure 2. The types of astigmatism in patients with Down syndrome patients and normal control group based on age groups
WTR: With-the-rule astigmatism, ATR: Against-the-rule astigmatism

years of age[18], in this study we considered the age range of 10 to 30 years.

Distribution of Refractive Errors

Non-cycloplegic SE values were reported as 1.43±2.86 D in the age group of 15-22 years (mean 17 years) in a study by Doyle et al.[16] and as -1.86±5.28 D in a sample aged 3 months to 60 years (mean 15 years) in a study by Alio et al.[8] In our DS group, with a mean age of 17 years, cycloplegic SE (-0.59±4.38 D) was lower than that in the mentioned studies. However, the cylinder error in our sample was 0.5 to 1.0 D higher than in these two studies. In other words, the lower SE in the present study was due to the lower spherical error. The effect of cyclopentolate on refractive measurements should be considered, especially in the ≤20 age group. The use of cyclopentolate in our study can explain the more positive SE[19] than in the study by Alio et al.[8] In the study by Doyle et al.[16], SE was positive (hyperopia) in 80% of cases, which differs considerably from the results of the present study (46% hyperopia). Given that the difference between cycloplegic and non-cycloplegic refraction is significant in hyperopics up to 30 years of age[12], the difference between the two studies is expected, albeit ethnicity and age may be influential factors as well.[20]

Prevalence of Refractive Errors and Visual Impairment

The prevalence rates of myopia, hyperopia, emmetropia (defined as SE >-0.5 and <0.5 D), and pure astigmatism in our DS group were 33.6%, 45.7%, 20.7%, and 20.3%, respectively. Of the myopic cases, 12.8% were extreme, and among hyperopic cases, 17.9% were high hyperopic. In some studies, cycloplegic evaluation of DS patients under 1 year to 18 years of age[9,10,11] showed higher rates of hyperopia (SE ≥0.75 D) than myopia (SE ≤-0.75 D) in these populations (59.0% vs. 9.0%[9], 28.0% vs. 25.0%[10], and 36.9% vs. 24.6%[11]). In a study by Adio and Wajuihian[7], myopia (SE ≤-0.5 D) was predominant compared to hyperopia in patients up to 28 years of age (38.1% vs. 9.5%). Another study in the 15- to 22-year age range reported a hyperopia prevalence of 80% in DS patients.[16] In the present study (10-30 years), the prevalence of hyperopia was approximately 46% (i.e., 1.4 times of the rate of myopia), and 17.9% had hyperopia greater than 4.0 D. Except for the Adio and Wajuihian[7] study, other studies with different age groups have shown hyperopia to be the most common refractive error in DS individuals. The difference in the frequency of refractive errors in these studies is due to differences in sample age, threshold for the definition of SE, and inducing cycloplegia.

Comparing the prevalence of refractive errors in the DS group of this study (33.6% for myopia and 45.6% for hyperopia) with the rates in the age- and gender-matched control group (86.3% for myopia and 6.6% for hyperopia) suggested that emmetropization in DS patients is defective or slow. Unlike normal populations, where the prevalence of hyperopia is higher in men and the prevalence of myopia is higher in women,[21,22] there was no significant inter-gender difference in our DS group in terms of the prevalence of refractive errors. Similarly, there

was no inter-gender difference in terms of astigmatism type as in healthy samples.[23] The ratio of oblique/ATR astigmatism in DS patients in comparison with the control group (2.06 vs. 0.75) points to a defective emmetropization process in DS patients.

In the current study, the prevalence of visual impairment was 11.7% in DS patients, while other studies reported rates of 46% (in a 50- to 59-year-old sample) up to 85% (in those ≥60 years of age), which might indicate a higher prevalence with age.[24,25,26] The prevalence of amblyopia in our sample was 36.3%. Others have reported rates of 8.5% for a sample age between 1 and 31 years and 13% in those between 6 months and 14 years of age.[27,28] Ugurlu ve Altinkurt[29] reported a prevalence of 36.4% for amblyopia in DS patients with a mean age of 13 years in Turkey, which is very close to our study. These variations are perhaps due to ethnic differences, sample age, or the prevalence and severity of refractive errors.

Conclusion

Overall, in our sample of 10- to 30-year-old DS patients, the prevalence of refractive errors, astigmatism, visual impairment, and amblyopia was higher than that of their age- and gender-matched controls, and emmetropization appeared to be either defective or slow. The prevalence of refractive and visual complications was similar between males and females. Cylinder error appears to be stable in this age range in DS patients, but the rotation of its axis was different from the controls. These findings are useful for refractive errors correction services for DS patients.

Ethics

Ethics Committee Approval: This project was approved by the Ethics Committee of Tehran University of Medical Sciences (ID: 1397-091) and adhered to the Declaration of Helsinki at all stages.

Informed Consent: Obtained.

Peer-review: Externally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: H.H., Concept: S.A., Design: S.A., Data Collection or Processing: H.H., S.M., Analysis or Interpretation: S.A., S.M., Literature Search: S.A., F.D.N., Writing: S.A., S.M., H.H., F.D.N.

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. World Health Organization (WHO). Blindness and vision impairment prevention. Priority eye diseases; http://www.who.int/blindness/causes/priority/en; 2018 [accessed December 17, 2018].
2. Pascolini D, Mariotti SP. Global estimates of visual impairment: 2010. Br J Ophthalmol. 2012;96:614-618.
3. Hashemi H, Fotouhi A, Yekta A, Pakzad R, Ostadimoghaddam H, Khabazkhoob M. Global and regional estimates of prevalence of refractive errors: Systematic review and meta-analysis. J Curr Ophthalmol. 2018;30:3-22.
4. Foster PJ, Jiang Y. Epidemiology of myopia. Eye (Lond). 2014; 28: 202-208.
5. Haddad F, Bourke J, Wong K, Leonard H. An investigation of the determinants of quality of life in adolescents and young adults with Down syndrome. PloS One. 2018;13:e0197394.
6. Shields N, Leonard H, Munteanu S, Bourke J, Lim P, Taylor NF, Downs J. Parent-reported health-related quality of life of children with Down syndrome: a descriptive study. Dev Med Child Neurol. 2018;60:402-408.
7. Adio AO, Wajuihian SO. Ophthalmic manifestations of children with Down syndrome in Port Harcourt, Nigeria. Clin Ophthalmol. 2012;6:1859-1864.
8. Alio JL, Vega-Estrada A, Sanz P, Osman AA, Kamal AM, Mamoon A, Soliman H. Corneal Morphologic Characteristics in Patients With Down Syndrome. JAMA Ophthalmol. 2018;136:971-978.
9. Fimiani F, Iovine A, Carelli R, Pansini M, Sebastio G, Magli A. Incidence of ocular pathologies in Italian children with Down syndrome. Eur J Ophthalmol. 2007;17:817-822.
10. Kim JH, Hwang JM, Kim HJ, Yu YS. Characteristic ocular findings in Asian children with Down syndrome. Eye (Lond). 2002;16:710-714.
11. Stirn Kranjc B. Ocular abnormalities and systemic disease in Down syndrome. Strabismus. 2012;20:74-77.
12. Morgan IG, Iribarren R, Fotouhi A, Grzybowski A. Cycloplegic refraction is the gold standard for epidemiological studies. Acta Ophthalmol. 2015;93:581-585.
13. Makateb A, Hashemi H, Farahi A, Mehravaran S, Khabazkhoob M, Asgari S. Ocular alignment, media, and eyelid disorders in Down syndrome. Strabismus. 2020;28:42-48.
14. Thibos LN, Wheeler W, Horner D. Power vectors: an application of Fourier analysis to the description and statistical analysis of refractive error. Optom Vis Sci. 1997;74:367-375.
15. Ohlsson J. Defining amblyopia: the need for a joint classification. Strabismus. 2005;13:15-20.
16. Doyle SJ, Bullock J, Gray C, Spencer A, Cunningham C. Emmetropisation, axial length, and corneal topography in teenagers with Down's syndrome. Br J Ophthalmol. 1998;82:793-796.
17. Matsumura H, Hirai H. Prevalence of myopia and refractive changes in students from 3 to 17 years of age. Surv Ophthalmol. 1999;44(Suppl 1):109-115.
18. Hashemi H, Nabovati P, Yekta A, Shokrollahzadeh F, Khabazkhoob M. The prevalence of refractive errors among adult rural populations in Iran. Clin Exp Optom. 2018;101:84-89.
19. Sankaridurg P, He X, Naduvilath T, Lv M, Ho A, Smith E 3rd, Erickson P, Zhu J, Zou H, Xu X. Comparison of noncycloplegic and cycloplegic autorefraction in categorizing refractive error data in children. Acta Ophthalmol. 2017;95:633-640.
20. Wen G, Tarczy-Hornoch K, McKean-Cowdin R, Cotter SA, Borchert M, Lin J, Kim J, Varma R; Multi-Ethnic Pediatric Eye Disease Study Group. Prevalence of myopia, hyperopia, and astigmatism in non-Hispanic white and Asian children: multi-ethnic pediatric eye disease study. Ophthalmology. 2013;120:2109-2116.
21. Czepita D, Mojsa A, Ustianowska M, Czepita M, Lachowicz E. Role of gender in the occurrence of refractive errors. Ann Acad Med Stetin. 2007;53:5-7.
22. Hashemi H, Fotouhi A, Mohammad K. The age- and gender-specific prevalences of refractive errors in Tehran: the Tehran Eye Study. Ophthalmic Epidemiol. 2004;11:213-225.
23. Fotouhi A, Hashemi H, Yekta AA, Mohammad K, Khoob MK. Characteristics of astigmatism in a population of schoolchildren, Dezful, Iran. Optom Vis Sci. 2011;88:1054-1059.
24. Evenhuis HM, Theunissen M, Denkers I, Verschuure H, Kemme H. Prevalence of visual and hearing impairment in a Dutch institutionalized population with intellectual disability. J Intellect Disabil Res. 2001;45:457-464.
25. van Splunder J, Stilma JS, Bernsen RM, Evenhuis HM. Prevalence of ocular diagnoses found on screening 1539 adults with intellectual disabilities. Ophthalmology. 2004;111:1457-1463.
26. Van Buggenhout GJ, Trommelen JC, Schoenmaker A, De Bal C, Verbeek JJ, Smeets DF, Ropers HH, Devriendt K, Hamel BC, Fryns JP. Down syndrome

in a population of elderly mentally retarded patients: genetic-diagnostic survey and implications for medical care. Am J Med Genet. 1999;85:376-384.
27. Hiles DA, Hoyme SH, McFarlane F. Down's syndrome and strabismus. Am Orthop J. 1974;24:63-68.
28. Jaeger EA. Ocular findings in Down's syndrome. Trans Am Ophthalmol Soc. 1980;158:808-845.
29. Ugurlu A, Altinkurt E. Ophthalmologic Manifestations and Retinal Findings in Children with Down Syndrome. J Ophthalmol. 2020;2020:9726261.

DOI: 10.4274/tjo.galenos.2020.28485
Turk J Ophthalmol 2021;51:206-211

Original Article

Comparison of Sociodemographic Features Between Behçet Uveitis and Other Non-infectious Uveitis

F. Nilüfer Yalçındağ*, Pınar Çakar Özdal**, Yılmaz Özyazgan***, Figen Batıoğlu*, İlknur Tugal-Tutkun****

*Ankara University Faculty of Medicine, Department of Ophthalmology, Ankara, Turkey
**University of Health Sciences Turkey Faculty of Medicine, Department of Ophthalmology, Ankara Ulucanlar Göz SUAM, Ankara, Turkey
***İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Department of Ophthalmology, İstanbul, Turkey
****İstanbul University, İstanbul Faculty of Medicine, Department of Ophthalmology, İstanbul, Turkey

Abstract

Objectives: To analyze and compare sociodemographic features between Behçet uveitis and other non-infectious uveitis.
Materials and Methods: The data of adults with non-infectious uveitis in the nationwide uveitis database were analyzed and the sociodemographic features of patients with and without Behçet disease were compared.
Results: This study included data of 4,978 eyes of 3,363 patients from 33 centers. The mean age at presentation was 38.7±13.3 (17-87) years. The mean age was 34.3±10.5 years in the Behçet uveitis group and 41.1±14.0 years in the other non-infectious uveitis group (p<0.001). Male predominance was seen in the Behçet uveitis group (67.7% vs. 32.3%) while female patients were more common in the other non-infectious uveitis group (54.4% vs. 45.6%, p<0.001). Regarding education level, the proportion of patients with low education was higher in the Behçet uveitis group than the other non-infectious uveitis group (49.6% vs. 43.4% in males, p=0.004; 61.5% vs. 59.2% in females, p=0.021). Having a low-income job or being currently unemployed, indicators of poor income, were more frequent in the Behçet uveitis group than in the other non-infectious uveitis group (32.0% vs. 22.8%, p<0.001). In the comparison of places of residence, the proportion of patients who lived in cities with low gross national product was 37.0% in the Behçet uveitis group and 31.1% in the other non-infectious uveitis group (p<0.001).
Conclusion: Patients with Behçet disease had lower education level and socioeconomic status than patients with other non-infectious uveitis entities.
Keywords: Behçet uveitis, non-infectious uveitis, sociodemographic, uveitis

Introduction

Uveitis is an important cause of visual impairment and vision loss in Western societies, accounting for approximately 10% of blindness.[1,2] Limitations associated with visual impairment can adversely affect patients' ability to work and may lead to absenteeism or loss of workforce. It can occur at all ages, but due to the generally early onset, it especially affects the working age group and creates a serious personal and economic burden.[3,4]

Although uveitis may develop due to infectious and non-infectious causes, it is often observed due to non-infectious causes.[5] Non-infectious uveitis may be idiopathic or occur due to systemic disease, and Behçet disease remains the most common non-infectious uveitis etiology in our country.[6] The aim of this study was to analyze and compare sociodemographic characteristics between Behçet uveitis and other non-infectious uveitis.

Address for Correspondence: F. Nilüfer Yalçındağ, Ankara University Faculty of Medicine, Department of Ophthalmology, Ankara, Turkey
E-mail: nil.yalcindag@gmail.com **ORCID-ID:** orcid.org/0000-0002-8963-5146
Received: 22.08.2020 **Accepted:** 05.11.2020

Cite this article as: Yalçındağ FN, Çakar Özdal P, Özyazgan Y, Batıoğlu F, Tugal-Tutkun İ. Comparison of Sociodemographic Features Between Behçet Uveitis and Other Non-infectious Uveitis. Turk J Ophthalmol 2021;51:206-211

Materials and Methods

The Behçet Uveitis Screening Trial (BUST), planned by the Uvea-Behçet Unit of the Turkish Ophthalmological Association, was initiated in November 2008 to determine the demographic and clinical characteristics of non-infectious uveitis patients presenting to secondary and tertiary health centers in Turkey. It is a multicenter, observational, national registry study with a total of 33 participating centers, including 21 university hospitals and 12 training and research hospitals. The study protocol was approved by the İstanbul University İstanbul Faculty of Medicine Ethics Committee and the Ministry of Health and was carried out in accordance with the Declaration of Helsinki. All patients included in the study provided informed consent.

During the study, the investigators were asked to include all patients with active or inactive uveitis who were presenting to their centers for the first time. Patients with masquerade syndromes such as lens-associated uveitis, postoperative or posttraumatic inflammation, exogenous endophthalmitis, and intraocular malignancies were excluded from the study. An electronic data collection system consisting of standard questions was created specifically for the registry and used to record the data online. The online registration system enabled duplicate registrations to be detected and prevented. Monitoring visits were made to all centers and patient records were checked by an external auditor to ensure data reliability and validity. Data collection was terminated at the end of October 2011 and the data of the patients who were registered between November 2008 and October 2011 were analyzed.

The general demographic and clinical characteristics of uveitis in Turkey according to the results of the BUST study have been published.[6] The present study analyzes data not included in that report and compares the sociodemographic characteristics of adult patients with Behçet uveitis and non-Behçet non-infectious uveitis.

Statistical Analysis

Data were analyzed using SPSS for Windows version 15.0 (SPSS Inc., Chicago, IL). Data distributions were calculated using analytical methods. Pearson's chi-square test was used in cross tabulation analysis. The Mann-Whitney test was used for nonparametric data. A p value <0.05 was considered statistically significant.

Results

The study included 4,978 eyes of 3,363 patients with non-infectious uveitis in 33 centers. Of these, 1,170 (34.8%) of the patients had Behçet uveitis and 2,193 (65.2%) had non-Behçet non-infectious uveitis.

Of the patients with non-infectious uveitis, 1,791 (53.3%) were male and 1,572 (46.7%) were female. The male to female ratio was 1.14:1. When the two groups were compared, males comprised 67.7% of the Behçet uveitis group (male to female ratio 2.09:1) and 45.6% of the other non-infectious uveitis group (male to female ratio 0.83:1) (p<0.001).

The mean age of the patients was 38.7 (17-87) years. However, there was a statistically significant difference in mean age between the two groups. The mean age was 34.3±10.5 years in the Behçet uveitis group and 41.1±14 years in the non-infectious uveitis group (p<0.001).

Of all non-infectious uveitis patients, 1615 (48%) had bilateral involvement and 1748 (52%) had unilateral involvement. When the two groups were compared, the rate of bilateral involvement was significantly higher in the Behçet uveitis group (65.6%, n=768) than in the other non-infectious uveitis group (38.6%, n=847 cases) (p<0.001). When involvement was compared within the 1,791 male patients, the rate of bilateral involvement was 65.9% (n=522) in the Behçet group and 32.3% (n=323) in the non-Behçet non-infectious uveitis group (p<0.001). Among female patients, the rate of bilateral involvement was 65.1% (n=246) in the Behçet group and 43.9% (524 cases) in the non-Behçet non-infectious uveitis group (p<0.001). The patients' education level, occupation, place of residence according to gross national product (GNP), and mode of presentation are summarized in Table 1. When all patients were evaluated together, there was no significant difference in education level between the Behçet uveitis and non-Behçet non-infectious uveitis groups (p>0.05). Low income indicators such as having a low-income job or being currently unemployed were more frequent in the Behçet uveitis group than in the other non-infectious uveitis group (32.0% vs. 22.8%, p<0.001). When the patients' places of residence were compared, the proportion of patients living in cities with low GNP was 37.0% in the Behçet uveitis group and 31.1% in the other non-infectious uveitis group (p<0.001) (Table 1).

Sociodemographic characteristics of male and female patients were compared between the Behçet uveitis and non-Behçet non-infectious uveitis groups. In males, the proportion of patients with low education (uneducated or primary school graduate) was higher in the Behçet uveitis group than in the other non-infectious uveitis group (49.6% vs. 43.4%), while a moderate to high education level (high school and university) was more common in the other non-infectious uveitis group than in the Behçet uveitis group (55.2% vs. 47.7%) (p=0.004). Similarly, low education level was more prevalent among women in the Behçet uveitis group than the other non-infectious uveitis group (61.5% vs. 59.2%), whereas moderate to high education level was more common in the other non-infectious uveitis group than in the Behçet uveitis group (39.8% vs. 32.8%) (p=0.021) (Table 1).

In addition, education level in the Behçet uveitis and non-Behçet non-infectious uveitis groups was evaluated according to male and female gender. When the patients were evaluated as a whole and separately in the Behçet and non-Behçet non-infectious patient groups, low education level was more common in females and a moderate to high education level was more common in males (p<0.001).

Low income indicators such as having a low-income job or being currently unemployed were more frequent among men in the Behçet uveitis group than in the other non-infectious uveitis group (37.5% vs. 31.3%, p<0.001). Similarly for women, having a low-income job, being unemployed, or being a homemaker were more common in the Behçet uveitis group than in the other non-infectious uveitis group (77.2% vs. 71.6%, p=0.018) (Table 1).

When we compared places of residence, the proportion of patients living in cities with low GNP was higher in the Behçet uveitis group compared to the other non-infectious uveitis group (38.3% vs. 30.0%, p<0.001). However, there was no statistically significant difference between the two groups in terms of GNP in women (p>0.05) (Table 1).

When patients' mode of presentation to the secondary and tertiary care centers was evaluated, it was determined that most patients presented by their own volition (48.2%). However, presentation by consultation was significantly more common in the Behçet uveitis group than in the other non-infectious uveitis group (28.7% vs. 13.7% in all patients; 28.9% vs. 13.2% in males; 28.3% vs. 14.2% in females, p<0.001) (Table 1).

Discussion

As opposed to causes of vision loss such as cataract and age-related macular degeneration that are associated with advanced age, uveitis is the fifth most common cause of vision loss in middle-aged adults.[7] According to the 2010 age and frequency table of the Turkish Statistical Institute (TSI) (http://www.tuik.gov.tr), 3% of individuals in the 35-44 year age range had vision problems. Non-infectious uveitis is also one of the potential etiologies included in this percentage. With national multicenter studies, standardization of diagnosis and data recording systems can provide a more comprehensive view of uveitis cases. As a result of the BUST study initiated for this purpose, a database has been established for uveitis cases in our country. According to the initial results of this study, Behçet uveitis is still the most common non-infectious cause of uveitis in our country.[6] Therefore, we decided to conduct further subanalyses of the data pertaining to Behçet patients. With better elucidation of the demographic and socioeconomic factors of the disease, more appropriate social, psychological, medical, and economic approaches to these patients can be planned.

The distribution and etiology of uveitis types are influenced by genetic, geographic, social, and environmental factors. The prevalence of Behçet uveitis is known to be high in Asian and Mediterranean countries.[8] Behçet uveitis also occurs more frequently in males.[9] In our study, Behçet uveitis was more common in men (67.7%). Similarly, in a large study of Behçet uveitis patients conducted in our country, the proportion of male patients was found to be 68%.[10] Although there has been no change in the incidence of Behçet disease in our country over the years, recent publications based in Japan have reported a decrease in incidence.[11,12] Similarly, a decrease in some clinical signs related to genital ulceration, ocular involvement, and skin lesions and a lower annual incidence of Behçet disease were reported in Korea.[13,14] This suggests that the etiology of the disease may be related to environmental factors. Of the environmental factors, two possible mechanisms for this epidemiological change are a change in the balance of atopy/allergy or a decrease in the frequency of infection.[15] Infections have long been proposed to be a triggering factor in the pathogenesis of Behçet disease.[16] Activation of stable Behçet disease has been reported after dental treatments and streptococcal antigen skin testing.[17] Poor oral health has been reported in Behçet patients and associated with more severe course.[18] Considering all of these mechanisms together, the decrease in incidence in Japan may be associated with improved oral hygiene. In a recent publication, a mouse model was developed to explain the relationship between gut microbiome composition and the pathogenesis of Behçet disease.[19] Further evidence supporting the hypothesis that Behçet disease develops due to environmental factors is its higher prevalence at lower socioeconomic levels. A study comparing socioeconomic status and personal hygiene habits of people with multiple sclerosis, headache, and neuro-Behçet disease showed that patients with neuro-Behçet disease had lower socioeconomic level and poorer hygiene habits.[20] In our study, the proportion of patients living in cities with low GNP was found to be higher in the Behçet uveitis group than in the other group. Having a low socioeconomic level may also be one of the potential risk factors for Behçet disease.

According to TSI data, the unemployment rate in our country was reported as 9.1% in 2011, the year in which this study was completed. In our study, the unemployment rate was 8.9% among all patients with non-infectious uveitis and 7.6% among all male patients. However, the actual unemployment rate in uveitis patients may be higher than that found in this study because unemployed patients may lose their health insurance and therefore not seek medical care unless they have very serious complaints. The unemployment rate among men was 8.5% in the Behçet group and 7% in the other non-infectious uveitis group. Among women, the unemployment rate was higher (10.2%) and showed no difference between the two groups. Being employed as a civil servant, which requires a higher education level, was lower in both male and female Behçet patients compared to the other group. In contrast, the frequency of being a laborer or self-employed was higher in the Behçet uveitis group compared to the other non-infectious uveitis group. There may be several explanations for these findings. Firstly, Behçet uveitis has earlier onset than uveitis of other non-infectious etiologies, so patients dealing with Behçet disease in their most active age period may have difficulty participating in employment. Secondly, since Behçet disease is actually a multisystemic obstructive vasculitis, they may lag in employment due to complications associated with other system involvement. According to TSI 2018 statistics, 14.2% of people who are not included in the workforce are unable to participate in employment due to disability. Some of our patients may also be included in this group. In addition, patients with Behçet uveitis have worse visual prognosis than patients with

Table 1. Information regarding educational background, occupation, place of residence according to gross national product (GNP), and mode of presentation for male, female, and all patients

	Male patients							Female patients							All patients						
	Non-Behçet non-infectious (n=999)		Behçet disease (n=792)		Total (n=1,791)			Non-Behçet non-infectious (n = 1194)		Behçet disease (n=378)		Total (n=1,572)			Non-Behçet non-infectious (n=2,193)		Behçet disease (n=1,170)		Total (n=3,363)		
	Number	(%)	Number	(%)	Number	(%)	p value	Number	(%)	Number	(%)	Number	(%)	p value	Number	(%)	Number	(%)	Number	(%)	p value
Education level							0,004							0,021							>0,05
Uneducated/ primary education	434	43.4	393	49.6	827	46.2		706	59.2	246	65.1	952	60.6		1140	52.0	639	54.6	1779	52.9	
Secondary education/ university	551	55.2	378	47.7	929	51.9		475	39.8	124	32.8	599	38.1		1026	46.8	502	42.9	1528	45.4	
Unknown	14	1.4	21	2.66	35	1.9		13	1.0	8	2.1	21	1.3		27	1.2	29	2.5	56	1.7	
Occupation							<0.001							0.018							<0.001
Retired	131	13.1	37	4.7	168	9.4		60	5.0	9	2.4	69	4.4		191	8.7	46	3.9	237	7.0	
Homemaker	-	-	-	-	-	-		668	55.9	226	59.8	894	56.8		668	30.5	226	19.3	894	26.6	
Laborer	243	24.3	230	29.0	473	26.4		67	5.6	25	6.6	92	5.9		310	14.1	255	22.8	565	16.8	
Unemployed	70	7.0	67	8.5	137	7.6		120	10.1	41	10.8	161	10.2		190	8.7	108	9.2	298	8.9	
Civil servant	146	14.6	78	9.8	224	12.5		122	10.2	22	5.8	144	9.2		268	12.2	100	8.5	368	10.9	
Student	77	7.7	47	5.9	124	6.9		61	5.1	16	4.2	77	4.9		138	6.3	63	5.4	201	6.0	
Freelance/ self-employed	320	32.0	319	40.3	639	35.7		90	7.5	35	9.3	125	8.0		410	18.7	354	30.3	764	22.7	
Unknown	12	1.2	14	1.8	26			6	0.5	4	1.1	10	0.6		18	0.8	18	1.5	36	1.1	
GNP							<0.001							>0.05							<0.001
Low	300	30.0	303	38.3	603	33.7		382	32.0	130	34.4	512	32.6		682	31.1	433	37.0	1115	33.2	
High	697	69.8	480	60.6	1177	65.7		807	67.6	244	64.6	1051	66.9		1504	68.6	724	61.9	2228	66.3	
Unknown	2	0.2	9	1.1	11	0.6		5	0.4	4	1.1	9	0.6		7	0.3	13	1.1	20	0.6	
Mode of presentation							<0.001							<0.001							<0.001
Referral	290	29.0	272	34.3	562	31.4		421	35.3	115	30.4	536	34.1		711	32.4	387	33.1	1098	32.7	
Consultation	132	13.2	229	28.9	361	20.2		169	14.2	107	28.3	276	17.6		301	13.7	336	28.7	637	18.9	
Patient's request	577	57.8	285	36.0	862	48.1		603	50.5	156	41.3	759	48.3		1180	53.8	441	37.7	1621	48.2	
Unknown	-	-	6		6	0.3		1	0.08	-	-	1	0.06		1	0.05	6	0.5	7	0.2	

GDP: Gross national product

non-infectious uveitis without systemic association, even when intensive therapy is initiated in the early stages of the disease.[4] Moreover, because these patients are followed by numerous specialists in branches such as dermatology, rheumatology, and ophthalmology, their frequent hospital visits may make them less desirable to potential employers. A study evaluating the risk of leaving the workforce over time for patients with non-infectious intermediate, posterior, and panuveitis showed that this rate was 11% for year 1, 31% for year 5, and 44% for year 10, and was significantly higher than the control group (p=0.007).[21] Similarly, the presence of systemic disease and relatively poor visual prognosis are potential factors that may affect patients' education. In this study, the proportion of patients who were unschooled or primary school graduates was also higher in the Behçet uveitis group than in the other non-infectious uveitis group. This finding may be important in explaining why patients with Behçet uveitis are more frequently unemployed, self-employed, or working as laborers.

In a study from the United States, it was reported that monthly health costs due to non-infectious uveitis varied by treatment method and were $935 in the corticosteroid group, $1,738 in the immunosuppressant group, and $1,439 in the biological agent group.[22] In fact, in cases of blindness due to non-infectious uveitis, annual health expenditures can be up to $17,846.[23] Considering both job loss and treatment costs together provides a better understanding of the socioeconomic dimension of the disease. Uveitis is also a disease that impacts quality of life. In a study conducted in patients with intermediate uveitis, a direct interaction between vision-related quality of life and general health-related quality of life was reported.[24] Especially in Behçet patients, it has been shown that general health status is more affected by visual function.[25] As expected, patients with systemic disease associated with non-infectious uveitis were found to have poorer quality of life scores than patients with only ocular findings.[26] In a study conducted in our country, it was shown that Behçet patients with ocular involvement were susceptible to psychosocial disorders such as anxiety and depression.[27] Moreover, in another study conducted in our country, general health sub-scales were examined in patients with active uveitis according to etiology, and scores were found to be significantly lower in Behçet uveitis than HLA-B27-associated uveitis.[28] Fatigue, depression, and anxiety scores were also reported to be higher in Behçet disease compared to healthy controls, and advanced regression analysis revealed a significant association between fatigue and anxiety, depression, and physical dysfunction.[29] Stressful life events have been shown to have an important role in leading to secondary problems in periods of relapse and remission in Behçet disease, with 79.4% of patients associating disease activation with a stress factor.[30] All these findings demonstrate the socioeconomic and psychological dimensions of the disease.

Study Limitations

In our study, the proportion of patients who were seen for consultation was higher in the Behçet uveitis group compared to the other non-infectious uveitis group. Behçet disease is common in our country, so this result may be because clinicians have high awareness of the disease and its ocular morbidity is well known. Since Behçet disease is a multisystemic obstructive vasculitis, a comprehensive interdisciplinary approach is essential for disease management.

Conclusion

In conclusion, Behçet uveitis is still the most common non-infectious uveitis etiology in Turkey. Patients with Behçet disease had lower education and socioeconomic levels than those with other non-infectious uveitis. Early diagnosis, early and adequate treatment, and preventing complications are essential to enable these patients to receive better education, remain employed, and work in better conditions. In addition, socioeconomic models can be developed to provide employment to patients already suffering from this disease, which has a high prevalence in our country. As patients reach a higher socioeconomic level, follow-up continuity and treatment adherence may improve, breaking the vicious cycle between disease, disease-related job loss, and treatment nonadherence due to job loss and thereby enabling these patients, most of whom are in their productive years, to be reintegrated into society.

Ethics

Ethics Committee Approval: The study protocol was approved by the İstanbul University İstanbul Faculty of Medicine Ethics Committee and the Ministry of Health and was carried out in accordance with the Declaration of Helsinki.

Informed Consent: Obtained.

Peer-review: Externally peer reviewed.

Authorship Contributions

Concept: F.N.Y., İ.T.T., Design: F.N.Y., Y.Ö., F.B., İ.T.T., Data Collection or Processing: F.N.Y., P.Ç.Ö., Y.Ö., F.B., İ.T.T., BUST Study Group, Analysis or Interpretation: F.N.Y., İ.T.T., Literature Search: F.N.Y., İ.T.T., Writing: F.N.Y., İ.T.T.

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

Financial Disclosure: This report was based on data from the BUST study, which was supported by the Turkish Ophthalmological Association with funding from Novartis, Turkey. Novartis had no influence on the study design, data interpretation, writing of the article, or the decision to submit the article for publication. Publication of this article is not contingent upon Novartis' approval.

***Contributors to the Behçet Uveitis Screening Trial (BUST) study** (listed in order of the number of patients included from the participating centers):

İlknur Tugal-Tutkun, Yılmaz Özyazgan, Didar Uçar, Pınar Özdal, Yıldız Boztok, Sibel Kadayıfçılar, Bora Eldem, F. Nilüfer Yalçındağ, Figen Batıoğlu, Özge Yanık, Nilüfer Berker, Yasemin Özdamar, Yonca Akova, Leyla Erkanlı, Ertuğrul Mirza, Merih Soylu, Yüksel Süllü, Gülten Sungur, Ali Osman Saatci, Nurettin Akyol, Adem Türk, Özlem Yıldırım, Tülay Akçetin, Cemil Apaydın, Sinan Emre, Özcan Kayıkçıoğlu, Haluk Kazokoğlu,

Sumru Önal, Muhittin Taşkapılı, Şengül Özdek, Gökhan Gürelik, Banu Öztürk, Suzan Güven Yılmaz, Halil Ateş, Ahmet Maden, Aras Saklamaz, A. Hakan Durukan, Güngör Sobacı, Zeliha Yazar, Gülay Güllülü, Pelin Yılmazbaş, Sema Dündar, Selçuk Sızmaz, Ayşen Topalkara, Ayşe Vural, Levent Karabaş, Muzaffer Öztürk, Şeyda Uğurlu, Ahmet Karakurt, Feyza Önder, Nur Ayrancıoğlu.

Acknowledgements: We would like to thank Özge Yanık Odabaş, Tuna Çelik Büyüktepe, Mehmet Fatih Kağan Değirmenci, and Emine Temel for their assistance with statistical analysis.

References

1. Jakob E, Reuland MS, Mackensen F, Harsch N, Fleckenstein M, Lorenz HM, Max R, Becker MD. Uveitis subtypes in a german interdisciplinary uveitis center--analysis of 1916 patients. J Rheumatol. 2009;36:127-136.
2. Nussenblatt RB. The natural history of uveitis. Int Ophthalmol. 1990;14:303-308.
3. Acharya NR, Tham VM, Esterberg E, Borkar DS, Parker JV, Vinoya AC, Uchida A. Incidence and prevalence of uveitis: results from the Pacific Ocular Inflammation Study. JAMA Ophthalmol. 2013;131:1405-1412.
4. Durrani OM, Tehrani NN, Marr JE, Moradi P, Stavrou P, Murray PI. Degree, duration, and causes of visual loss in uveitis. Br J Ophthalmol. 2004;88:1159-1162.
5. Miserocchi E, Fogliato G, Modorati G, Bandello F. Review on the worldwide epidemiology of uveitis. Eur J Ophthalmol. 2013;23:705-717.
6. alçındağ FN, Özdal PC, Özyazgan Y, Batıoğlu F, Tugal-Tutkun I; BUST Study Group. Demographic and Clinical Characteristics of Uveitis in Turkey: The First National Registry Report. Ocul Immunol Inflamm. 2018;26:17-26.
7. Suttorp-Schulten MS, Rothova A. The possible impact of uveitis in blindness: a literature survey. Br J Ophthalmol. 1996;80:844-848.
8. Chang JH, Wakefield D. Uveitis: a global perspective. Ocul Immunol Inflamm. 2002;10:263-279.
9. Tugal-Tutkun I. Behçet Hastalığı. Turkiye Klinikleri J Ophthalmol-Special Topics. 2008;1:44-50.
10. Tugal-Tutkun I, Onal S, Altan-Yaycioglu R, Huseyin Altunbas H, Urgancioglu M. Uveitis in Behçet disease: an analysis of 880 patients. Am J Ophthalmol. 2004;138:373-380.
11. Goto H, Mochizuki M, Yamaki K, Kotake S, Usui M, Ohno S. Epidemiological survey of intraocular inflammation in Japan. Jpn J Ophthalmol. 2007;51:41-44.
12. Ohguro N, Sonoda KH, Takeuchi M, Matsumura M, Mochizuki M. The 2009 prospective multi-center epidemiologic survey of uveitis in Japan. Jpn J Ophthalmol. 2012;56:432-435.
13. Kim DY, Choi MJ, Cho S, Kim DW, Bang D. Changing clinical expression of Behcet disease in Korea during three decades (1983-2012): chronological analysis of 3674 hospital-based patients. Br J Dermatol. 2014;170:458-461.
14. Lee YB, Lee SY, Choi JY, Lee JH, Chae HS, Kim JW, Han KD, Park YG, Yu DS. Incidence, prevalence, and mortality of Adamantiades-Behcet's disease in Korea: a nationwide, population-based study (2006-2015). J Eur Acad Dermatol Venereol. 2018;32:999-1003.
15. Direskeneli H, Mumcu G. A possible decline in the incidence and severity of Behcet's disease: implications for an infectious etiology and oral health. Clin Exp Rheumatol. 2010;28(4 Suppl 60):86-90.
16. Mumcu G, Direskeneli H. Triggering agents and microbiome as environmental factors on Behcet's syndrome. Intern Emerg Med. 2019;14:653-660.
17. Mizushima Y, Matsuda T, Hoshi K, Ohno S. Induction of Behcet's disease symptoms after dental treatment and streptococcal antigen skin test. J Rheumatol. 1988;15:1029-1030.
18. Mumcu G, Ergun T, Inanc N, Fresko I, Atalay T, Hayran O, Direskeneli H. Oral health is impaired in Behcet's disease and is associated with disease severity. Rheumatology (Oxford). 2004;43:1028-1033.
19. Ye Z, Zhang N, Wu C, Zhang X, Wang Q, Huang X, Du L, Cao Q, Tang J, Zhou C, Hou S, He Y, Xu Q, Xiong X, Kijlstra A, Qin N, Yang P. A metagenomic study of the gut microbiome in Behcet's disease. Microbiome. 2018;6:135.
20. Pehlivan M, Kürtüncü M, Tüzün E, Shugaiv E, Mutlu M, Eraksoy M, Akman-Demir G. The comparison of socio-economic conditions and personal hygiene habits of neuro-Behcet's disease and multiple sclerosis patients. Int J Hyg Environ Health. 2011;214:335-337.
21. Thorne JE, Skup M, Tundia N, Macaulay D, Revol C, Chao J, Joshi A, Dick AD. Direct and indirect resource use, healthcare costs and work force absence in patients with non-infectious intermediate, posterior or panuveitis. Acta Ophthalmol. 2016;94:331-339.
22. Chu DS, Johnson SJ, Mallya UG, Davis MR, Sorg RA, Duh MS. Healthcare costs and utilization for privately insured patients treated for non-infectious uveitis in the USA. J Ophthalmic Inflamm Infect. 2013;3:64.
23. Kirbach SE, Hayes OA, Cifaldi MA. The Economic Burden of Uveitis [abstract]. Arthritis Rheum. 2010 (62): 329-330.
24. Murphy CC, Hughes EH, Frost NA, Dick AD. Quality of life and visual function in patients with intermediate uveitis. Br J Ophthalmol. 2005;89:1161-1165.
25. Onal S, Savar F, Akman M, Kazokoglu H. Vision- and health-related quality of life in patients with Behcet uveitis. Arch Ophthalmol. 2010;128:1265-1271.
26. Schiffman RM, Jacobsen G, Whitcup SM. Visual functioning and general health status in patients with uveitis. Arch Ophthalmol. 2001;119:841-849.
27. Tanriverdi N, Taşkintuna, Dürü C, Ozdal P, Ortaç S, Firat E. Health-related quality of life in Behcet patients with ocular involvement. Jpn J Ophthalmol. 2003;47:85-92.
28. Onal S, Oray M, Yasa C, Akman M, Uludag G, Koc Akbay A, Tugal-Tutkun I. Screening for Depression and Anxiety in Patients with Active Uveitis. Ocul Immunol Inflamm. 2018;26:1078-1093.
29. Ilhan B, Can M, Alibaz-Oner F, Yilmaz-Oner S, Polat-Korkmaz O, Ozen G, Mumcu G, Maradit Kremers H, Direskeneli H. Fatigue in patients with Behcet's syndrome: relationship with quality of life, depression, anxiety, disability and disease activity. Int J Rheum Dis. 2018;21:2139-2145.
30. Karlidag R, Unal S, Evereklioglu C, Sipahi B, Er H, Yologlu S. Stressful life events, anxiety, depression and coping mechanisms in patients with Behcet's disease. J Eur Acad Dermatol Venereol. 2003;17:670-675.

DOI: 10.4274/tjo.galenos.2020.47639
Turk J Ophthalmol 2021;51:212-217

Original Article

The Microbiological Profile of Bicanalicular Silicone Tubes Placed During External Dacryocystorhinostomy

Gökçen Özcan*, Banu Melek Hoşal*, Devran Gerçeker**

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

Abstract

Objectives: To identify microbiological growth on bicanalicular silicone tubes (BST) placed during dacryocystorhinostomy (DCR) surgery and to analyze the association between culture results and surgical outcomes and BST removal time.

Materials and Methods: A total of 80 lacrimal drainage systems of 68 patients who had external DCR with bicanalicular silicone intubation were included the study. Twenty-five tubes (31.3%) were removed up to 8 weeks, 28 tubes (35.0%) were removed between 9 and 11 weeks, and the remaining 27 tubes (33.7%) were removed 12 weeks or more after surgery. The tubes were transferred to Stuart medium and sent for microbiologic examination. The disc diffusion method was used to determine antibiotic resistance.

Results: Culture positivity was observed for 96.2% of the tubes. Among a total of 109 isolates, 63 were gram-positive bacteria (57.8%), 37 were gram-negative bacteria (34%), and 9 were fungi (8.2%). The most commonly isolated gram-positive and gram-negative bacteria were *Staphylococcus aureus* (66.6%) and *Enterobacter* spp. (29.7%), respectively. Penicillin, clindamycin, erythromycin, and tetracycline resistances were higher among gram-positive pathogens. Cephalothin, amoxicillin-clavulanic acid, and ampicillin resistances were higher among gram-negative pathogens. There was no significant difference in terms of the microbiological profile between the three groups of removed tubes. *Haemophilus influenzae* was isolated at a significantly higher rate in patients with surgical failure (p=0.04).

Conclusion: Although a variety of agents were isolated from removed BST, gram-positive organisms were more frequent than gram-negatives and fungi. *S. aureus* and *Enterobacter* were the most common gram-positive and gram-negative isolates. Later BST removal was associated with the isolation of significantly more bacterial strains per tube. There was no correlation between multiple infections and surgical failure. *H. influenzae* was more common in failed DCR cases.

Keywords: Bicanalicular silicone tube, external dacryocystorhinostomy, microbiology, nasolacrimal duct obstruction

Introduction

External dacryocystorhinostomy (DCR) is the gold standard therapeutic procedure for nasolacrimal duct obstruction (NLDO). Bicanalicular silicone tube intubation has been widely used in DCR surgery since its introduction by Gibbs in 1967.[1,2] However, the benefit of bicanalicular silicone tube intubation in DCR surgery remains controversial.[3,4,5] Kim et al.[6] reported that silicone intubation improves surgical success rate, whereas Allen and Berlin[7] asserted that it has a negative impact on primary DCR surgery.

Choung and Khwarg[8] conducted a study and suggested that patients with primary NLDO who have large lacrimal sacs, intact canalicular systems, and wide nasal cavities do not require tube placement during external DCR. Consequently, common indications for bicanalicular silicone tube intubation in DCR are revision surgeries, common canalicular stenosis, fibrotic lacrimal sac, and inadequate anastomosis of lacrimal sac and nasal mucosal flap.[9,10] The most frequent complications considered to be related with silicone tube intubation are punctal slitting and peripunctal granuloma formation, canalicular laceration, tube

Address for Correspondence: Gökçen Özcan, Ankara University Faculty of Medicine, Department of Ophthalmology, Ankara, Turkey
E-mail: drgokcencondu@gmail.com **ORCID-ID:** orcid.org/0000-0002-2616-5941
Received: 04.04.2020 **Accepted:** 23.09.2020

Cite this article as: Özcan G, Hoşal BM, Gerçeker D. The Microbiological Profile of Bicanalicular Silicone Tubes Placed During External Dacryocystorhinostomy. Turk J Ophthalmol 2021;51:212-217

displacement or loss, chronic nasal or conjunctival irritation, and corneal abrasion.[11]

Microbiological growth over the silicone tubes and its effect on surgical outcomes has been analyzed in a few studies. Although Ali et al.[12] reported that the organisms isolated from silicone tubes did not influence the success rate of DCR, Kim et al.[13] found that the rate of *Pseudomonas aeruginosa* infection was significantly higher in those with final surgical failure.

In this study, we aimed to identify the microbiological profile and antibiotic resistance of agents colonizing silicone tubes removed after DCR. We also analyzed the relationship between the culture results and surgical outcomes and tube removal time.

Materials and Methods

This study was a retrospective observational case series and included a total of 80 eyes of 68 adult patients who underwent external DCR surgery and silicone tube intubation in Ankara University Faculty of Medicine Ophthalmology Department. The study protocol was approved by the Ethics Committee of Ankara University of Medical Sciences and was carried out in accordance with the ethical guidelines of the Declaration of Helsinki. Thirteen of the patients were men (19.1%) and 55 were women (80.9%). The mean age of the participants was 55.1 years (±13.9, range 30-82 years). The number of patients with bilateral involvement was 12 (17.6%). Fifteen patients had diabetes mellitus (22%), one patient had scleroderma (1.4%), and one patient had history chemotherapy because of breast carcinoma (1.4%). Eight eyes (10%) had history of acute dacryocystitis and 12 eyes (15%) had history of chronic dacryocystitis before the operation. Patients using systemic and topical antibiotics prior to surgery were not included in the study. NLDO was confirmed using lacrimal irrigation before surgery. The otolaryngology department was consulted to detect the presence of intranasal pathologies before surgery. Thirteen eyes (16.2%) underwent revision and 67 eyes (83.8%) underwent primary external DCR surgery by a single surgeon (M.B.H.). The indications for silicone intubation were recurrent NLDO, common canalicular obstruction, fibrotic lacrimal sac, or inadequate lacrimal or nasal mucosal flaps for successful anastomosis.

Bicanalicular tubes were planned to be removed at 8 to 12 weeks after surgery. The tubes were removed through the nasal cavity using aseptic precautions and transferred to Stuart medium. Gram staining was performed first for all the collected samples. All the samples were cultured on blood agar, eosin methylene blue (EMB) agar, and chocolate agar and in brain-heart infusion broth for isolation of aerobic or facultative anaerobic bacteria. Chocolate, blood and EMB agars were incubated at 37°C in a 5%-10% CO_2 atmosphere for 24-72 hours. For the differentiation of fungal isolates, Sabouraud dextrose agar was incubated at both 25°C and 37°C for 7 days and contained chloramphenicol. The disk diffusion method was used to determine the antibiotic resistance profile of all bacterial isolates using European Committee on Antimicrobial Susceptibility Testing guidelines.

Statistical Analysis

Categorical variables were compared using chi-square or Fisher's exact test as appropriate. Survival analyses on categorical variables were performed using the Kaplan-Meier method and significant differences between groups were identified using the log-rank test. P-values less than 0.05 were considered to be statistically significant. Statistical analyses were performed using SPSS (Statistical Package for Social Sciences; version 11.5).

Results

The mean follow-up period after the surgery was 8.7 months (±9.5, range 2-60 months). The overall success rate was 80%; the success rate for primary DCR was 85.1% and for revision DCR was 53.9% (p=0.04). The mean time to reocclusion of the nasolacrimal passage was 4.4 months (±3, range 1 to 11 months). The mean time for the bicanalicular tube removal was 12.2 weeks (±5.7 range: 6-32 weeks).

Microorganisms were isolated from 77 tubes (96.2%). There was no microbiological growth on 3 silicone tubes (3.8%). A total of 109 isolates were identified. Of these, 63 were gram-positive bacteria (57.8%), 37 were gram-negative bacteria (34%), and the remaining 9 were fungi (8.2%) (Table 1). Of all 80 tubes, 39 had single bacterial species growth (48.8%), 25 had two bacterial species growth (31.3%), and 12 had three bacterial species growth (15%). There was no correlation between multiple growth and surgical failure (p=0.09). We grouped the tube removal times into three categories: up to 8 weeks after surgery (25 tubes, 31.3%), 9 to 11 weeks after surgery (28 tubes, 35%), and 12 weeks or more after surgery (27 tubes, 33.7%). There was no significant difference between these three groups in terms of microbiological profile or surgical outcomes. However, later tube removal was associated with a higher number of bacterial strains isolated for each tube. Triple bacterial growth was more common in tubes that remained 12 weeks or more compared to the tubes removed before 12 weeks (p=0.04).

Among the gram-positive organisms, *Staphylococcus aureus* was the most common isolate (66.6%), followed by *Corynebacterium* species (22.2%). The most common antibiotic resistances for *S. aureus* and coagulase-negative staphylococci (CNS) were penicillin and erythromycin. The rate of methicillin resistance among all *Staphylococcus* spp. was 18.75%. The most common antibiotic resistances for *Corynebacterium* spp. were penicillin and clindamycin. In general, gram-positive bacteria were more sensitive to gentamicin and cefotaxime (Table 2).

The most common gram-negative organisms were *Enterobacter* spp. (29.7%), *Haemophilus influenzae* (21.6%), and *P. aeruginosa* (18.9%). The most common antibiotic resistance was to ampicillin and cephalotin for *Enterobacter* spp., trimethoprim-sulfamethoxazole and cefuroxime for *H. influenzae*, and imipenem for *P. aeruginosa*. The rate of extended-spectrum beta-lactamase resistance among *Enterobacteriaceae*

was 12.5%. As a whole, gram-negative bacteria were more sensitive to imipenem and aztreonam (Table 3).

Yeasts (7.5%) were more commonly isolated than molds (5%). The most common fungi found in specimens were *Fusarium* species (44.4%), followed by *Aspergillus niger* (33.3%) and *Candida albicans* (22.2%). Molds were more commonly isolated in patients older than 65 years of age (p=0.03).

Among all isolated agents, *Enterobacter* spp. growth showed a significant correlation with diabetes mellitus (p=0.03). However, there was no difference in surgical outcomes. Success rate and microbiologic profile were similar in the patients with and without history of dacryocystitis. There was no statistically significant difference in terms of microbiological isolates of bicanalicular silicone tubes between revision and primary cases.

We compared the surgical failure with the growth of each infectious agent and found that *H. influenzae* was isolated more in patients with surgical failure (p=0.04). Four of the 9 patients with *H. influenzae* isolated in culture had surgical failure (44.4%) (Table 4).

Discussion

The normal flora of the human conjunctiva is diverse and mostly consists of gram-positive bacteria. CNS is the most commonly isolated group of bacteria, detected in up to 100% of positive conjunctival cultures taken from patients preoperatively, with *Staphylococcus epidermis* the predominant species. Other organisms commonly constituting the ocular flora are *Propionibacterium, Corynebacterium* spp., *P. aeruginosa,* and *H. influenzae*.[14,15] The normal nasal flora also includes *Corynebacterium, Streptococcus*, *Acinetobacter, Proteus, Mycoplasma* spp. and *Escherichia coli*. From the nasopharynx, *H. influenzae, Streptococcus pneumoniae, Streptococcus pyogenes,*

Table 1. Summary of microbiological growth in removed silicone tubes (n=80)

	No growth, n=3 (3.8%)	**One bacterial sp., n=39 (48.8%)**				**Two bacterial spp., n=25 (31.3%)**		**Three bacterial spp., n=12 (15%)**		**Fungal growth, n=9 (11.25%)**			
		Gram-positive only, n=29 (36.3%)		**Gram-negative only, n=10 (12.5%)**						**Yeast, n=6 (7.5%)**		**Mold, n=4 (5%)**	
Female	2	23	p=0.5	9	p=0.3	20	p=0.7	12	p=0.08	6	p=0.3	4	p=0.4
Male	1	6		1		5		0		0		0	
Age <65 years	3	22	p=0.4	7	p=0.7	16	p=0.4	9	p=0.7	6	p=0.1	1	**p=0.03**
Age >65 years	0	7		3		9		3		0		3	
Tube removal ≤8 weeks (n=25)	1	10	p=0.3	6	p=0.2	8	p=0.8	0	**p=0.04**	1	p=0.2	1	p=0.8
Tube removal 9-11 weeks (n=28)	1	12		1		8		5		3		2	
Tube removal >12 weeks (n=27)	1	7		3		9		7		2		1	

Table 2. Antibiotic resistance of gram-positive isolates (n=63)

	***Staphylococcus aureus*, n=42 (66.6%)**	**Coagulase-negative staphylococci , n=11 (17.4%)**	***Streptococcus pneumoniae*, n=9 (9.5%)**	***Corynebacterium* spp. n=14 (22.2%)**
Penicillin	92.8%	81.8%	0	14.3%
Clindamycin	11.9%	5.4%	0	28.6%
Erythromycin	14.2%	72.7%	0	7.1%
Tetracycline	7.0%	45.4%	0	21.4%
Cephalothin	4.7%	45.4%	0	0
Amoxicillin-clavulanic acid	4.7%	45.4%	0	7.1%
Ceftriaxone	0	0	0	7.1%
Trimethoprim-sulfamethoxazole	0	9.0%	0	7.1%
Mupirocin	2.3%	9.0%	0	0
Rifampicin	4.7%	9.0%	0	7.1%
Ciprofloxacin	4.7%	36.3%	0	7.1%
Gentamicin	2.3%	0	0	7.1%
Fusidic acid	0	36.3%	0	0
Cefotaxime	0	9.0%	0	0
Susceptible to all antibiotics	7%	18.1%	100%	64.2%

Table 3. Antibiotic resistance of gram-negative isolates (n=37)

	Haemophilus influenzae, n=8 (21.6%)	*Pseudomonas aeruginosa*, n=7 (18.9%)	*Stenotrophomonas maltofili*, n=5 (13.5%)	*Escherichia coli*, n=2 (5.4%)	*Klebsiella* spp., n=3 (%8,1)	*Enterobacter* spp., n=11 (29.7%)	*Citrobacter koseri*, n=2 (5.4%)	*Proteus* spp., n=1 (2.7%)	*Serratia* spp., n=2 (5.4%)	*Pantoea agglomerans*, n=2 (5.4%)	*Morexella* spp., n=3 (8.1%)
Cephalothin	0	0	0	50%	0	81.8%	0	0	50%	0	0
Amoxicillin-clavulanic acid	0	14.2%	0	50%	0	63.6%	0	0	100%	0	0
Trimethoprim-sulfamethoxazole	12.5%	0	20%	50%	33%	0	0	0	0	0	0
Gentamicin	0	14.2%	0	50%	33%	0	0	0	0	0	0
Imipenem	0	28.2%	0	0	0	0	0	0	0	0	0
Levofloxacin	0	0	20%	50%	0	0	0	0	0	0	0
Aztreonam	0	14.2%	0	0	0	0	0	0	0	0	0
Ampicillin	0	14.2%	0	100%	100%*	81.8%	100%*	0	50%	50%	100%
Ceftazidime	0	0	40%	0	0	0	0	0	0	0	0
Tigecycline	0	0	0	0	0	0	0	0	50%	0	0
Cefuroxime	12.5%	0	0	0	0	0	0	0	0	0	0
Susceptible to all antibiotics	75%	71.4%	40%	0	0	9.1%	0	100%	0	50%	0

and *Neisseria meningitides* can be isolated. Among the fungal flora, *Aspergillus, Cladosporium, Penicillium,* and *Alternaria* genera has been isolated from the noses of healthy adults.[16,17]

Kim et al.[13] identified the microbiologic profile of 39 silicone tubes placed during DCR in the Korean population and determined that 94.9% of the tubes had microbiological growth. They isolated gram-positive bacteria from 73.1%, gram-negative bacteria from 23.1%, and fungi from 3.8% of the tubes. *S. aureus* was the most common gram-positive isolate (73.9%), *P. aeruginosa* was the most common gram-negative isolate (12.8%), and *Aspergillus* (5.4%) *and Fusarium* (5.4%) were the most common fungi.[13]

Ali et al.[12] analyzed 50 silicone tubes retrieved after DCR in the Indian population and microbiological growth was noted in 88% of all stents cultured. They reported that fungal isolates were cultured from significant number (60%) of stents and the most common fungi was *Aspergillus* (66.6%). Gram-negative bacteria (54.5%) were more common than gram-positive bacteria (45.5%). The most common strains among the gram-negative and gram-positive bacteria were *P. aeruginosa* (27%) and *S. aureus* (18%), respectively. Gram-positive organisms were commonly sensitive to cephalosporins and vancomycin, whereas gram-negative organisms were sensitive to quinolones and aminoglycosides.[12]

Nemati et al.[18] included 72 eyes in a study conducted in the Iranian population and reported culture positivity in 66.4% of the tubes. They identified gram-positive agents in 62%, fungi in 48.6%, and gram-negative agents in 20% of the tubes. *Staphylococcus epidermidis* (36.4%), *Aspergillus fumigatus* (47.64%), and *Enterobacter aerogenes* (29.8%) were the most common bacterial and fungal species isolated from the tubes cultured. Of the antibiotics studied, the highest antibiotic resistance rates were to cefazolin and cloxacillin.[18]

Goel et al.[19] conducted a similar study in the Nepalese population and reported 100% positivity in cultures of 24 silicone tubes. Of the total isolates, gram-positive bacteria were found in 66.6% and gram-negative bacteria in 33.3% of the tubes, while no fungi were isolated. The most common gram-positive isolate was *S. aureus* (50%) and the most common gram-negative isolate was *E. coli* (20.8%).[19]

In our study, there was 96.2% culture positivity from 80 bicanalicular silicone tubes. A total of 109 agents were isolated, of which 57.8% were gram-positive bacteria, 34% were gram-negative bacteria, and 8.2% were fungi. *S. aureus* was the most common gram-positive organism (66.6%), *Enterobacter* spp. was the most common gram-negative organism (29.7%), and *Fusarium* species were the most common fungi (44.4%) in the Turkish population. Among the gram-positive pathogens, resistance to penicillin, clindamycin, erythromycin, and tetracycline was more common. Among gram-negative pathogens, resistance to

Table 4. Factors potentially associated with surgical outcome			
	Success, n=64 (80.0%)	**Failure, n=16 (20.0%)**	**P values**
Age (years), mean ± SD	53.2 (±3.4)	54.7 (±4.7)	p=0.080
Primary DCR (n=67)	57 (85.1%)	10 (14.9%)	**p=0.040**
Revision DCR (n=13)	7 (53.9%)	6 (46.1%)	
Acute dacryocystitis (n=8)	5 (62.5%)	3 (37.5%)	p=0.200
Chronic dacryocystitis (n=12)	8 (66.4%)	4 (33.3%)	p=0.197
Diabetes mellitus (n=15)	7 (66.4%)	5 (33.3%)	p=0.601
Haemophilus influenzae isolation (n=9)	5 (55.6%)	4 (44.4%)	**p=0.004**
Pseudomonas aeruginosa isolation (n=7)	4 (57.1%)	3 (42.9%)	p=0.166
Fungi isolation (n=9)	3 (33.3%)	p=0.261	p=0,261
SD: Standard deviation, DCR: Dacryocystorhinostomy			

cephalotin, amoxicillin-clavulanic acid, and ampicillin was more common. Generally, gram-positives were more sensitive to gentamicin and cefotaxime and gram-negatives were more sensitive to imipenem and aztreonam.

The high prevalence of fungal growth in the studies by Ali et al.[12] and Nemati et al.[18] might be related to a tropical and moist climate, as the climate is drier in Turkey than South India and the Iranian coast of the Caspian Sea. Increased *Enterobacter* spp. among our isolates may be linked to the low socioeconomic profile of the patients and poor hygiene habits. Similarly to our results, Nemati et al.[18] and Goel et al.[19] reported high rates of enteric floral growth among the gram-negative isolates obtained from silicone tubes.

Charalampidou et al.[20] compared surgical outcomes according to the timing of silicone tube removal. They removed 52.3% of the silicone tubes in 8-16 weeks, 13.3% before 8 weeks, and 34.4% after 16 weeks. They suggested that the timing of silicone tube removal after external DCR does not affect the long-term outcome of surgery. We grouped tube removal time into three categories: up to 8 weeks after surgery (31.3%), 9 to 11 weeks after surgery (35%), and 12 weeks or more after surgery (33.7%). There was no significant difference in terms of the microbiological profile and success rate between the three groups. As a result, the timing of the tube removal may be determined according to patient characteristics or surgeon preference.

Cultures should include the distal part of the silicone tubes. Becker[21] compared the results of cultures of the proximal and distal segments of silicone tubes after external DCR and found that the proximal tube segments were culture positive in 28% and the distal tube segments were culture positive in 89% of lacrimal systems. Nearly all (91%) of the proximal tube cultures were either negative or grew different organisms than the distal segment cultures.[21]

The organisms isolated were not associated with the success rate of DCR in the studies by Ali et al.[12] and Goel et al.[19] However, Kim et al.[13] reported that surgical failure and revision surgeries were associated with *Pseudomonas* infection. In our study, *H. influenzae* growth was associated with surgical failure, although we were unable to determine the exact relationship between the surgical failure and *H. influenzae* growth. Likewise, Kim et al.[13] could not explain the impact of *P. aeruginosa* growth on surgical failure. *H. influenzae* and *P. aeruginosa* are both biofilm-producing pathogens and silicone tubes aggravate their adherence. *H. influenzae* and *P. aeruginosa* also produce immunoglobulin A protease, an important virulence factor, to eliminate tear film immune defense and increase colonization. Silicone tubes coated with antibiotic, antiseptic, nano-silver, or cationic polymers may reduce biofilm formation and bacterial adhesion.[22] Histopathologic studies are essential for better understanding the mechanism by which these agents contribute to surgical failure.

Conclusion

In conclusion, *S. aureus* and *Enterobacter* spp. were the most commonly isolated gram-positive and gram-negative bacteria, respectively. The timing of silicone tube removal did not affect surgical outcomes. Tubes removed at or after 12 weeks were more likely to culture three bacterial strain than tubes removed before 12 weeks. *H. influenzae* was associated with unfavorable surgical outcomes. Supportive investigations are needed to gain knowledge and a better understanding of the variables effecting surgical outcomes.

Ethics

Ethics Committee Approval: Ankara University Faculty of Medicine Clinical Research Ethics Committee (source no: 05-397-19).

Peer-review: Externally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: B.M.H., Concept: G.Ö., B.M.H., Design: G.Ö., B.M.H., Analysis or Interpretation: G.Ö., Literature Search: G.Ö., B.M.H., D.G., Writing: G.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. Gibbs DC. New probe for the intubation of lacrimal canaliculi with silicone rubber tubing. Br J Ophthalmol. 1967;51:198.
2. Soll DB. Silicone intubation: an alternative to dacryocystorhinostomy. Ophthalmology. 1978;85:1259-1266.
3. Xie C, Zhang L, Liu Y, Ma H, Li S. Comparing the Success Rate of Dacryocystorhinostomy With and Without Silicone Intubation : A Trial Sequential Analysis of Randomized Control Trials. Sci Rep. 2017;7:1936.
4. Feng YF, Cai JQ, Zhang JY, Han XH. A meta-analysis of primary dacryocystorhinostomy with and without silicone intubation. Can J Ophthalmol. 2011;46:521-527.
5. Gu Z, Cao Z. Silicone intubation and endoscopic dacryocystorhinostomy: a meta-analysis. J Otolaryngol Head Neck Surg. 2010;39:710-713.

6. Kim NJ, Kim JH, Hwang SW, Choung HK, Lee YJ, Khwarg SI. Lacrimal silicone intubation for anatomically successful but functionally failed external dacryocystorhinostomy. Korean J Ophthalmol. 2007;21:70-73.
7. Allen K, Berlin AJ. Dacryocystorhinostomy failure: association with nasolacrimal silicone intubation. Ophthal Surg. 1989;20:486-489.
8. Choung HK, Khwarg SI. Selective non-intubation of a silicone tube in external dacryocystorhinostomy. Acta Ophthalmol Scand. 2007;85:329-332.
9. Buttanri IB, Serin D. Silicone Intubation Indications in External Dacryocystorhinostomy. Med Hypothesis Discov Innov Ophthalmol. 2014;3:101-102.
10. Nemet AY, Fung A, Martin PA, Benger R, Kourt G, Danks JJ, Tong JC. Lacrimal drainage obstruction and dacryocystorhinostomy in children. Eye (Lond). 2008;22:918-924.
11. Anderson RL, Edwards JJ. Indications, complications and results with silicone stents. Ophthalmology. 1979;86:1474-1487.
12. Ali MJ, Manderwad G, Naik MN. The Microbiological Spectrum and Antibiotic Sensitivity Profile of Extubated Silicone Stents Following Dacryocystorhinostomy. Orbit. 2013;32:298-303.
13. Kim SE, Lee SJ, Lee SY, Yoon JS. Clinical Significance of Microbial Growth on the Surfaces of Silicone Tubes Removed From Dacryocystorhinostomy Patients. Am J Ophthalmol. 2012;153:253-257.
14. Graham JE, Moore JE, Jiru X, Moore JE, Goodall EA, Dooley JS, Hayes VE, Dartt DA, Downes CS, Moore TC. Ocular pathogen or commensal: a PCR-based study of surface bacterial flora in normal and dry eyes. Invest Ophthalmol Vis Sci. 2007;48:5616-5623.
15. Suto C, Morinaga M, Yagi T, Tsuji C, Toshida H. Conjunctival sac bacterial flora isolated prior to cataract surgery. Infect Drug Resist. 2012;5:37-41.
16. Haug RH. Microorganisms of the nose and paranasal sinuses. Oral Maxillofac Surg Clin North Am. 2012;24:191-196.
17. Sellart-Altisent M, Torres-Rodríguez JM, Gómez de Ana S, Alvarado-Ramírez E. Nasal fungal microbiota in allergic and healthy subjects. Rev Iberoam Micol. 2007;24:125-130.
18. Nemati S, Mojtahedi ALI, Montazeri S, Pahlavan PA. Microbial etiology and antibacterial resistance patterns of dacryocystorhinostomy cases in the north of iran. Asian J Pharm Clin Res. 2018;11:407-411.
19. Goel R, Nagpal S, Kamal S, Kumar S, Mishra B, Loomba PS. Study of microbial growth on silicone tubes after transcanalicular laser-assisted dacryocystorhinostomy and correlation with patency. Nepal J Ophthalmol. 2016;8:119-127.
20. Charalampidou S, Tim F. Does the Timing of Silicone Tube Removal Following External Dacryocystorhinostomy Affect Patients Symptoms ? Orbit. 2009;28:115-119.
21. Becker BB. Cultures of Proximal and Distal Segments of Silicone Tubes After Dacryocystorhinostomy. Ophthal Plast Reconstr Surg. 2019;35:42-44.
22. Francolini I, Vuotto C, Piozzi A, Donelli G. Antifouling and antimicrobial biomaterials: an overview. APMIS. 2017;125:392-417.

DOI: 10.4274/tjo.galenos.2020.48376
Turk J Ophthalmol 2021;51:218-224

Original Article

Evaluation of the Effects of Silicone Oil on the Macula with Optical Coherence Tomography in Patients with Rhegmatogenous Retinal Detachment

Duygu Er*, Hakan Öner**, Mahmut Kaya**, Oya Dönmez***

*University of Health Sciences Turkey Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital, Ankara, Turkey
**Dokuz Eylül University Faculty of Medicine, Department of Ophthalmology, İzmir, Turkey
***Private Tınaztepe Galen Hospital, İzmir, Turkey

Abstract

Objectives: The effects of silicone endotamponade duration on the macula were evaluated in patients with rhegmatogenous retinal detachment.

Materials and Methods: Sixty-five eyes of 65 cases with rhegmatogenous retinal detachment that underwent pars plana vitrectomy and silicone endotamponade were included in the study. All cases were classified in three groups according to duration of silicone tamponade: ≤3 months, 3-6 months, and ≥6 months. All cases were evaluated at 1 week, 1 month, and 3 months after silicone injection, just before and at 1 month after silicone removal in terms of intraretinal pathologies in the macula by using spectral-domain optical coherence tomography (SD-OCT).

Results: Sixteen (26.6%) of the patients were female and 49 (75.4%) were male. The mean age of the patients was 58.1±12.1 years (18-82); the mean follow-up time was 12.4±4 months (6-20). The mean duration of silicone tamponade was 6.7±2.3 months (2-12). In 26.6% of patients with ellipsoid zone/outer limiting membrane defect, a statistically significant improvement in reflectivity was detected after silicone oil removal (p=0.016). There was a significant increase in central foveal thickness after silicone removal in eyes with duration of silicone more than 3 months (p=0.003 for 3-6 months, p=0.006 for ≥6 months). The prevalence of cystoid macular edema before and after silicone removal was also significantly higher in the eyes with silicone duration of 6 months or longer (p<0.001).

Conclusion: In eyes with silicone endotamponade, structural changes in the macula may differ according to the duration of silicone oil in the eye.

Keywords: Macula, optical coherence tomography, pars plana vitrectomy, rhegmatogenous retinal detachment, silicone oil

Introduction

Silicone oil was first used in vitreoretinal surgery by Cibis in 1962 and has since become one of the preferred intraocular tamponade materials in the treatment of retinal detachment cases.[1] Due to its high postoperative anatomical and functional success, it is often used in the surgical treatment of proliferative vitreoretinopathy (PVR), recurrent detachments, proliferative diabetic retinopathy, retinal detachment associated with giant retinal tears, and detachments complicated by ocular trauma.[2] However, complications such as silicone-induced cataract, glaucoma, corneal decompensation, and band keratopathy, as well as microstructural alterations due to mechanical or biochemical damage to the retina have been reported when used as a long-term intraocular tamponade.[3,4,5] A study in rabbit eyes showed that silicone infiltrated the internal limiting membrane (ILM) tissue after 3 months and then passed the ILM and reached the inner retinal layers after 12-18 months.[6]

Address for Correspondence: Duygu Er, University of Health Sciences Turkey Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital, Ankara, Turkey
E-mail: dr.duyguer@hotmail.com **ORCID-ID:** orcid.org/0000-0003-4114-2315
Received: 06.06.2020 **Accepted:** 23.09.2020

Cite this article as: Er D, Öner H, Kaya M, Dönmez O. Evaluation of the Effects of Silicone Oil on the Macula with Optical Coherence Tomography in Patients with Rhegmatogenous Retinal Detachment. Turk J Ophthalmol 2021;51:218-224

In some cases, visual results are not very satisfactory despite anatomically successful treatment of the retinal detachment.[7,8] Postoperative low visual acuity may result from epiretinal membrane, cystoid macular edema (CME), retinal folds, and/or persistent foveal detachment.[9,10,11]

In order to reduce these complications, silicone should be removed from the eye as soon as stable retinal attachment is achieved. Silicone removal within 3-6 months postoperatively is generally recommended to minimize the potential side effects, but this period is still controversial. Although silicone removal causes relapse in 3.5-13.2% of cases, preventing silicone emulsification is still used as the main criterion instead of silicone-induced macular changes.[12,13]

Spectral domain optical coherence tomography (SD-OCT) provides high-resolution cross-sectional retinal images regardless of silicone. This enables microstructural changes in the retina to be monitored by SD-OCT even in the presence of silicone.[14,15]

In this prospective study, we aimed to evaluate intraretinal alterations in the macula with different periods of silicone duration using SD-OCT.

Materials and Methods

This prospective study included patients who underwent surgical treatment for rhegmatogenous retinal detachment in the retina unit of Dokuz Eylul University, Department of Ophthalmology, had regular follow-up, and showed complete macular attachment. Ethics committee approval was obtained before the study and the potential risks and benefits of surgery were explained to all patients and informed consent forms were obtained in accordance with the principles of the Declaration of Helsinki.

Patients with age-related macular degeneration, vitreomacular traction, retinal vein occlusion, diabetic retinopathy, retinal dystrophy, uveitis, glaucoma, corneal opacity, and posterior capsule opacification and those who developed recurrent detachment after silicone removal were not included in the study. In addition, patients with disrupted ellipsoid zone and/or external limiting membrane (EZ/ELM) reflectivity, CME, or subfoveal fluid (SFF) at postoperative 1 week examination were also excluded from the study.

The patients' age, sex, best corrected visual acuity (BCVA), intraocular pressure, and anterior segment findings were recorded preoperatively. All operations were performed by the same physician (H.Ö.). In all cases, a 3-port 23- or 25-gauge pars plana vitrectomy was performed. The detached retina was flattened using perfluorocarbon fluid (perfluorodecalin) and endolaser photocoagulation was performed around the tears and in 360 degrees to the retina. After air-fluid exchange, 1300 cSt silicone oil (Oxane®, Bausch & Lomb, Inc.) was used in patients with PVR stage B and C. During silicone removal, the silicone oil was actively removed by 23 or 25-gauge transconjunctival vitrectomy. Retinal reattachment was observed in all patients in follow-up.

The patients were divided into three groups according to the duration of intraocular silicone endotamponade: 3 months or less, 3-6 months, and 6 months or more. These groups were evaluated for microstructural alterations in the macula using SD-OCT (Heidelberg HRA-OCT Spectralis®, Heidelberg Engineering GmbH, Heidelberg, Germany). SD-OCT examinations were mainly focused on EZ/ELM damage (photoreceptor layer effects), central macular thickness (CMT), and the presence of CME and SFS. EZ/ELM damage was defined as disrupted integrity of the reflective lines over the retinal pigment epithelium (RPE) in the 2.0 mm diameter area corresponding to the central fovea. CME was defined as the presence of intraretinal cystoid fluid accumulations and intraretinal hyporeflective areas separated by hyperreflective septa. The presence of a dome-shaped subretinal hyporeflective space centered on the fovea was evaluated as SFF. In patients with SFF, CMT was measured manually in the SFS region by calculating the retinal thickness remaining over the fluid.

BCVA, intraocular pressure, fundus examination, and SD-OCT measurements were performed routinely at 1 week, 1 month, and 3 months after detachment surgery, before silicone removal, and at 1 month after silicone removal. Images were obtained from a 20x20 degree (6x6 mm) scan area consisting of 49 sections using horizontal scan patterns. OCT findings at 1 week after silicone injection were compared with later OCT findings.

Statistical Analysis

The data were analyzed using SPSS 15.0 software (SPSS Inc, Chicago, IL, USA). Descriptive analysis was performed using mean, standard deviation, and percentage values. The Kolmogorov-Smirnov test was used to evaluate whether the data showed normal distribution. Measurements were compared between eyes with parametric t-test or nonparametric Mann-Whitney U test. OCT findings and CMT in the silicone duration groups were compared using Kruskal-Wallis test. Statistical significance was accepted as $p<0.05$.

Results

The study included 65 eyes of 65 patients who underwent anatomically successful surgical treatment of rhegmatogenous retinal detachment. Of the patients, 16 (26.6%) were women and 49 (75.4%) were men. The patients' mean age was 58.1±12.1 years (range, 18-82). The mean follow-up period was 12.4±4 months (range, 6-20). All patients had a posterior chamber intraocular lens before pars plana vitrectomy. Surgical treatment consisted of 3-port, 23 or 25-gauge pars plana vitrectomy, and silicone tamponade in all cases. The mean duration of intraocular silicone was 6.7±2.3 months (range, 2-12).

There were 12 eyes in the group with ≤3 months silicone duration, 31 eyes in the 3-6 months group, and 22 eyes in the ≥6 months group. Intraretinal SD-OCT findings according to intraocular silicone duration are shown in Tables 1, 2, and 3.

The results of the statistical analysis comparing CMT values measured after vitrectomy and silicone removal are shown in Table 4. Eyes with silicone duration longer than 3 months showed a statistically significant increase in CMT between

values measured after silicone injection and after silicone removal ($p<0.05$), while this increase was not significant in the group with silicone duration of 3 months or less ($p>0.05$).

When SD-OCT findings were compared according to intraocular silicone duration, no difference was observed between the groups in terms of EZ/ELM changes or SFS, whereas the development of CME was significantly more frequent in the group with silicone duration of 6 months or more than in the other two groups ($p<0.001$). Of all eyes that developed CME, 21.5% showed an increase in CME after silicone removal, but this increase was not significant ($p>0.05$).

Comparison of SD-OCT findings immediately before and after silicone intake in all eyes regardless of intraocular silicone duration revealed significant differences in EZ/ELM continuity and SFF ($p=0.016$ and $p<0.001$, respectively). Restored reflectivity was observed in 26.6% of patients with EZ/ELM defects after silicone removal, which was determined to be statistically significant ($p=0.016$). Statistically significant SFS resolution was observed after silicone removal in all patients (100%) with SFS ($p<0.001$) (Figures 1, 2, 3).

Discussion

Depending on how long the silicone oil used to ensure anatomical success of retinal detachment surgery remains in the eye, there may be additional complications such as cataracts, glaucoma, and keratopathy, as well as microstructural damage to the retina due to mechanical stress or biochemical toxicity, and these changes can now be easily detected with SD-OCT.[6,7]

The duration of silicone oil in the eye can range from 2 to 13 months.[16,17,18,19,20,21,22] In many studies, it has been stated that the ideal timing of silicone removal is between 3 and 6 months, and silicone emulsifies after 6 months.[23] In contrast, Jiang and Li[23] stated that silicone removal should be performed at 2-3 months. Despite the lack of consensus on the timing of silicone removal, it has been established that it should be done when the retina is anatomically attached and stable.[15] Bae et al.[24] reported that the silicone removal time should be decided by clinicians based on a benefit-risk analysis. In our study, the mean silicone duration was 6.7±2.3 months (range, 2-12). Of the 65 patients, silicone remained in the eye for less than 6 months in 43 eyes (66.1%) and 6 months or longer in 22 eyes (33.8%).

Caramoy et al.[25] determined that silicone primarily caused thinning of the retinal ganglion cell layer and inner plexiform layer. This retinal thinning was assumed to be a result of mechanical pressure from the silicone on the retina. Therefore, SD-OCT studies have shown that timely silicone removal may result in resolution of microstructural changes in the retina, restoration of the photoreceptor layer and ELM, and improved vision.[24,25] Bae et al.[24] observed recovery of ELM reflectivity in 12.5% of patients after silicone removal and emphasized the importance of early silicone removal to prevent macular changes.

In our study, we evaluated EZ and ELM changes together as a better indicator of photoreceptor integrity, and SD-OCT confirmed that the EZ/ELM was intact at postoperative week 1 in all eyes included in the study. When EZ/ELM reflectivity was evaluated in correlation with silicone duration, of the 12 eyes with silicone duration ≤3 months, defects were observed in 1 eye (8.3%) at 1 month after silicone injection and in 3 eyes (25%) at 3 months or before silicone removal. The prevalence of defects in this group increased to 50% (6 eyes) after silicone removal. This increase may be due to persistent deterioration of the affected photoreceptors despite early silicone removal. In some studies,

Table 1. Optical coherence tomography (OCT) findings of patients with silicone duration ≤3 months

OCT finding	Postop 1 week	Postop 1 month	Postop 3 months	Before silicone removal	1 month after silicone intake
EZ/ELM defect	0	1 (8.3%)	3 (25%)	3 (25%)	6 (50%)
CME	0	4 (33.3%)	4 (33.3%)	4 (33.3%)	2 (16.7%)
SFF	0	1 (8.3%)	1 (8.3%)	1 (8.3%)	0

EZ/ELM: Ellipsoid zone ± external limiting membrane, CME: Cystoid macular edema, SFF: Subfoveal fluid, Postop: Postoperative

Table 2. Optical coherence tomography (OCT) findings of patients with silicone duration of 3-6 months

OCT finding	Postop 1 week	Postop 1 month	Postop 3 months	Before silicone removal	1 month after silicone intake
EZ/ELM defect	0	8 (25.8%)	9 (29%)	10 (32.3%)	3 (9.7%)
CME	0	3 (9.7%)	4 (12.9%)	4 (12.9%)	13 (41.9%)
SFF	0	4 (12.9%)	4 (12.9%)	4 (12.9%)	0

EZ/ELM: Ellipsoid zone ± external limiting membrane, CME: Cystoid macular edema, SFF: Subfoveal fluid, Postop: Postoperative

Table 3. Optical coherence tomography (OCT) findings of patients with silicone duration ≥6 months

OCT finding	Postop 1 week	Postop 1 month	Postop 3 months	Before silicone removal	1 month after silicone intake
EZ/ELM defect	0	2 (9.1%)	1 (4.5%)	2 (9.1%)	2 (9.1%)
CME	0	6 (27.3%)	10 (45.5%)	11 (50.0%)	13 (59.1%)
SFF	0	1 (4.5%)	1 (4.5%)	1 (4.5%)	0

EZ/ELM: Ellipsoid zone ± external limiting membrane, CME: Cystoid macular edema, SFF: Subfoveal fluid, Postop: Postoperative

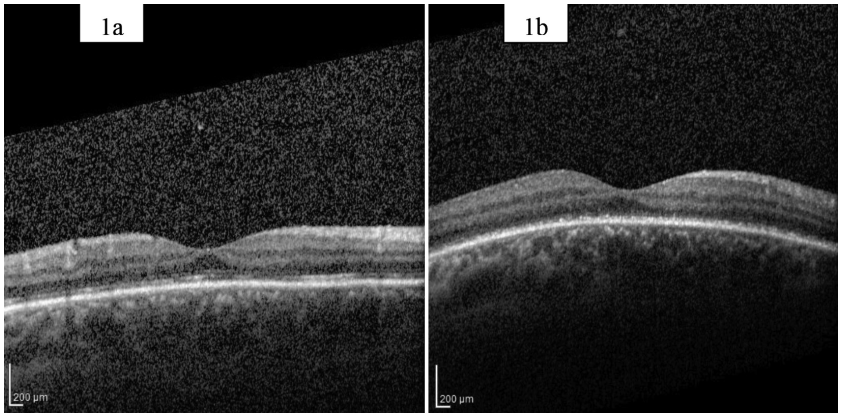

Figure 1. Optical coherence tomography sections of an eye with silicone duration of 5 months. a) Appearance of the macula 1 week after silicone injection. b) Immediately before silicone removal, irregularities in the ellipsoid zone and disruption of the external limiting membrane structure are observed

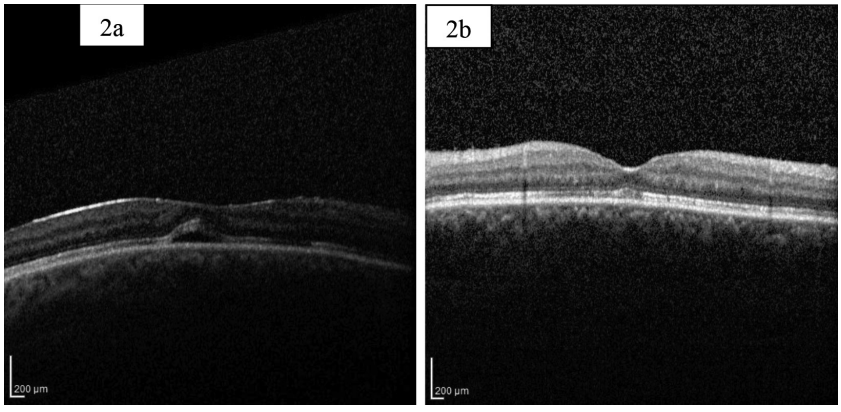

Figure 2. Optical coherence tomography sections of an eye with silicone duration of 4 months. a) Subretinal fluid is observed at 3 months. b) The subretinal fluid had spontaneously resolved by 1 month after silicone removal

Table 4. Comparison of central macular thickness values after silicone injection and removal

	CMT (µm)		
	Silicone duration ≤3 months	**Silicone duration 3-6 months**	**Silicone duration ≥6 months**
Postop 1 week p	258 0.220	229 **<0.001**	227 **<0.001**
Postop 1 month p	272 0.110	244 **<0.001**	256 **0.001**
Postop 3 months p	262 0.071	275 **0.007**	286 **0.006**
Before silicone removal p	280 0.084	276 **0.003**	315 **0.006**
1 month after silicone removal	286	334	366

Postop: Postoperative, CMT: Central macular thickness

it has been reported that the inflammatory response to silicone in the retina develops approximately 1 month after silicone injection and continues after silicone removal.[24,26]

In addition, silicone oil triggers the mitogenic effect in RPE cells.[27] Although silicone has been shown in the literature to be toxic to cultured RPE cells, no significant structural changes on OCT have been reported in the RPE after silicone injection.[28] We believe that there may be regeneration of the EZ/ELM layers over time, especially in eyes with intact RPE. However, we think that even if the RPE layer is intact, this regeneration process may start at the earliest 4 months after silicone administration, and degeneration may continue even if the silicone is removed during this period. In fact, unlike the eyes in which the silicone was removed earlier, we observed that the EZ/ELM defect improved significantly or did not worsen at 1 month after silicone removal when performed later than 3 months. Bae et al.[24] reported resolution of the EZ defect in 4.9% of eyes at 6-month follow-up, while Eibenberger et al.[29] reported this restoration in 33% of eyes at 3-year follow-up.

The influence of silicone on CME is not yet fully understood. However, CME is thought to occur secondary to an increase in vascular permeability due to the accumulation of inflammatory factors between the silicone and retina.[23,30,31,32] In the literature, CME has been detected at different rates in eyes with silicone. Bae et al.[24] reported that CME occurred in 19.6% of eyes that

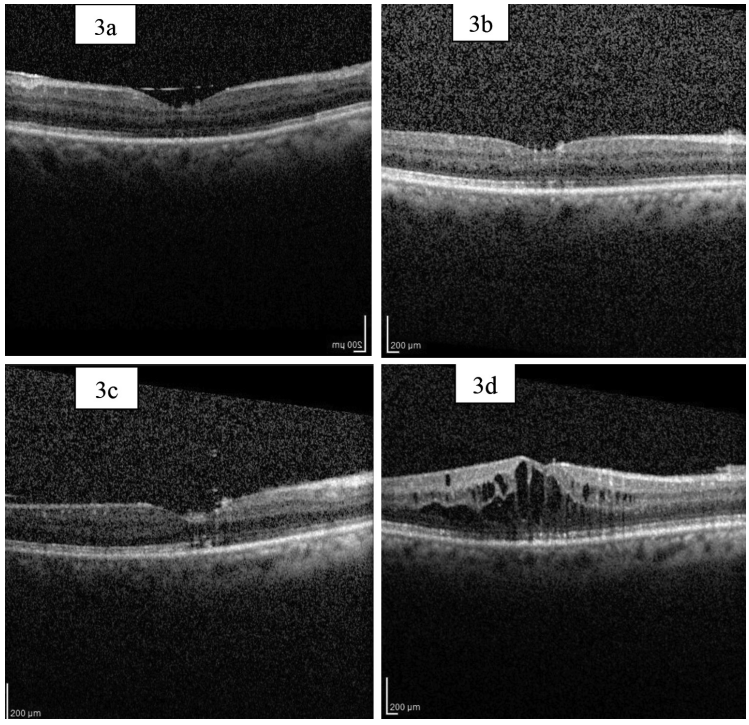

Figure 3. Optical coherence tomography sections of an eye with silicone duration of 7 months. a) Appearance of the macula at 1 week after silicone injection. b) Ellipsoid zone and external limiting membrane reflectivity are within normal limits 1 month after silicone removal. c) Disruption of ellipsoid zone and external limiting membrane reflectivity is observed immediately before silicone removal. d) Cystoid macular edema is observed 1 month after silicone removal

received silicone and resolved in all eyes after silicone removal. Bonnet[33] determined the prevalence of CME to be 51%. In contrast, Kiss et al.[32] observed CME in 17.1% of eyes that received silicone and reported that this rate increased to 47% after silicone removal. On the other hand, Eibenberger et al.[29] reported microcystic changes in the inner nuclear layer in 21% of eyes after silicone removal. In another study, it was stated that growth factors accumulating under the silicone diffuse into the vitreous cavity after silicone removal, thereby leading to CME resolution due to the decrease in the inflammatory response causing edema.[24] In our study, 44.6% of the eyes had CME after silicone injection, while this rate was 43.0% after silicone removal. When all eyes were examined together, CME was detected in 18 eyes (27.6%) immediately before silicone removal. CME occurred significantly more frequently in the group with silicone duration of 6 months or longer compared to the other two groups ($p<0.001$). After silicone removal, CME resolved in eyes with silicone duration of 3 months or less but increased in eyes with silicone duration longer than 3 months. Silicone duration longer than 6 months may increase its toxic effect and more CME due to the increased inflammatory response. CME may also continue after silicone removal due to the toxic retinal effects associated with prolonged silicone duration.

There are studies indicating that silicone causes some thinning of the inner retinal layers due to mechanical pressure on the retina, high intraocular pressure, or retinal dehydration.[34,35] It has also been reported in the literature that potassium released from Müller cells causes neuronal degeneration due to its inability to pass into the silicone, and for this reason retinal thinning can be observed in the presence of silicone endotamponade.[17] These series are supported by our findings that CMT measured after silicone removal increased significantly in the longer duration groups but not in eyes with silicone duration of less than 3 months.

Another phenomenon seen after surgery in vitrectomized eyes that receive silicone is the accumulation of SFF. It is reported to occur at rates of 0-40% after vitrectomy surgery.[31,32,33,34,35,36] Veckeneer et al.[37] reported that eyes with prolonged detachment were at risk of developing more intense SFF. However, in our study, no SFF was detected in SD-OCT measurements taken immediately after surgery but developed later in 9.2% of the eyes. Therefore, we think that this SFF may be a reactive exudation to silicone or that silicone may have an effect on the pump function of the RPE, which spontaneously resolved in all cases after silicone removal.

Conclusion

In conclusion, eyes with rhegmatogenous retinal detachment and silicone endotamponade show silicone-induced macular changes, and these structural disruptions can vary depending on the duration of silicone oil in the eye. We believe silicone removal before 3 months is appropriate to

minimize these structural changes in the retina. Moreover, we believe that the toxic effects on the retina may continue even after silicone removal and can be better demonstrated in new studies with larger patient groups.

Ethics

Ethics Committee Approval: Dokuz Eylul University Faculty of Medicine Non-invasive Research Ethics Committee no: 791-GOA.

Informed Consent: Obtained.

Peer-review: Externally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: H.Ö., Concept: D.E., Design: D.E., Data Collection or Processing: D.E., O.D., Analysis or Interpretation: D.E., M.K., Literature Search: D.E., OD., Writing: D.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. Cibis PA, Becker B, Okun E, Canaan S. The use of liquid silicone in retinal detachment surgery. Arch Ophthalmol. 1962;68:590-599.
2. Sima P, Zoran T. Long term results of vitreus surgery for proliferative diabetic retinopathy. Doc Ophthalmol. 1994;87:223-232.
3. No authors listed. The silicone study group. Vitrectomy with silicone oil or sulfur hexafluoride gas in eyes with severe proliferative vitreoretinopathy; results of a randomized clinical trial. Silicone study report 1. Arch Ophtalmol. 1992;110:770-779.
4. No authors listed. The silicone study group. Vitrectomy with silicone oil or sulfur hexafluoride gas in eyes with severe proliferative vitreoretinopathy; results of a randomized clinical trial. Silicone study report 2. Arch Ophtalmol. 1992;110:780-792.
5. Ünsal E, Karini B, Çubuk MÖ, Eltutar K. Silikon Yağı Tamponadı Kullanılmış Yırtıklı Retina Dekolmanı Olgularında Cerrahi Sonuçlarımız ve İlişkili Faktörler. Ret-Vit. 2018;27:109-116.
6. Suzuki M, Okada T, Takeuchi S, Ishii Y, Yamashita H, Hori S. Effect of silicone oil on ocular tissues. Jpn J Ophthalmol. 1991;35:282-291.
7. Avcı R, Şahin S, Yücel AA, Gelişken Ö. Kronik Oküler Hipotonide Cerrahi Tedavi Yaklaşımları. Ret-Vit.1996;2:562-527. http://retinavitreus.com/abstract.php?lang=tr&id=535
8. Guzel H, Özkan Ş, Şener B. Kliniğimizde son üç yıl içinde yapılan retina dekolmanı ameliyatı sonuçları. Turk J Ophthalmol. 1986;16:146-152.
9. Cleary PE, Leaver PK. Macular abnormalities in the reattached retina. Br J Ophthalmol. 1978;62:595-603.
10. Tani P, Robertson DM, Langworthy A. Prognosis for central vision and anatomic reattachment in rhegmatogenous retinal detachment with macula detached. Am J Ophthalmol. 1981;92:611-620.
11. Çetin EN, Scanlon C, Saxena S, Akduman L. The Visual Outcome and the Related Factors in Macula off Rhegmatogenous Retinal Detachment. Ret-Vit. 2013;21:183-188.
12. Oster SF, Mojana F, Bartsch DU, Goldbaum M, Freeman WR. Dynamics of the macular hole silicone oil tamponade interface with patient positioning as imaged by spectral domain optical coherence tomography. Retina. 2010;30:924-929.
13. Göbel W, Guthoff R. Morphology of macular holes after pars plana vitrectomy with silicone oil endotamponade: a pilot study with high resolution Fourier domain OCT. (Cirrus OCT) Ophtalmologe. 2010;107:452-459.
14. Choudhary MM, Saeed MU, Ali A. Removal of silicone oil: prognostic factors and incidence of retinal redetachment. Retina. 2012;32:2034-2038.
15. Teke MY, Balikoglu-Yilmaz M, Yuksekkaya P, Citirik M, Elgin U, Kose T, Ozturk F. Surgical outcomes and incidence of retinal redetachment in cases with complicated retinal detachment after silicone oil removal: univariate and multiple risk factors analysis. Retina. 2014;34:1926-1938.
16. Bozan E, Özdek Ş, Gürelik G, Konuk O, Hasanreisoğlu B. İntravitreal Silikon Alınması Sonrası Nüks Retina Dekolmanı. Turkiye Klinikleri J Ophthalmol. 2004;13:13-17.
17. Smith AJ, Telander DG, Zawadzki RJ, Choi SS, Morse LS, Werner JS, Park SS. High-resolution Fourier-domain optical coherence tomography and microperimetric findings after macula-off retinal detachment repair. Ophthalmology. 2008;115:1923-1929.
18. Wakabayashi T, Oshima Y, Fujimoto H, Murakami Y, Sakaguchi H, Kusaka S, Tano Y. Foveal microstructure and visual acuity after retinal detachment repair: imaging analysis by Fourier-domain optical coherence tomography. Ophthalmology. 2009;116:519-528.
19. Hutton WL, Azen SP, Blumenkranz MS, Lai MY, McCuen BW, Han DP, Flynn Jr HW, Ramsay RC, Ryan SJ. The effects of silicone oil removal. Silicone Study Report 6. Arch Ophthalmol. 1994;112:778-785.
20. Jonas JB, Budde WM, Knorr HL. Timing of retinal detachment after removal of intraocular silicone oil tamponade. Am J Ophthalmol. 1999;128:628-631.
21. Bassat IB, Desatnik H, Alhalel A, Treister G, Moisseiev J. Reduced rate of retinal detachment following silicone oil removal. Retina. 2000;20:597-603.
22. Laidlaw DA, Karia N, Bunce C, Aylward GW, Gregor ZJ. Is prophylactic 360-degree laser retinopexy protective? Risk factors for retinal redetachment after removal of silicone oil. Ophthalmology. 2002;109:153-158.
23. Jiang Y, Li X. The best timing of silicone oil removal. Zhonghua Yan Ke Za Zhi.1997;33:39-41.
24. Bae SH, Hwang JS, Gon Yu H. Comparative analysis of macular microstructure by spectral domain optical coherence tomography before and after silicone oil removal. Retina. 2012;32:1874-1883.
25. Caramoy A, Droege K, Kirchhof B, Fauser S. Retinal layers measurements in healthy eyes and in eyes receiving silicone oil-based endotamponade. Acta Ophthal. 2014;92:292-97.
26. Wolf S, Schön V, Meier P, Wiedemann P. Silicone oil-RMN3 mixture ("heavy silicone oil") as internal tamponade for complicated retinal detachment. Retina. 2003;23:335-342.
27. Asaria RH, Kon CH, Bunce C, Sethi CS, Limb GA, Khaw PT, Aylward GW, Charteris DG. Silicone oil concentrates fibrogenic growth factors in the retro-oil fluid. Br J Ophthalmol. 2004;88:1439-1442.
28. Inoue M, Iriyama A, Kadonosono K, Tamaki Y, Yanagi Y. Effects of perfluorocarbon liquids and silicone oil on human retinal pigment epithelial cells and retinal ganglion cells. Retina. 2009;29:677-681.
29. Eibenberger K, Sacu S, Rezar-Dreindl S, Schmidt-Erfurth U, Georgopoulos M. Silicone Oil Tamponade in Rhegmatogenous Retinal Detachment: Functional and Morphological Results. Curr Eye Res. 2020;45:38-45.
30. Purtskhvanidze K, Hillenkamp J, Tode J, Junge O, Hedderich J, Roider J, Treumer F. Thinning of inner retinal layers after vitrectomy with silicone oil versus gas endotamponade in eyes with macula-off retinal detachment. Ophthalmologica. 2017;238:124-132.
31. Lee SH, Han JW, Byeon SH, Kim SS, Koh HJ, Lee SC, Kim M. Retinal layer segmentation after silicone oil or gas tamponade for macula-on retinal detachment using optical coherence tomography. Retina. 2018;38:310-319.
32. Kiss CG, Richter-Müksch S, Sacu S, Benesch T, Velikay-Parel M. Anatomy and function of the macula after surgery for retinal detachment complicated by proliferative vitreoretinopathy. Am J Ophthalmol. 2007;144:872-877.
33. Bonnet M. Macular changes and fluorescein angiographic findings after repair of proliferative vitreoretinopathy. Retina. 1994;14:404-410.
34. Benson SE, Schlottmann PG, Bunce C, Xing W, Charteris DG. Optical coherence tomography analysis of the macula after vitrectomy surgery for retinal detachment. Ophthalmology. 2006;113:1179-1183.
35. Shimoda Y, Sano M, Hashimoto H, Yokota Y, Kishi S. Restoration of photoreceptor outer segment after vitrectomy for retinal detachment. Am J Ophthalmol. 2010;149:284-290.

36. Theodossiadis PG, Georgalas IG, Emfietzoglou J, Kyriaki TE, Pantelia E, Gogas PS, Moschos MN, Theodossiadis GP. Optical coherence tomography findings in the macula after treatment of rhegmatogenous retinal detachments with spared macula preoperatively. Retina. 2003;23:69-75.

37. Veckeneer M, Derycke L, Lindstedt EW, Meurs JV, Cornelissen M, Bracke M, Aken EV. Persistent subretinal fluid after surgery for rhegmatogenous retinal detachment: hypothesis and review. Graefes Arch Clin Exp Ophthalmol. 2012;250:795-802.

DOI: 10.4274/tjo.galenos.2020.07377
Turk J Ophthalmol 2021;51:225-230

Original Article

Immediate Sequential Bilateral Vitrectomy Surgery for Retinopathy of Prematurity: A Single Surgeon Experience

Şengül Özdek*, Mehmet Cüneyt Özmen*, Duygu Yalınbaş**, Hatice Tuba Atalay*, Demet Coşkun***

*Gazi University Faculty of Medicine, Department of Ophthalmology, Ankara, Turkey
**Cumhuriyet University Faculty of Medicine, Department of Ophthalmology, Sivas, Turkey
***Gazi University Faculty of Medicine, Department of Anesthesiology and Reanimation, Ankara, Turkey

Abstract

Objectives: We report the safety and efficacy of simultaneous bilateral vitrectomy for stage 4 and stage 5 retinopathy of prematurity (ROP).

Materials and Methods: Babies who had immediate sequential bilateral vitrectomy surgery for stage 4 or stage 5 ROP were included in this retrospective study. Clinical history, demographic characteristics of the patients, surgical procedure details, perioperative and postoperative ophthalmic and systemic complications, and postoperative anatomical success rates were evaluated. General anesthesia features were also recorded.

Results: Seventy eyes of 35 babies who had immediate sequential bilateral vitrectomy surgery for stage 4 or stage 5 ROP were reviewed. At the time of surgery, the mean age was 41.4±4.9 weeks. There was preoperative plus disease in 58.6% of the eyes. The mean surgery/eye ratio was 1.2. Mean anesthesia time was 95±64 minutes. The mean follow-up was 28.1 months (3 to 84 months). Anatomical success was 95.7% for stage 4A (44/46 eyes), 83.3% for stage 4B (15/18 eyes), and 50% for stage 5 (3/6 eyes) ROP. Patients with stage 5 ROP had significantly less anatomical success than stage 4A and 4B (p=0.004). None of the patients had endophthalmitis and anesthesia-related severe complications.

Conclusion: Immediate sequential bilateral vitrectomy surgery can be considered an option for patients with active bilateral stage 4 and stage 5 ROP. The risk of endophthalmitis should be weighed against the risks of disease progression and anesthesia-related complications.

Keywords: Retinopathy of prematurity, sequential bilateral surgery, vitrectomy

Introduction

The incidence of retinopathy of prematurity (ROP) is increasing with advances in neonatal care.[1] Even with careful screening and treatment, ROP still progresses to stage 4 or 5 and needs surgery in 12% of eyes.[2] Treatment for stage 4 and stage 5 ROP includes scleral buckling and vitrectomy with or without lensectomy.[3,4,5,6,7] Lens-sparing vitrectomy (LSV) in stage 4 and 5 ROP offers the greatest hope for visual rehabilitation of the phakic eye, but the decision to proceed with surgery must be weighed against the risks of iatrogenic retinal breaks and surgical aphakia, complications that have more significant consequences for infants than for adults.[8,9]

The timing of surgery for ROP should be planned carefully. Early intervention when the eye is highly vascularized can have as devastating results as waiting too long for the eye to become quiet.[10,11,12,13,14] The ideal timing for vitrectomy is when vascular

Address for Correspondence: Şengül Özdek, Gazi University Faculty of Medicine, Department of Ophthalmology, Ankara, Turkey
Phone: +90 530 966 21 42 E-mail: sozdek@gazi.edu.tr **ORCID-ID:** orcid.org/0000-0002-7494-4106
Received: 14.05.2020 **Accepted:** 06.09.2020

Cite this article as: Özdek Ş, Özmen MC, Yalınbaş D, Atalay HT, Coşkun D. Immediate Sequential Bilateral Vitrectomy Surgery for Retinopathy of Prematurity: A Single Surgeon Experience. Turk J Ophthalmol 2021;51:225-230

activity is reducing and retinal detachment is beginning.[11] When both eyes show similar findings and need immediate surgery, waiting for days or weeks between eyes might lead to blindness in the latter eye in high-risk ROP cases.[11,15,16] Furthermore, general anesthesia-related complications increase in preterm babies when anesthesia is repeated after a short interval. Both of these factors encourage performing bilateral surgery in the same session (i.e., immediate sequential bilateral vitrectomy surgery).[11,13,16,17,18,19,20,21,22]

Here, we present our experience with immediate sequential bilateral vitrectomy surgery (ISBVS) for stage 4 and 5 ROP cases.

Materials and Methods

Patient Selection

This study is a retrospective cohort study conducted in the Ophthalmology Department of Gazi University Medical School in Ankara, Turkey. Institutional Review Board approval was obtained. The study complied with the Health Insurance Portability and Accountability Act of 1996 and adhered to the tenets of the Declaration of Helsinki.

Charts from September 2010 to October 2019 were reviewed. Patients who underwent surgery for ROP and had surgery on both eyes on the same day were identified. The detailed risks of simultaneous surgery, such as the risk of bilateral endophthalmitis, were explained to the parents of babies who underwent simultaneous bilateral surgery and their informed consent was obtained. All of the patients presented with stage 4 or stage 5 ROP.

Surgical Procedures

All surgeries were performed by the same surgeon (S.O.). None of the patients received anti-VEGF or laser treatment to prepare for surgery in the preoperative period due to an increased risk of retinal traction. Before each surgery, a fundus examination was done with a binocular indirect ophthalmoscope to determine the sclerotomy sites. All sclerotomies were performed 1.5 mm from the limbus, after conjunctival peritomy, and all were sutured at the end of the surgery. Superior sclerotomies were 23 gauge (G), with or without (valved) cannulas, and the inferotemporal sclerotomy was made with a 23G 4-mm sutured infusion cannula. Following central core vitrectomy, detachment of the posterior hyaloid in the posterior pole was attempted with the help of diluted triamcinolone. If the posterior hyaloid did not detach easily, the vitreous was only trimmed for a more complete vitrectomy, leaving the posterior hyaloid attached. Even if the posterior hyaloid could be detached easily from the posterior pole, detachment beyond the arcuate was not attempted, and peripheral detachment was avoided to decrease the risk of retinal break and hemorrhage. LSV was intended for each case when possible; however, the lens was sacrificed when there was extensive anterior traction extending up to the posterior lens capsule or tractions extending to the far periphery. Fibrovascular membranes that caused retinal tractions were removed or trimmed as much as possible to relieve the retina. Endolaser was applied to the peripheral avascular retina intraoperatively as needed. At the end of the surgery, air or gas was used as a tamponade at the surgeon's discretion. At the end of each surgery, a subconjunctival antibiotic and steroid mixture was injected. Then the surgical team re-scrubbed, a new set of surgical instruments were used, and the fellow eye was prepared as a new patient.[12,14] All of the babies were examined on postoperative day 1, at week 2, month 1, 3, and 6, and every 6 months thereafter.

General Anesthesia

General anesthesia was induced with sevorane, combined with O_2 and air, and analgesia was achieved with remifentanil infusion during the operation in all patients. Laryngeal mask or endotracheal intubation was selected according to the anesthesia teams' experience. Postoperatively, the patients were transferred to the neonatal ward or neonatal intensive care unit (NICU), with incubators with 2 l/min O_2.

Chart Reviews

From the patient charts, gestational age, birth weight, sex, stage of ROP and presence of plus disease at the time of surgery, previous treatments, age at the time of surgery, intraoperative procedures, complications (vitreous hemorrhages necessitating secondary surgery, iatrogenic break, lensectomy need, and glaucoma), postoperative results including anatomical outcome and visual acuity results (Lea, tumbling E, and ETDRS charts were used according to patient cooperation), and follow-up time were collected. Additionally, regarding general anesthesia, duration of anesthesia, induction technique, airway management (endotracheal intubation or laryngeal mask), analgesia modalities, perioperative adverse events, and need for postoperative monitoring or ventilation in a post-anesthesia care unit and/or NICU were recorded.

Outcomes

Anatomical success was defined as complete retinal reattachment with undistorted or minimally distorted macula for stage 4A, complete retinal attachment or partial residual peripheral retinal detachment not involving the macular region for stage 4B, and attachment of any part of posterior pole for stage 5.

Statistical Analysis

Statistical analysis was performed with SPSS version 20.0 software (IBM Corp, Armonk, NY, USA). Continuous data were expressed as mean ± standard deviation and qualitative data were expressed as frequency and percent. The distribution of the data was analyzed using Shapiro-Wilk test. Differences between groups were analyzed with Mann-Whitney U (for two groups with continuous variables) and the Kruskal-Wallis test with Conover test as post-hoc analysis (for more than two groups with continuous variables). For categorical data, the Pearson χ^2 test was used with Bonferroni correction. A p value less than 0.05 was considered statistically significant.

Results

Patients

Seventy eyes of 35 patients who underwent surgery on both eyes simultaneously were included in the study. Mean gestational age at birth was 28.6±2.9 weeks (range: 23 to 35 weeks), mean birth weight was 1284.7±463.2 g (range: 670 to 2500 g). Eighteen of 35 patients were male (51.4%). The mean gestational age at surgery was 41.4±4.9 weeks (range: 33 to 58 weeks). Forty-six eyes were stage 4A, 18 eyes were stage 4B, and 6 eyes were stage 5. Patients were followed-up for 28.1±19.9 months (range: 3 to 84 months). The ROP staging and preoperative characteristics are summarized in Table 1. There was plus disease in 41 eyes (58.6%) preoperatively. Patients with stage 4A and 5 ROP had statistically significantly more plus disease than those with stage 4B (p=0.002, Pearson χ^2 test). Sixty eyes had received preoperative laser treatment (85.7%). Eight eyes did not receive any treatment before surgery (11.4%). Of the 60 eyes that received preoperative laser treatment, 24 (34.3%) had also received anti-VEGF (0.625 mg bevacizumab) treatment before surgery. Laser and anti-VEGF treatments had been performed elsewhere before referral of the babies to our center for surgery. The mean interval between initial laser treatment and surgery was 29.7±22 days and the mean interval between anti-VEGF treatment and surgery was 14.4±7.2 days. The mean post-conceptional age at surgery was statistically significantly lower in stage 5 eyes than in stage 4A and 4B eyes (p=0.03, Kruskal-Wallis test).

Surgery

LSV could be performed in most cases, and lensectomy-vitrectomy was done in 13 eyes (18.6%) due to extensive anterior fibrovascular proliferation (Table 2). Subjects with stage 4B ROP had more lensectomy than stage 4A and 5 (p=0.03, Pearson χ^2 test). Posterior hyaloid detachment (PHD) could be performed in 34 eyes (48.6%). Air was the tamponade of choice in the majority of the eyes (75.7%). Sixteen eyes (22.9%) needed additional surgery due to vitreous hemorrhage, residual traction, or cataract (mean interval between surgeries, 11.6±14.9 weeks). The mean surgery/eye ratio was 1.2. Secondary surgery need was significantly more likely in stage 5 eyes (p=0.02, Pearson χ^2 test) (Table 2). Postoperative vitreous hemorrhage was observed in a total of 8 eyes (11.4%), 7 of which had a preoperative plus disease. The rate of postoperative vitreous hemorrhage was statistically significantly higher in eyes with preoperative plus disease than those without (p=0.04, Pearson χ^2 test). However, this rate did not differ significantly between eyes that received preoperative anti-VEGF treatment (2/26 eyes) and those that did not (6/44 eyes, p=0.36, Pearson χ^2 test).

Postoperative Outcomes

Overall anatomical success was achieved in 62 eyes (88.6%), being highest in eyes with stage 4A (95.7%) and lowest in eyes with stage 5 (50%). Stage 5 eyes had significantly less anatomical success than stage 4A and 4B (p=0.004, Pearson χ^2 test).

Thirty-four patients finished their first year follow-up. Fifty-nine of the eyes were able to follow small objects at 1 year. Forty-three eyes had refraction recorded in their charts in the first year. The refractive status of the phakic eyes and aphakic eyes were -6.51±4.92 and 16.21±7.6, respectively (p<0.001, Mann-Whitney U test). Among patients with longer follow-up, the mean LogMAR acuity was 1.1±0.27 (range: 0.5-1.5, 16 eyes) at 3 years and 0.76±0.31 (range: 0.5-1.5, 9 eyes) at 4 years.

Success rates tended to be lower in the presence of preoperative plus disease (85.4% vs. 93.1%) and postoperative vitreous hemorrhage (75% vs. 90.3%), but the difference was not statistically significant (p=0.45 and p=0.22, Pearson χ^2 test for all, respectively). Anatomical success was achieved in 14 of the 16 reoperated eyes.

Twelve patients had esotropia, three of which underwent strabismus surgery, and one of the patients had exotropia. Seven eyes had glaucoma; five were controlled with topical

Table 1. Demographics and baseline characteristics of patients who had immediate sequential bilateral vitrectomy surgery for stage 4 or 5 retinopathy of prematurity

Demographics and baseline characteristics	All eyes (n=70)	Stage 4A (n=46)	Stage 4B (n=18)	Stage 5 (n=6)	p value*
Gestational age (weeks), mean ± SD	28.6±2.9	28.7±3.1	29.1±2.8	26.8±1.3	0.15
Birth weight (g), mean ± SD	1284.7±463.2	1306.5±467.9	1330.0±483.8	981.7±268.9	0.20
Sex (male/female), n	36/34	25/21	10/8	1/5	0.20
Plus disease, n (%)	41 (58.6)	30 (65.2)	5 (27.8)	6 (100)	**0.002**
Preoperative treatment, n (%)					
None	8 (11.4)	4 (8.7)	4 (22.2)	0 (0)	0.43
Laser only	36 (51.4)	23 (50)	8 (44.4)	5 (83.3)	0.43
Anti-VEGF only	2 (2.9)	2 (4.3)	0 (0)	0 (0)	0.43
Laser and anti-VEGF	24 (34.3)	17 (37)	6 (33.3)	1 (16.7)	0.43
Postconceptional age at surgery (weeks), mean ± SD	41.4±4.9	41.2±4.6	43.2±5.8	37.5±2.7	**0.03**

*Pearson χ^2 test was used for categorical variables and Kruskal-Wallis test was used for numeric variables. Boldface values indicate statistical significance (p<0.05).
SD: Standard deviation, n: Number, VEGF: Vascular endothelial growth factor

Table 2. Surgical procedures and outcomes of patients who had immediate sequential bilateral vitrectomy surgery for ROP					
Surgical procedures and outcomes	**All eyes (n=70)**	**Stage 4A (n=46)**	**Stage 4B (n=18)**	**Stage 5 (n=6)**	**p value***
Lens sparing vitrectomy, n (%)	57 (81.4)	41 (89)	11 (61)	5 (83)	**0.03****
Lensectomy and vitrectomy, n (%)	13 (18.6)	5 (11)	7 (39)	1 (17)	
Tamponade, n (%)					
Air	53 (75.7)	35 (76)	12 (66.7)	6 (100)	0.32
Gas	3 (4.2)	1 (2.2)	2 (11)	0	
Induction posterior hyaloid detachment, n (%)	34 (48.6)	20 (43)	10 (55.5)	4 (66.7)	0.83
Postoperative vitreous hemorrhage, n (%)	8 (11.4)	5 (11)	1 (5.6)	2 (33.3)	0.36
Secondary surgery, n (%)	16 (22.9)	9 (19.4)	4 (22.2)	3 (50)	**0.02**
Anatomical success, n (%)	62 (88.6)	44 (95.7)	15 (83.3)	3 (50)	**0.004**

*Pearson χ^2 test was used for categorical variables. Boldface values indicate statistical significance ($p<0.05$)
ROP: Retinopathy of prematurity

medical treatment, while two eyes of one patient needed glaucoma surgery (right eye: Ahmed glaucoma valve and left eye: Harms trabeculotomy). Five eyes that developed glaucoma were phakic, and there was no statistically significant difference between phakic and aphakic eyes in terms of glaucoma development (p=0.95, Pearson χ^2 test). None of the patients had endophthalmitis. Ocular and systemic complications are summarized in Table 3.

General Anesthesia

The mean duration of general anesthesia was 95±64 minutes. There was no difference between the anatomical success group and non-success group (p=0.82, Mann-Whitney U test). The laryngeal mask was used in 8 patients (22.8%). Two patients were admitted to the NICU, one due to the need for mechanical ventilation and the other because of hydrocephalus. The patient who needed mechanical ventilation had longer general anesthesia duration (205 minutes) and was extubated 2 hours after surgery. There were no severe anesthesia-related complications such as requirement for re-intubation, desaturation, apneic episodes, seizures, cyanosis, cardiac arrest, aspiration pneumonia, embolism, malignant hyperthermia, sepsis, or death (Table 3).

Table 3. Ocular and systemic complications	
Complications	**n (%)**
Ocular	
Choroidal hemorrhage	0
Hypotony	0
Endophthalmitis	0
Cataract	2 (2.8)
Iatrogenic retinal tear†	1 (1.4)
Vitreous hemorrhage	8 (11.4)
Glaucoma	7 (10)
Strabismus (esotropia)	12 patients (34)
Nystagmus	14 (20)
Phthisis	3 (4.3)
Systemic	
Postoperative need for NICU	2 patients (5.7)
Postoperative mechanical ventilation	1 patient (2.8)

†Peripheral superior iatrogenic retinal tear treated with laser and gas tamponade. Retina remained attached during 44 months of follow-up.
NICU: Neonatal intensive care unit

Discussion

ISBVS in ROP can be rationalized in many ways. The patients are infants with many comorbidities, including bronchopulmonary dysplasia (BPD), which increases the risk of anesthesia administration and sometimes makes it impossible to repeat anesthesia.[17,18,19,22] Infants with BPD have especially high risk of developing respiratory problems such as bronchospasm and atelectasis in the perioperative period.[23] Additionally, when there is active ROP in both eyes, delaying surgery in the second eye may not be feasible.[15]

Bilateral simultaneous cataract surgeries in pediatric patients have been previously reported.[20,21,24,25] Postoperative endophthalmitis is the most frightening complication after bilateral simultaneous intraocular surgeries. Previous studies reported endophthalmitis rates in pediatric and adult cataract surgery between 0.15 and 1.1%.[25] The endophthalmitis risk after adult vitreoretinal surgery is reported to be between 0.03% and 0.08%.[26,27,28] Although pediatric vitrectomy surgeries might not have similar endophthalmitis rates and it is not certain that each eye has independent endophthalmitis risk[29], it has been calculated that the risk for bilateral endophthalmitis after ISBVS would be 1 case in 150,000 to 1,000,000.[13] This rate is much lower than the general anesthesia-related mortality rate in the pediatric population. To reduce the risk of bilateral endophthalmitis, we treated each eye as a new patient, as described in the methods.[11,13] None of our patients had endophthalmitis.

The mortality rate for pediatric patients subjected to general anesthesia ranges between 0.2 and 12.8 per 10,000.[21,30] It is estimated that simultaneous bilateral surgery reduces anesthesia-

related complications by 50% for sequential surgery, especially in high-risk patients such as premature infants.[20] For preterm neonates, the risks of general anesthesia, such as intracranial hemorrhage, hypoxia, oxygen toxicity, postoperative apnea, bradycardia, and hypothermia, are greater than for term infants.[22] Subjecting the infant to this risk for a second time in a short period might increase the risk of anesthesia-related complications. Besides, deterioration of the infant's general status after the first surgery may delay the surgery of the contralateral eye. None of our patients had serious complications related to general anesthesia.

We performed ISBVS when both eyes had active stage 4 and 5 ROP disease, and delaying a second surgery would lead to disease progression in the latter eye. Most of these bilateral surgeries were done on stage 4A ROP because of the relatively short surgical time and less general anesthesia time. This complies with a previous international multicenter study, which suggests performing ISBVS for patients in whom the surgical intervention would be relatively short.[13]

Shah et al.[11] reported favorable results in their cases of simultaneous bilateral surgeries only in stage 4A ROP. Although most of our cases were also stage 4, we had 6 eyes with stage 5 ROP in our series, though the fellow eyes were stage 4 in all of these cases. Additionally, all of the stage 5 eyes were recent stage 5 cases who had been lasered before, which fixed the peripheral retina and prevented anterior closed-funnel retinal detachment.

Our results imply that preoperative plus disease is a good predictor of postoperative vitreous hemorrhage. PHD could be easily achieved in almost half of the eyes (48.6%) in the present series, contrary to the usual expectations in pediatric eyes. The anatomical success rate in our cases was 95.7% for stage 4A, 83.3% for stage 4B, and 50% for stage 5 eyes, similar to previous reports.[11,12,14,31,32,33]

A large international multicentric retrospective study on ISBVS for pediatric retinal disorders reported ISBVS to be a feasible and safe treatment paradigm for pediatric patients with bilateral vitreoretinal pathological features when repeated general anesthesia is undesirable or impractical.[13] These findings are supported by another recent study from India.[16]

Study Limitation

The drawbacks of this study are that it is retrospective and has a relatively small sample size because it is a single surgeon experience. However, there are only a few papers on this subject and it needs to be clarified with more experiences.

Conclusion

In conclusion, as ROP is usually a rapidly progressive disease when untreated during the active stage, ISBVS should be considered in bilateral cases when there is a risk of rapid progression in both eyes and when comorbidities of the infant make a second general anesthesia undesirable. All precautions should be taken to reduce the risk of endophthalmitis. The risk of endophthalmitis should be weighed over the risk of anesthesia-related complications and disease progression.

Ethics

Ethics Committee Approval: Gazi University Faculty of Medicine Clinical Research Ethics Committee (date: 19.06.2017, decision no: 312).

Informed Consent: Written consent was obtained from the legal guardian of all patients.

Peer-review: Internally and externally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: Ş.Ö., Concept: Ş.Ö., M.C.Ö., Design: Ş.Ö., M.C.Ö., Data Collection or Processing: Ş.Ö., M.C.Ö., D.Y., H.T.A., D.C., Analysis or Interpretation: Ş.Ö., M.C.Ö., Literature Search: M.C.Ö., D.Y., H.T.A., Writing: M.C.Ö., D.Y.

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. Painter SL, Wilkinson AR, Desai P, Goldacre MJ, Patel CK. Incidence and treatment of retinopathy of prematurity in England between 1990 and 2011: database study. Br J Ophthalmol. 2015;99:807-811.
2. Early Treatment For Retinopathy Of Prematurity Cooperative Group. Revised indications for the treatment of retinopathy of prematurity: results of the early treatment for retinopathy of prematurity randomized trial. Arch Ophthalmol. 2003;121:1684-1694.
3. Capone A Jr, Trese MT. Lens-sparing vitreous surgery for tractional stage 4A retinopathy of prematurity retinal detachments. Ophthalmology. 2001;108:2068-2070.
4. Greven C, Tasman W. Scleral buckling in stages 4B and 5 retinopathy of prematurity. Ophthalmology. 1990;97:817-820.
5. H Hinz BJ, de Juan E Jr, Repka MX. Scleral buckling surgery for active stage 4A retinopathy of prematurity. Ophthalmology. 1998;105:1827-1830.
6. Trese MT, Droste PJ. Long-term postoperative results of a consecutive series of stages 4 and 5 retinopathy of prematurity. Ophthalmology. 1998;105:992-997.
7. Zilis JD, deJuan E, Machemer R. Advanced retinopathy of prematurity. The anatomic and visual results of vitreous surgery. Ophthalmology. 1990;97:821-826.
8. Henderson BA, Schneider J. Same-day cataract surgery should not be the standard of care for patients with bilateral visually significant cataract. Surv Ophthalmol. 2012;57:580-583.
9. Shah PK, Prabhu V, Karandikar SS, Ranjan R, Narendran V, Kalpana N. Retinopathy of prematurity: Past, present and future. World J Clin Pediatr. 2016;5:35-46.
10. Maguire AM, Trese MT. Lens-sparing vitreoretinal surgery in infants. Arch Ophthalmol. 1992;110:284-286.
11. Shah PK, Narendran V, Kalpana N. Safety and efficacy of simultaneous bilateral 25-gauge lens-sparing vitrectomy for vascularly active stage 4 retinopathy of prematurity. Eye (Lond). 2015;29:1046-1050.
12. Shah PK, Narendran V, Kalpana N, Tawansy KA. Anatomical and visual outcome of stages 4 and 5 retinopathy of prematurity. Eye. 2009;23:176-180.
13. Yonekawa Y, Wu WC, Kusaka S, Robinson J, Tsujioka D, Kang KB, Shapiro MJ, Padhi TR, Jain L, Sears JE, Kuriyan AE, Berrocal AM, Quiram PA, Gerber AE, Paul Chan RV, Jonas KE, Wong SC, Patel CK, Abbey AM, Spencer R, Blair MP, Chang EY, Papakostas TD, Vavvas DG, Sisk RA, Ferrone PJ, Henderson RH, Olsen KR, Hartnett ME, Chau FY, Mukai S, Murray TG, Thomas BJ, Meza PA, Drenser KA, Trese MT, Capone A Jr. Immediate Sequential Bilateral Pediatric Vitreoretinal Surgery: An International Multicenter Study. Ophthalmology. 2016;123:1802-1808.
14. Yu YS, Kim SJ, Kim SY, Choung HK, Park GH, Heo JW. Lens-sparing vitrectomy for stage 4 and stage 5 retinopathy of prematurity. Korean J Ophthalmol. 2006;20:113-117.

15. Repka MX, Tung B, Good WV, Capone A Jr, Shapiro MJ. Outcome of eyes developing retinal detachment during the Early Treatment for Retinopathy of Prematurity study. Arch Ophthalmol. 2011;129:1175-1179.
16. Chandra P, Kumawat D, Tewari R, Sinha R. Surgical outcomes of immediate sequential bilateral vitreoretinal surgery for advancing retinopathy of prematurity. Indian J Ophthalmol. 2019;67:903-907.
17. Meza PA. Anesthesia for infants and children. In: Hartnett ME, Trese MT, Capone A Jr, eds. Pediatric retina. (2nd ed). Philadelphia; Lippincott Williams & Wilkins; 2014:577-585.
18. Sinner B, Becke K, Engelhard K. General anaesthetics and the developing brain: an overview. Anaesthesia. 2014;69:1009-1022.
19. Steward DJ. Preterm infants are more prone to complications following minor surgery than are term infants. Anesthesiology. 1982;56:304-306.
20. Guo S, Nelson LB, Calhoun J, Levin A. Simultaneous surgery for bilateral congenital cataracts. J Pediatr Ophthalmol Strabismus. 1990;27:23-25.
21. Magli A, Fimiani F, Passaro V, Iovine A. Simultaneous surgery in bilateral congenital cataract. Eur J Ophthalmol. 2009;19:24-27.
22. Taneja B, Srivastava V, Saxena KN. Physiological and anaesthetic considerations for the preterm neonate undergoing surgery. J Neonatal Surg. 2012;1:14.
23. Coskun D, Ahmet A, Tezer T, Ozdek S. Anesthetic management in the case of premature infant with bronchopulmonary dysplasia and retinopathy of prematurity. J Med Cases. 2010;1:10-13.
24. Lansingh VC, Eckert KA, Strauss G. Benefits and risks of immediately sequential bilateral cataract surgery: a literature review. Clin Exp Ophthalmol. 2015;43:666-672.
25. Nallasamy S, Davidson SL, Kuhn I, Mills MD, Forbes BJ, Stricker PA, Anninger WV. Simultaneous bilateral intraocular surgery in children. J AAPOS. 2010;14:15-19.
26. Govetto A, Virgili G, Menchini F, Lanzetta P, Menchini U. A systematic review of endophthalmitis after microincisional versus 20-gauge vitrectomy. Ophthalmology. 2013;120:2286-2291.
27. Shimada H, Nakashizuka H, Hattori T, Mori R, Mizutani Y, Yuzawa M. Incidence of endophthalmitis after 20- and 25-gauge vitrectomy causes and prevention. Ophthalmology. 2008;115:2215-2220.
28. Oshima Y, Kadonosono K, Yamaji H, Inoue M, Yoshida M, Kimura H, Ohji M, Shiraga F, Hamasaki T; Japan Microincision Vitrectomy Surgery Study Group. Multicenter survey with a systematic overview of acute-onset endophthalmitis after transconjunctival microincision vitrectomy surgery. Am J Ophthalmol. 2010;150:716-725.
29. Schachat AP. Simultaneous bilateral endophthalmitis after immediate sequential bilateral cataract surgery: what's the risk of functional blindness? Am J Ophthalmol. 2014;158:410-411.
30. van der Griend BF, Lister NA, McKenzie IM, Martin N, Ragg PG, Sheppard SJ, Davidson AJ. Postoperative mortality in children after 101,885 anesthetics at a tertiary pediatric hospital. Anesth Analg. 2011;112:1440-1447.
31. Bhende P, Gopal L, Sharma T, Verma A, Biswas RK. Functional and anatomical outcomes after primary lens-sparing pars plana vitrectomy for Stage 4 retinopathy of prematurity. Indian J Ophthalmol. 2009;57:267-271.
32. Gadkari S, Kamdar R, Kulkarni S, Kakade N, Taras S, Deshpande M. Vitreoretinal surgery for advanced retinopathy of prematurity: presentation and outcomes from a developing country. Can J Ophthalmol. 2015;50:54-60.
33. Karacorlu M, Hocaoglu M, Sayman Muslubas I, Arf S. Long-term functional results following vitrectomy for advanced retinopathy of prematurity. Br J Ophthalmol. 2017;101:730-734.

DOI: 10.4274/tjo.galenos.2021.68252
Turk J Ophthalmol 2021;51:231-242

Review

COVID-19 and the Use of Immunomodulatory Agents in Ophthalmology

Mehmet Fatih Kağan Değirmenci*, F. Nilüfer Yalçındağ**, İlknur Tugal-Tutkun***

*Çankırı State Hospital, Clinic of Ophthalmology, Çankırı, Turkey
**Ankara University Faculty of Medicine, Department of Ophthalmology, Ankara, Turkey
***İstanbul University, İstanbul Faculty of Medicine, Department of Ophthalmology, İstanbul, Turkey

Abstract

Immunomodulatory agents are often used in the systemic treatment of non-infectious uveitis. These drugs consist of corticosteroids, conventional immunosuppressives, and biological agents. As it is known that they suppress the immune system, the most important concern associated with immunomodulatory therapy (IMT) is the increased risk of infection. The World Health Organization declared COVID-19 a pandemic on 11 March 2020. Although severe acute respiratory distress syndrome secondary to SARS-CoV-2 infection may develop in all people, patients who receive IMT may be at higher risk in terms of both the transmission of the infection and more severe disease course. Therefore, guidelines on the management of patients receiving IMT due to uveitis during the pandemic are needed. In this review, we examined the immunomodulatory drugs used in the treatment of uveitis in terms of infectious complications and the data of patients who received IMT during the COVID-19 pandemic and discussed recommendations for the use of these drugs. According to the latest information, patients who receive IMT may continue their treatment as long as there are no disruptions in regular complete blood count (especially white blood cell count >4,000/μL) and liver and kidney function tests. Patients diagnosed with COVID-19 should be managed with a multidisciplinary approach.

Keywords: COVID-19, immunomodulatory therapy, immunosuppressive, non-infectious uveitis, SARS-CoV-2

Introduction

Coronavirus disease 2019 (COVID-19), caused by the novel coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first reported in the city of Wuhan (Hubei province, China). After spreading to other cities and countries, the World Health Organization declared it a pandemic on March 11, 2020 (World Health Organization, Situation Report-51). Due to the virus' unclear route of transmission, its rapid spread, and the considerable rate of serious complications it causes, the disease has become a global public health problem of worldwide concern. Although the information we have about COVID-19 is limited, it is steadily increasing. Patients using immunomodulatory therapy (IMT), both conventional and biological agents, constitute a population that is potentially vulnerable to infectious diseases and require diligent and close follow-up.

The aim of this review was to investigate the safety and use of immunomodulatory drugs for the treatment of ocular diseases during the COVID-19 pandemic.

COVID-19

Genome sequencing revealed that SARS-CoV-2 is very similar to two bat-derived SARS-like coronaviruses and less similar to SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV).[1] It has been suggested that SARS-CoV-2 is a novel infectious agent that emerged as a result of

Address for Correspondence: Mehmet Fatih Kağan Değirmenci, Çankırı State Hospital, Clinic of Ophthalmology, Çankırı, Turkey
E-mail: mfkdegirmenci@ankara.edu.tr **ORCID-ID:** orcid.org/0000-0003-2358-9535
Received: 26.08.2020 **Accepted:** 01.03.2021

Cite this article as: Değirmenci MFK, Yalçındağ FN, Tugal-Tutkun İ. COVID-19 and the Use of Immunomodulatory Agents in Ophthalmology. Turk J Ophthalmol 2021;51:231-242

mutations and recombinations in different genomic regions.

There is still no definite consensus regarding the treatment of patients. Many different drugs have been tried in clinical studies, with hydroxychloroquine and antiviral agents being adopted early in the pandemic.[2] Corticosteroids were used in an attempt to control the cytokine storm in severe cases, but they were found to delay viral clearance time and had no effect on mortality.[3] Tocilizumab, a recombinant human monoclonal antibody developed against interleukin (IL)-6 receptor, was shown to be effective in COVID-19 patients with cytokine storm.[4] Results are not yet available for clinical studies of sarilumab, another IL-6 receptor antibody. Studies with the Janus kinase inhibitor baricitinib have not yielded favorable results.[5]

Risk Factors for Severe COVID-19

Disease-related mortality rates differ by region (5.6%-15.2%).[6] The risk of death is higher in older patients and those with comorbidities such as hypertension, diabetes mellitus, cardiovascular disease, and chronic lung disease.[7] It was also stated that in previous studies of SARS and MERS infections, which have similar risk factors to COVID-19, immunosuppressed individuals were not found to be at higher risk.[7] In a retrospective study reporting the clinical course and outcomes of COVID-19 patients, advanced age, need for oxygen support, dementia, and presence of neurological disease at admission were listed as risk factors.[8] Another study also suggested that the disease is more severe in smokers, but pharmaceutical nicotine may be beneficial in the treatment of COVID-19 due to its immunomodulatory effects.[9]

Immunomodulatory Therapy and COVID-19

It is known that people whose immune systems are suppressed for any reason are at risk of infectious diseases. Ophthalmologists use many different immunomodulatory drugs (conventional immunosuppressants, biological agents, and new small-molecule inhibitory agents) in the treatment of non-infectious uveitis.

The relationship between immunosuppressive drug use and COVID-19 has been a subject of research during the pandemic. Most studies in the literature are case reports and observational studies and involved patients receiving IMT due to organ transplantation and systemic autoimmune diseases. There are few publications on the management of patients with non-infectious uveitis who require IMT.

Systemic Corticosteroids

Systemic corticosteroids are used to control inflammation, especially in cases of vision-threatening acute uveitis. Long-term systemic corticosteroid use causes significant immunosuppression and increases the risk of infection. In three different patients receiving corticosteroid therapy due to organ transplantation, the course of COVID-19 infection was reported to be similar to the normal population.[10,11,12] A study of 600 patients receiving immunosuppressive therapy for rheumatic diseases showed that patients using corticosteroids (≥10 mg/day) had a higher hospitalization rate than patients using other immunosuppressants.[13]

Conventional Immunosuppressive Drugs

Methotrexate: Methotrexate is one of the conventional immunosuppressive drugs and is mostly used in children with chronic anterior and intermediate uveitis.[14] Methotrexate slightly increases the risk of infection but does not pose a risk for the development of serious infection.[15] Although there is no definitive data regarding the effect of methotrexate use on COVID-19 transmission risk and disease course, it is not considered contraindicated.[16]

Azathioprine: This drug is most commonly used in ophthalmology practice to treat Behçet uveitis (BU).[17] It can also be used in idiopathic posterior uveitis, Vogt-Koyanagi-Harada disease, and less frequently in cases of uveitis associated with juvenile idiopathic arthritis (JIA).[18,19] Another study evaluating 230 patients diagnosed with inflammatory bowel disease showed that azathioprine did not increase the risk of upper respiratory tract infection.[20] In a retrospective study of 46,030 patients with rheumatoid arthritis (RA), it was reported that although the incidence of influenza was higher than in the healthy population, it was not associated with azathioprine use.[21] There is no report in the literature regarding the presence of a relationship between azathioprine use and COVID-19 transmission risk and disease course.

Mycophenolate mofetil: Mycophenolate mofetil, another agent previously used in organ transplantation and systemic autoimmune diseases, is used less frequently in the treatment of uveitis than other immunosuppressants. It can be used in patients with panuveitis, posterior uveitis, retinal vasculitis, and scleritis due to various etiologies.[22,23] Studies in transplant patients have shown that it moderately increases the risk of infection. Ritter and Pirofski[24] concluded in their review that the drug especially predisposes to upper respiratory tract infection, urinary tract infection, and herpes virus-related infections. There are no available literature data on the relationship between mycophenolate mofetil use and COVID-19.

Cyclosporine-A: This drug can be used to treat patients with many different panuveitis and posterior uveitis entities, especially BU.[25] Studies in dermatology patients have demonstrated a slight increase in the risk of upper respiratory tract infection.[26] de Wilde et al.[27] showed that cyclosporine-A (Cs-A) suppressed MERS-CoV replication in vitro. In a clinic following 2,493 kidney transplant patients, evaluation of the clinical course and outcomes of 19 patients with SARS-CoV-2 revealed that those using Cs-A had a better clinical course than those using other immunosuppressive agents.[28] In a multicenter study conducted with kidney transplant patients in our country, examination of patients diagnosed with COVID-19 showed that none of the patients using Cs-A developed severe pneumonia.[29] In another study of kidney transplant patients, it was reported that Cs-A could be used as an effective and reliable immunosuppressant when needed in patients diagnosed as having COVID-19.[30]

Tacrolimus: Tacrolimus is another immunomodulatory agent occasionally used in cases of intermediate uveitis, posterior uveitis, and panuveitis.[31] It was shown to suppress MERS-CoV replication similar to Cs-A in an *in vitro* study.[32] A study

investigating factors associated with mortality in 53 COVID-19 patients with a history of kidney transplantation showed that having dyspnea at admission, being over 60 years old, and tacrolimus use increased the risk of death.[33]

Cyclophosphamide: Although not highly preferred in ocular inflammatory diseases today, cyclophosphamide is another immunosuppressant previously used in patients with BU, pars planitis, and sympathetic ophthalmia.[34] Durrani et al.[35] evaluated the short-term efficacy and safety of intravenous pulse cyclophosphamide in 38 patients with ocular inflammatory disease and reported that 18% of patients in the study developed upper respiratory tract infection. In a study including 7 bone marrow transplant patients with COVID-19, it was noted that 4 of the patients used cyclophosphamide and all of them had mild COVID-19.[36]

Biologic Agents

Over the last two decades, biologic agents have provided a major advance in the treatment of systemic autoimmune diseases. In later years, they started to be used in the treatment of ocular inflammatory diseases. Etanercept, the first approved anti-tumor necrosis factor alpha (anti-TNF-α) agent, was shown to be ineffective in the treatment of uveitis after some time and to cause uveitis de novo in patients receiving the drug due to systemic autoimmune disease.[37]

Infliximab: Infliximab, another anti-TNF-α agent, is currently used in patients with uveitis associated with a wide range of etiologies. It is most commonly needed in BU and uveitis in sarcoidosis.[38] It was also shown to be effective in the treatment of uveitis associated with JIA, Crohn's disease, and ankylosing spondylitis (AS).[39,40,41] Infliximab is a low risk agent in terms of infectious complications.[42] In a study comparing the long-term safety of infliximab and non-biologic agents (systemic corticosteroids, azathioprine, and methotrexate) in the treatment of Crohn's disease, 6273 patients were evaluated and infectious complications were reported to be more common in those using infliximab.[43] The incidence of bacterial infection was 2.69% per year and that of viral infection was 0.97% per year. In the study, there is no clear data on the safety of infliximab during the COVID-19 pandemic. A study including 7 patients who used various biologic agents due to psoriasis and were diagnosed as having COVID-19 showed that patients receiving infliximab had a poorer prognosis.[44] However, there are case reports showing the successful use of infliximab to treat COVID-19 in patients with systemic autoimmune disease.[45,46] In another study, it was suggested that infliximab could be used in the treatment of patients with ulcerative colitis during the COVID-19 pandemic.[47]

Adalimumab: This drug is another anti-TNF-α agent that has been used to treat uveitis. Successful outcomes have been reported with adalimumab in patients with idiopathic uveitis and uveitis secondary to systemic diseases such as Behçet disease (BD), sarcoidosis, JIA, AS, and Crohn's disease.[38,48] Adalimumab is the only biologic agent licensed for the treatment of uveitis; others are used off-label. Infections were found to be the most common drug-related complications in patients using adalimumab for systemic autoimmune disease.[49] However, it has been shown that advanced age, comorbid diseases, and RA are risk factors, whereas patients with AS, psoriasis, and JIA have a significantly lower risk of serious infection.[49] In a study of 217 patients with panuveitis, posterior uveitis, and intermediate uveitis of various etiologies, it was reported that non-serious upper respiratory tract and urinary tract infections were more common in patients using adalimumab compared to the placebo group, while the risk of serious infection was similar in the two groups.[50] There are case reports in the literature regarding the risk of COVID-19 in patients using adalimumab. A 57-year-old psoriasis patient taking adalimumab for approximately 2 years was diagnosed as having COVID-19 manifesting with fever, malaise, and anosmia.[51] According to the report, the patient exhibited no breathing difficulties during follow-up and did not need oxygen support. Adalimumab treatment was continued 3 weeks after discharge and there was no recurrence of symptoms associated with COVID-19 during follow-up. In another 30-year-old patient taking adalimumab for Crohn's disease, COVID-19 infection presented with symptoms of fever and mild dyspnea and resolved rapidly.[52] The authors attributed this to the patient's young age and the role of TNF-α overproduction in severe respiratory failure. For this reason, they suggested that adalimumab can be used for therapeutic purposes in some COVID-19 patients.

Certolizumab and golimumab: There are no large and long-term studies on the use of certolizumab and golimumab, other anti-TNF-α agents used in systemic autoimmune diseases, in ocular inflammation. In a study examining 30 eyes of 21 patients, it was shown that aqueous flare measurements were significantly reduced and visual acuity was preserved in the long term with both certolizumab and golimumab.[53] When the results of three phase 3, randomized, placebo-controlled trials on the long-term safety of certolizumab use in psoriasis patients were analyzed together, the rate of infection was shown to be 1.5% per year, which was reported to be similar to other biologic agents.[54] There is still no information in the literature regarding the relationship between certolizumab or golimumab use and COVID-19 infection.

In a study evaluating 600 rheumatic patients with COVID-19, it was found that anti-TNF-α use reduced the risk of hospitalization.[13]

Tocilizumab: Tocilizumab, another of the biologic agents more recently used to treat uveitis, is an IL-6 receptor antagonist. In previous years, it was approved for the treatment of RA and JIA. There are reports that it is successful in the treatment of uveitis. In a randomized, controlled, multicenter study, 37 patients with non-infectious intermediate uveitis, posterior uveitis, and panuveitis received tocilizumab infusion at one of two different doses.[55] At both doses, tocilizumab increased visual acuity and decreased vitreous haze and central macular thickness. The efficacy and safety of tocilizumab and methotrexate were evaluated in patients with RA.[56] During the 24-week follow-up period, serious infectious complications occurred in 1.4%

of patients receiving tocilizumab, similar to methotrexate.[56] Severe infections requiring hospitalization occurred in 24% of patients using tocilizumab. However, 52% of all patients were also receiving corticosteroid therapy, suggesting that the high incidence of infection was not due to tocilizumab alone. In a study of 141,869 patients comparing tocilizumab with anti-TNF-α agents in terms of risk of serious infection, both groups had similar rates of infectious complications.[57] It was observed that 4.68% of patients treated with tocilizumab developed serious infections per year. There is currently no known relationship between tocilizumab use and the development of COVID-19 infection. There are publications reporting that for patients who require systemic immunosuppressive therapy and contract COVID-19, tocilizumab may be beneficial for both the comorbid condition and COVID-19.[58,59] Luo et al.[4] used tocilizumab to suppress severe systemic immune response in 15 patients with COVID-19. They stated that 11 of the patients responded well to treatment and that tocilizumab may be beneficial for severe patients at risk of cytokine storm.

Secukinumab: Secukinumab, another agent shown to be effective in autoinflammatory diseases, is an IL-17A antagonist. The results of three randomized controlled clinical trials to evaluate the efficacy of subcutaneous secukinumab in the treatment of non-infectious uveitis were analyzed and there was no significant difference in uveitis recurrence between the secukinumab and placebo groups.[60] In a study of patients with psoriatic arthritis, a dose-dependent increase in the risk of serious infection was observed, with 2.1 of 100 patients in the group receiving the highest dose of secukinumab developing a serious infection within 1 year.[61] Carugno et al.[62] described a case of COVID-19 in a patient who had been using secukinumab for 2 years due to psoriatic arthritis. They reported that the patient had a mild clinical course and that IL-17 inhibitors may even have a role in the treatment of COVID-19. In another publication, it was reported that IL-17A has a role in lung and heart damage in various diseases and that IL-17A inhibitors may be a potential treatment to prevent damage.[63] In contrast, Sharmeen et al.[64] reported that secukinumab use was associated with severe COVID-19 course. In another study, analysis of clinical course in 41 COVID-19 patients receiving IMT (including secukinumab) due to rheumatologic diseases revealed no difference from the normal population.[65]

Canakinumab: This is another biologic agent that acts as an IL-1 beta inhibitor. It can be used in the treatment of psoriasis, chronic obstructive pulmonary disease, gout, and BD. Anakinra is another biologic agent that exhibits similar activity by binding to the IL-1 beta receptor. In BD patients with ocular involvement, canakinumab and anakinra have been shown to control ocular inflammation.[66] In a retrospective chart review of 475 patients receiving canakinumab and anakinra for various autoimmune and autoinflammatory diseases, it was reported that 3 patients developed severe bacterial infections, resulting in death for 2 of those patients.[67] It has been reported that anakinra yields positive results in controlling the cytokine storm in patients with secondary hemophagocytic syndrome and has the potential to be used in severe COVID-19 cases.[68] The results of a preliminary study indicated that canakinumab and anakinra are safe during the COVID-19 pandemic and beneficial in COVID-19 patients with cytokine storm.[69]

Interferons: These are a group of cytokines produced by host cells in response to the presence of viruses, bacteria, parasites, and tumor cells. Of the three types, interferon-α and interferon-β reduce autoimmune activity. Systemic recombinant interferon-α-2a therapy has been shown to be effective against the extraocular findings of BD.[31] It is also effective in the treatment of BU and intermediate uveitis.[70,71,72] The most common complication associated with interferon therapy is influenza-like symptoms. In fact, the resolution of these symptoms suggests the formation of anti-interferon antibodies.[73] No infectious complications related to interferon use have been reported in the treatment of uveitis. Considering its role in the natural immune system, infection related to treatment is not expected. It is thought that interferon could be used in the treatment of COVID-19 because it naturally stimulates an antiviral reaction, and clinical studies on this are ongoing. The use of interferon in combination with other therapies has been reported with no adverse effects in case reports.[74,75] However, interferon-α preparations are no longer available on the market, only pegylated forms are available. Experience with the use of pegylated interferons in the treatment of uveitis is very limited.

Rituximab: Rituximab, which was first used in the treatment of lymphoma, targets the CD20 antigen on the B cell surface and causes B cell depletion. In subsequent years, it was used in RA and later for the treatment of granulomatous polyangiitis. There are retrospective case series in the literature regarding its role in the treatment of uveitis. It was shown to control inflammation during treatment in 8 patients with uveitis secondary to JIA.[76] Nine of 11 patients with refractory non-infectious posterior uveitis had improved visual acuity and regression of fluorescein angiography findings.[77] There are reports that it induced remission in patients with BU.[78,79] The use of rituximab in multiple sclerosis significantly increases the risk of infection.[80] However, there are insufficient data demonstrating the side effect profile of rituximab in patients with uveitis.[77] There are case reports describing a more severe course of COVID-19 in patients using rituximab due to rheumatologic diseases.[81,82] As rituximab causes B-cell depletion, it was suggested that the risk/benefit ratio should be considered when using the drug during the pandemic, as it may impair the development of immunity in response to SARS-CoV-2 infection or to future vaccines.[83] It has been shown that multiple sclerosis patients' rituximab dose interval can be extended during the COVID-19 pandemic with no adverse effect on the course of multiple sclerosis.[84]

Abatacept: This drug inhibits T cell activation by cleaving the bond between cytotoxic T lymphocyte-associated antigen-4 and immunoglobulin G, thereby suppressing T cell-dependent antibody production. It has similar efficacy to anti-TNF-α drugs in the treatment of RA. It can also induce remission in cases of JIA-associated uveitis.[85] Patients using abatacept generally have an increased risk of infection. A large study evaluating the results

of five different clinical trials showed that the incidence of serious infections was low in RA patients using abatacept.[86] Literature data regarding the effect of abatacept use on the risk of SARS-CoV-2 transmission or the clinical course of COVID-19 are not yet available.

Alemtuzumab: Alemtuzumab is a monoclonal antibody that reduces T and B lymphocyte counts by binding to CD52 on the cell surface of lymphocytes. The 12-year long-term outcomes of alemtuzumab use in multiple sclerosis patients were recently published.[87] Its efficacy has been demonstrated both clinically and on magnetic resonance imaging. There are case reports related to its use in the treatment of uveitis. In one report, alemtuzumab induced remission in a case of refractory panuveitis.[88] It was also shown to induce remission in another patient with refractory intermediate uveitis and macular edema associated with multiple sclerosis. The highest risk of serious infectious complications with alemtuzumab use in patients with multiple sclerosis was reported to be the first year of treatment (3.3%/year).[87] In the same study, it was observed that the incidence of serious infections decreased in the long term (0.8%/year) in patients with 12-year follow-up. An analysis of 399 patients receiving different treatments for multiple sclerosis (including alemtuzumab) indicated that COVID-19 incidence and disease course were similar to those in the normal population.[89]

SARS-CoV-2 Ocular Involvement

Ocular involvement caused by SARS-CoV-2 was first reported in China.[90] A patient who tested positive for SARS-CoV-2 after risky contact developed redness of the eyes days before developing pneumonia. After this case, it was thought that the use of protective glasses and/or visors could prevent the spread of the disease. The retina and retinal pigment epithelial cells were shown in previous years to have ACE2 receptors, by which the virus attaches to and infects cells.[91] Recently, ACE2 receptor gene expression has also been demonstrated in conjunctival cells.[92] This finding supports the hypothesis that SARS-CoV-2 can be transmitted directly through the ocular surface.

Coronaviruses have been shown to cause conjunctivitis, anterior uveitis, retinitis, and optic neuritis in animal models.[93] In a study conducted in China, tear and conjunctival secretion samples obtained twice a few days apart from 30 COVID-19 patients were tested for the presence of SARS-CoV-2 and in only one of the patients, both samples tested positive.[94] Ocular findings have been shown to occur in approximately one-third of COVID-19 patients, with the most frequent being conjunctival hyperemia, chemosis, and epiphora.[95,96] Clinical risk factors for ocular involvement include advanced age, high fever, increased neutrophil to lymphocyte ratio, and high acute phase reactant levels.[96] A study evaluating the presence of virus RNA in retinal samples obtained from 14 patients who died from COVID-19 revealed SARS-CoV-2 RNA in 3 of the 14 tested eyes.[97] In another study evaluating the optical coherence tomography findings of 12 COVID-19 patients aged 25-69 years, hyperreflective lesions in the ganglion cell and inner plexiform layers were observed in both eyes of all patients and soft exudates and microhemorrhages were observed in the posterior segment examination of 4 patients.[98] However, in a letter to the editor regarding this article, Vavvas et al.[99] pointed out that soft exudates can be seen in many diseases and that the exudate in the example image could actually be myelinated nerve fiber and a reevaluation after 6-8 weeks is necessary to differentiate. They also argued that the hyperreflective bands in the images may have been normal vessel shadowing and that these two findings may not be retinal changes associated with COVID-19. Bettach et al.[100] reported a case of bilateral acute anterior uveitis secondary to COVID-19 infection. A 54-year-old woman who was treated for COVID-19 in the intensive care unit presented to the outpatient clinic with blurred vision 2 weeks after discharge. At initial examination, her visual acuity was 0.5 in both eyes and slit-lamp examination revealed bilateral conjunctival hyperemia, central corneal edema, Descemet's membrane folds, keratic precipitates, and +1 cells in the anterior chamber. The patient's findings improved with topical steroid and cycloplegia.

Uveitis Management During the COVID-19 Pandemic

Non-infectious uveitis is a group of sight-threatening inflammatory disorders and may be associated with systemic diseases. Immunomodulatory drugs have long been used in systemic inflammatory diseases and are often used in the treatment of non-infectious uveitis. In addition to corticosteroids (topical, peri/retrobulbar, intravitreal, systemic), conventional immunosuppressants and biological agents are used to protect against the side effects of corticosteroids, especially in patients who require long-term treatment.[101] These drugs are known to suppress the immune system; therefore, the most important problem is the increased risk of infection.

The global SARS-CoV-2 pandemic is a unique phenomenon that has brought many unprecedented challenges. One of these challenges for ophthalmologists is managing non-infectious uveitis patients who need IMT during the pandemic. Opinions and recommendations on this topic are being published from various parts of the world.

In parallel with the recommendations of the International Uveitis Study Group (IUSG), Tugal-Tutkun of our country wrote an article titled "Recommendations for Uveitis Patients Using Immunomodulatory Drugs" and published these recommendations on the website of the Turkish Ophthalmological Association (https://coronavirus.todnet.org/post/recommendations-for-uveitis-patients-using-immunomodulatory-drugs). First, the author emphasized that patients using immunomodulatory drugs should adhere strictly to social distancing/isolation and personal protection. It was stated that international uveitis associations do not recommend discontinuing drugs, but depending on the course of ocular inflammation and with physician supervision, the administration interval can be extended, the dose can be reduced, or the drug can be completely discontinued. However, the author also noted that IMT should be discontinued in case of any suspicion of infection or high-risk contact. The vital importance of patients

having regular complete blood count (especially white blood cell count should be >4,000/μL) and liver (alanine transaminase, aspartate transaminases, gama-glutamil transpeptidaz) and kidney function (serum creatinine and urea) tests in terms of the risk of COVID-19 infection was emphasized.

Later, a consensus guide on the management of uveitis during the COVID-19 pandemic prepared by the IUSG, International Ocular Inflammation Society, and Foster Ocular Inflammation Society was published.[102] This guide emphasized that treatment should be adapted based on the patient's COVID-19 status. The recommendations for patients under systemic immunosuppression are divided into two groups. In the first case, the consensus was to continue IMT in patients with no clinical signs of COVID-19. General recommendations for patients were made, such as staying at home as much as possible, complying with social distancing (being at least 1.5-2 m away from others), using masks when in contact with people or in risky areas such as hospitals, washing hands frequently with soap for at least 20 seconds, especially after touching door handles and light switches, and not touching the face without first washing hands. It was stated that a total white blood cell count higher than 4,000/μL minimized the risk of infection and that patients should continue to undergo complete blood count tests regularly in the centers closest to their homes. Cs-A was reported to be safe at non-high doses and not predispose to viral infections (except varicella-zoster virus). Finally, it was recommended to contact patients by phone because they could discontinue their medication without being advised by a doctor. In the second case, it was stated that patients with suspected or confirmed COVID-19 can continue immunomodulatory drugs if they are asymptomatic and have a total white blood cell count above 4,000/μL, while for symptomatic patients, immunomodulatory drugs other than interferon and tocilizumab can be discontinued and local treatment solutions may be considered. It was noted that systemic corticosteroids should not be discontinued abruptly and that dose reduction should be gradual in terms of adrenal suppression. In patients with severe acute uveitis attacks (new-onset uveitis or reactivation) who require high-dose intravenous methylprednisolone therapy, local treatment options (periocular and intravitreal steroids) alone or in combination with low-dose systemic corticosteroids should be considered.

Apart from the consensus guide above, there are publications related to the approach to ophthalmology patients during the COVID-19 pandemic. Gupta et al.[103] published information and their recommendations on the treatment and follow-up of vitreoretinal and uveal diseases. In addition to the above consensus guideline recommendations for uveitis patients, they reported that the COVID-19 pandemic is not an absolute contraindication to initiating immunosuppressive therapy. Another publication presented recommendations that can be made in the follow-up, diagnosis, and treatment of uveitis patients.[104] Patients with controlled uveitis should be followed remotely (by telephone, etc.) except for emergencies, and routine test results should be evaluated. As few tests as possible should be performed for diagnosis and follow-up. For patients who may require new treatment or treatment changes, personal protective equipment should be used diligently during examination. Finally, it was stated that IMT should be continued in patients without suspected or confirmed COVID-19, and IMT should be discontinued/reduced and local treatment options considered for infected patients. Similar recommendations were made in a study from Hong Kong.[105] The authors recommended that patients under systemic treatment comply with general prevention measures, be followed up remotely as much as possible, use protective equipment when they need to be examined in person, and postpone elective surgeries. In newly diagnosed cases, they suggested first evaluating local treatment options but stated that biologic agents could be used when necessary in conditions such as BU. They recommended that systemic therapy should be reduced as much as possible or discontinued in patients diagnosed with COVID-19 while receiving IMT.[105] A review investigating the effects of the use of immunosuppressives for ocular inflammatory diseases during the pandemic evaluated the new SARS-CoV-2 virus as well as information obtained during previous SARS and MERS outbreaks.[106] It was stated that immunosuppression does not increase the risk of transmission or clinical severity of COVID-19, and immunosuppressive drugs can even be used to suppress the cytokine storm in severe COVID-19 cases. Similar recommendations were also made in a study reporting the common views of authors from different countries.[107] It was stated that newly diagnosed patients should be followed up regularly until inflammation is controlled and that local treatment options should be preferred whenever possible. However, it was noted that systemic corticosteroids and immunomodulatory drugs can be used in patients with severe sight-threatening uveitis. They reported that treatment should be interrupted in patients who are receiving immunosuppressive treatment and test positive for SARS-CoV-2. In an online survey study, 139 ocular inflammatory disease experts from all over the world were asked questions concerning the use of IMT in non-infectious uveitis cases during the COVID-19 pandemic and a detailed treatment algorithm was created for patients.[108] The experts were presented with patient scenarios divided into different categories and groups and provided yes/no responses in terms of IMT. In the first category, patients were divided into four groups according to COVID-19 signs and symptoms: 1. Healthy, 2. Healthy with a history of contact with a COVID-19 patient, 3. Showing symptoms of COVID-19, and 4. Confirmed COVID-19 diagnosis. In the second category, patients were divided into three groups according to systemic risk factors and immunosuppression level: 1. At-risk patients, 2. High-risk patients, and 3. Very high-risk patients. At-risk patients were defined as those using immunosuppressants other than biologic agents. High-risk patients were defined as patients with one of the following risk factors: biologic agent use, high-dose immunosuppressive use, multiple immunosuppressive use, presence of active systemic inflammatory disease, presence of heart, lung, and/or kidney disease, neutropenia, smoking, pregnancy, being over 60 years of age, or previous history of infection while taking IMT. Very high-risk patients were defined

as those having two or more of the above risk factors. The consensus options for the management of patients classified by risk group are summarized in Table 1, Table 2, and Table 3.[108]

Real-life Data During the COVID-19 Pandemic

Information pertaining to patients receiving IMT due to rheumatologic and inflammatory bowel diseases during the COVID-19 pandemic is recorded in international databases.

Experiences with patients using immunosuppressants during the COVID-19 pandemic are also shared in the SECURE-IBD database, which provides current real-life data on inflammatory bowel diseases. Finally, according to data last updated on January 5, 2021, a total of 4,280 cases worldwide were shared (https://covidibd.org/current-data/. Updated 01/05/2021). It was observed that 39% of 296 patients who contracted COVID-19 while using oral or parenteral corticosteroids were hospitalized and 14% had a severe course. Thirty-three patients infected with SARS-CoV-2 while using methotrexate were reported. Of those, 10 patients were admitted for inpatient treatment and only 2 patients had a clinically severe disease. Another 362 patients diagnosed with COVID-19 were using azathioprine and 76% of those patients were followed up on an outpatient basis. It was reported that 5% of the patients needed intensive care, 4% received ventilator support, and 8 people died (2%). COVID-19 was diagnosed in 1,418 patients using various anti-TNF-α molecules (monotherapy). Of these, 89% were treated as outpatients and only 2% had severe infection. Of 394 COVID-19 patients using azathioprine or methotrexate in combination with anti-TNF-α, 81% were treated as outpatients, 3% needed intensive care, and 2% required ventilator support. Fifteen patients (4%) died during treatment.

EULAR (European League Against Rheumatism), which conducts studies on rheumatic diseases, collects data pertaining to patients with rheumatic diseases who are diagnosed as having COVID-19. Their latest report (dated: 01/12/2021) presents data from a total of 3,590 patients (https://www.eular.org/myUploadData/files/eular_covid_19_registry_report_1_dec.pdf). When all patients were considered, it was reported that 46% needed inpatient treatment. Seventy-nine percent of the patients were infected with SARS-CoV-2 while using any immunosuppressant, and of those patients, 56% were using conventional immunosuppressants and 38% used biologics. The proportion of Behçet patients enrolled in this database is 1%, and the report included no separate analysis of Behçet patients. In June of last year, EULAR also published recommendations on the management of rheumatologic and musculoskeletal diseases.[109] It was recommended that patients without suspected or confirmed COVID-19 should continue their treatment unchanged. Patients who have contact with anyone diagnosed as having COVID-19 should have a SARS-CoV-2 test even if they have no symptoms, and a multidisciplinary approach to treatment was recommended for patients with a confirmed COVID-19 diagnosis.

Very recently, two case series of BD patients diagnosed with COVID-19 were published.[110,111] In a series presenting 4 BD patients with COVID-19 (upper respiratory tract infection in 3 and viral pneumonia in 1 patient), 3 of the patients were hospitalized for treatment and all patients had mild COVID-19 and recovered without any complications. Activation of cutaneous and mucosal findings of BD was observed during COVID-19 infection in one patient and 15 days after recovering from COVID-19 in another patient. Two of the patients in this series were using conventional immunosuppressants (one methotrexate, the other azathioprine) combined with oral corticosteroids at the time of COVID-19 diagnosis, and it was reported that methotrexate therapy was discontinued in the former patient after being diagnosed with COVID-19.[110] The other series presented 10 BD patients with COVID-19, of whom 6 developed viral pneumonia, 8 were hospitalized, and 2 were admitted to the intensive care unit. One of the patients died of severe respiratory failure, one developed deep vein thrombosis, and 3 patients had recurrence of oral aphthae and arthralgia associated with BD. All patients except the deceased patient were using colchicine and/or an immunomodulatory drug at

Table 1. Consensus treatment recommendations for at-risk patients* (follow from left to right)[106]

Not using CS		Healthy patient	Initiate
		COVID-19 patient (suspected or confirmed)	Do not initiate
Using oral CS	Using low-dose CS	Healthy patient (with or without contact)	Continue
	Using high-dose CS	Healthy patient	Continue
		COVID-19 patient (suspected or confirmed)	Dose can be reduced, drug can be discontinued if confirmed
	If considering intravenous CS	COVID-19 patient (suspected or confirmed)	Do not initiate
	If considering local CS	Healthy patient with contact or COVID-19 patient (suspected or confirmed) not receiving oral CS	It is preferred over systemic therapy
		All patients receiving low-dose oral CS	It is preferred instead of increasing the systemic therapy dose
Using conventional immunosuppressants		Healthy patient	Continue
		Healthy patient with contact	Continue
		COVID-19 patient (suspected or confirmed)	Dose can be reduced or treatment discontinued

CS: Corticosteroid, *See text, COVID-19: Coronavirus disease-19

Table 2. Consensus treatment recommendations for high-risk patients** (follow from left to right)[106]			
Not using CS		COVID-19 patient (suspected or confirmed)	Do not initiate treatment
Using oral CS	Using low-dose CS	Healthy patient	Continue treatment
		Positive COVID-19 test	Dose can be reduced or treatment discontinued
	Using high-dose CS	Healthy patient	Consider continuing treatment
		COVID-19 patient (suspected or confirmed)	Dose can be reduced or treatment discontinued
	If considering intravenous CS	Healthy patient with contact or COVID-19 patient (suspected or confirmed)	Do not initiate
	If considering local CS	Healthy patient with contact or COVID-19 patient (suspected or confirmed) not receiving oral CS	It is preferred over systemic therapy
		All patients receiving low-dose oral CS	It is preferred instead of increasing the systemic therapy dose
Using conventional immunosuppressants		Healthy patient	Continue
		COVID-19 patient (suspected or confirmed)	Dose can be reduced or treatment discontinued
Using or considering treatment with a biologic agent		Healthy patient (including those using tocilizumab)	Continue
		Healthy patient with contact	Do not initiate
			Do not change treatment to tocilizumab
		COVID-19 patient (suspected or confirmed)	Discontinue
CS: Corticosteroid, **See text, COVID-19: Coronavirus disease-19			

Table 3. Consensus treatment recommendations for very high-risk patients*** (follow from left to right)[106]			
Not using CS		COVID-19 patient (suspected or confirmed)	Do not initiate
Using oral CS	Using low-dose CS	Healthy patient	Continue
		COVID-19 patient (suspected or confirmed)	Dose can be reduced or treatment discontinued
	Using high-dose CS	COVID-19 patient (suspected or confirmed)	Dose can be reduced or treatment discontinued
	If considering intravenous CS	Healthy patient with contact or COVID-19 patient (suspected or confirmed)	Do not initiate
	If considering local CS	All patients not receiving oral CS or receiving low-dose oral CS	It is preferred instead of increasing the systemic therapy dose
immunosuppressive drug		Healthy patient	Continue
		Healthy patient with contact	Do not initiate
		COVID-19 patient (suspected or confirmed)	Dose can be reduced or treatment discontinued
Using or considering treatment with a biologic agent		Healthy patient (including those using tocilizumab)	Continue
		Healthy patient with contact	Do not initiate
		COVID-19 patient (suspected or confirmed)	Discontinue
CS: Corticosteroid, ***See text, COVID-19: Coronavirus disease-19			

the time of COVID-19 diagnosis (colchicine in 5, azathioprine in 3, anti-TNF-α agents in 3, and oral corticosteroids in 2 patients).[111]

Conclusions

In the light of previous clinical experience and the information obtained during the COVID-19 pandemic, albeit short term data, IMT does not appear to increase the risk of SARS-CoV-2 infection or the severity of the disease. Except for patients receiving high-dose systemic corticosteroid therapy and those at risk for severe COVID-19 infection, guidelines generally recommend continuing IMT for patients who need it. Each patient's condition should be evaluated individually when making treatment decisions. Patients should be treated using a multidisciplinary approach, taking into account systemic risk factors, the patient's potential COVID-19 infection status, and the type and severity of uveitis.

Ethics

Peer-review: Internally and externally peer reviewed.

Authorship Contributions

Concept: M.F.K.D., F.N.Y., İ.T.T., Design: M.F.K.D., F.N.Y., İ.T.T., Analysis or Interpretation: M.F.K.D., F.N.Y., İ.T.T.,

Literature Search: M.F.K.D., F.N.Y., İ.T.T., Writing: M.F.K.D., F.N.Y., İ.T.T.

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. Lu R, Zhao X, Li J, Niu P, Yang B, Wu H, Wang W, Song H, Huang B, Zhu N, Bi Y, Ma X, Zhan F, Wang L, Hu T, Zhou H, Hu Z, Zhou W, Zhao L, Chen J, Meng Y, Wang J, Lin Y, Yuan J, Xie Z, Ma J, Liu WJ, Wang D, Xu W, Holmes EC, Gao GF, Wu G, Chen W, Shi W, Tan W. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet. 2020;395:565-574.
2. Li H, Zhou Y, Zhang M, Wang H, Zhao Q, Liu J. Updated Approaches against SARS-CoV-2. Antimicrob Agents Chemother. 2020;64:e00483.
3. Russell CD, Millar JE, Baillie JK. Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. Lancet. 2020;395:473-475.
4. Luo P, Liu Y, Qiu L, Liu X, Liu D, Li J. Tocilizumab treatment in COVID-19: A single center experience. J Med Virol. 2020;92:814-818.
5. Praveen D, Puvvada RC, M VA. Janus kinase inhibitor baricitinib is not an ideal option for management of COVID-19. Int J Antimicrob Agents. 2020;55:105967.
6. Baud D, Qi X, Nielsen-Saines K, Musso D, Pomar L, Favre G. Real estimates of mortality following COVID-19 infection. Lancet Infect Dis. 2020;20:773.
7. Yang J, Zheng Y, Gou X, Pu K, Chen Z, Guo Q, Ji R, Wang H, Wang Y, Zhou Y. Prevalence of comorbidities and its effects in patients infected with SARS-CoV-2: a systematic review and meta-analysis. Int J Infect Dis. 2020;94:91-95.
8. Kim SW, Kim SM, Kim YK, Kim JY, Lee YM, Kim BO, Hwangbo S, Park T. Clinical Characteristics and Outcomes of COVID-19 Cohort Patients in Daegu Metropolitan City Outbreak in 2020. J Korean Med Sci. 2021;36:e12.
9. Farsalinos K, Barbouni A, Niaura R. Systematic review of the prevalence of current smoking among hospitalized COVID-19 patients in China: could nicotine be a therapeutic option? Intern Emerg Med. 2020;15:845-852.
10. Zhu L, Xu X, Ma K, Yang J, Guan H, Chen S, Chen Z, Chen G. Successful recovery of COVID-19 pneumonia in a renal transplant recipient with long-term immunosuppression. Am J Transplant. 2020;20:1859-1863.
11. Guillen E, Pineiro GJ, Revuelta I, Rodriguez D, Bodro M, Moreno A, Campistol JM, Diekmann F, Ventura-Aguiar P. Case report of COVID-19 in a kidney transplant recipient: Does immunosuppression alter the clinical presentation? Am J Transplant. 2020;20:1875-1878.
12. Liu B, Wang Y, Zhao Y, Shi H, Zeng F, Chen Z. Successful treatment of severe COVID-19 pneumonia in a liver transplant recipient. Am J Transplant. 2020;20:1891-1895.
13. Gianfrancesco M, Hyrich KL, Al-Adely S, Carmona L, Danila MI, Gossec L, Izadi Z, Jacobsohn L, Katz P, Lawson-Tovey S, Mateus EF, Rush S, Schmajuk G, Simard J, Strangfeld A, Trupin L, Wysham KD, Bhana S, Costello W, Grainger R, Hausmann JS, Liew JW, Sirotich E, Sufka P, Wallace ZS, Yazdany J, Machado PM, Robinson PC; COVID-19 Global Rheumatology Alliance. Characteristics associated with hospitalisation for COVID-19 in people with rheumatic disease: data from the COVID-19 Global Rheumatology Alliance physician-reported registry. Ann Rheum Dis. 2020;79:859-866.
14. Henderson LA, Zurakowski D, Angeles-Han ST, Lasky A, Rabinovich CE, Lo MS; Childhood Arthritis and Rheumatology Research Alliance (CARRA) Registry Investigators. Medication use in juvenile uveitis patients enrolled in the Childhood Arthritis and Rheumatology Research Alliance Registry. Pediatr Rheumatol Online J. 2016;14:9.
15. Ibrahim A, Ahmed M, Conway R, Carey JJ. Risk of Infection with Methotrexate Therapy in Inflammatory Diseases: A Systematic Review and Meta-Analysis. J Clin Med. 2018;8:15.
16. Russell B, Moss C, George G, Santaolalla A, Cope A, Papa S, Van Hemelrijck M. Associations between immune-suppressive and stimulating drugs and novel COVID-19-a systematic review of current evidence. Ecancermedicalscience. 2020;14:1022.
17. Arevalo JF, Lasave AF, Al Jindan MY, Al Sabaani NA, Al-Mahmood AM, Al-Zahrani YA, Al Dhibi HA; KKESH Uveitis Survey Study Group; KKESH Uveitis Survey Study Group. Uveitis in Behçet disease in a tertiary center over 25 years: the KKESH Uveitis Survey Study Group. Am J Ophthalmol. 2015;159:177-184.
18. Lodhi SA, Reddy JL, Peram V. Clinical spectrum and management options in Vogt-Koyanagi-Harada disease. Clin Ophthalmol. 2017;11:1399-1406.
19. Goebel JC, Roesel M, Heinz C, Michels H, Ganser G, Heiligenhaus A. Azathioprine as a treatment option for uveitis in patients with juvenile idiopathic arthritis. Br J Ophthalmol. 2011;95:209-213.
20. Seksik P, Cosnes J, Sokol H, Nion-Larmurier I, Gendre JP, Beaugerie L. Incidence of benign upper respiratory tract infections, HSV and HPV cutaneous infections in inflammatory bowel disease patients treated with azathioprine. Aliment Pharmacol Ther. 2009;29:1106-1113.
21. Blumentals WA, Arreglado A, Napalkov P, Toovey S. Rheumatoid arthritis and the incidence of influenza and influenza-related complications: a retrospective cohort study. BMC Musculoskelet Disord. 2012;13:158.
22. Thorne JE, Jabs DA, Qazi FA, Nguyen QD, Kempen JH, Dunn JP. Mycophenolate mofetil therapy for inflammatory eye disease. Ophthalmology. 2005;112:1472-1477.
23. Yalçındağ FN, Amer R, Forrester JV. Mycophenolate mofetil in the treatment of ocular inflammation in ANCA-associated vasculitis. J Ocul Pharmacol Ther. 2008;24:249-254.
24. Ritter ML, Pirofski L. Mycophenolate mofetil: effects on cellular immune subsets, infectious complications, and antimicrobial activity. Transpl Infect Dis. 2009;11:290-297.
25. Foster CS, Kothari S, Anesi SD, Vitale AT, Chu D, Metzinger JL, Cerón O. The Ocular Immunology and Uveitis Foundation preferred practice patterns of uveitis management. Surv Ophthalmol. 2016;61:1-17.
26. Berth-Jones J, Exton LS, Ladoyanni E, Mohd Mustapa MF, Tebbs VM, Yesudian PD, Levell NJ. British Association of Dermatologists guidelines for the safe and effective prescribing of oral ciclosporin in dermatology 2018. Br J Dermatol. 2019;180:1312-1338.
27. de Wilde AH, Raj VS, Oudshoorn D, Bestebroer TM, van Nieuwkoop S, Limpens RWAL, Posthuma CC, van der Meer Y, Bárcena M, Haagmans BL, Snijder EJ, van den Hoogen BG. MERS-coronavirus replication induces severe in vitro cytopathology and is strongly inhibited by cyclosporin A or interferon-α treatment. J Gen Virol. 2013;94:1749-1760.
28. Ghaffari Rahbar M, Nafar M, Khoshdel A, Dalili N, Abrishami A, Firouzan A, Poorrezagholi F, Samadian F, Ziaie S, Fatemizadeh S, Samavat S. Low rate of COVID-19 pneumonia in kidney transplant recipients-A battle between infection and immune response? Transpl Infect Dis. 2020;22:e13406.
29. Demir E, Uyar M, Parmaksiz E, Sinangil A, Yelken B, Dirim AB, Merhametsiz O, Yadigar S, Atan Ucar Z, Ucar AR, Demir ME, Mese M, Akin EB, Garayeva N, Safak S, Oto OA, Yazici H, Turkmen A. COVID-19 in kidney transplant recipients: A multicenter experience in Istanbul. Transpl Infect Dis. 2020;22:e13371.
30. Rodriguez-Cubillo B, de la Higuera MAM, Lucena R, Franci EV, Hurtado M, Romero NC, Moreno AR, Valencia D, Velo M, Fornie IS, Sanchez-Fructuoso AI. Should cyclosporine be useful in renal transplant recipients affected by SARS-CoV-2? Am J Transplant. 2020;20:3173-3181.
31. Murphy CC, Greiner K, Plskova J, Duncan L, Frost NA, Forrester JV, Dick AD. Cyclosporine vs tacrolimus therapy for posterior and intermediate uveitis. Arch Ophthalmol. 2005;123:634-641.
32. Carbajo-Lozoya J, Müller MA, Kallies S, Thiel V, Drosten C, von Brunn A. Replication of human coronaviruses SARS-CoV, HCoV-NL63 and HCoV-229E is inhibited by the drug FK506. Virus Res. 2012; 165:112-117.
33. B Bossini N, Alberici F, Delbarba E, Valerio F, Manenti C, Possenti S, Econimo L, Maffei C, Pola A, Terlizzi V, Salviani C, Moscato M, Pasquali S, Zambetti N, Tonoli M, Affatato S, Pecchini P, Viola FB, Malberti F, Depetri G, Gaggiotti M, Scolari F; Brescia Renal COVID task force. Kidney transplant patients

with SARS-CoV-2 infection: the brescia renal COVID task force experience. Am J Transplant. 2020;20:3019-3029.
34. Davatchi F, Sadeghi Abdollahi B, Shams H, Shahram F, Nadji A, Chams-Davatchi C, Faezi T, Akhlaghi M, Ghodsi Z, Ashofteh F, Mohtasham N. Combination of pulse cyclophosphamide and azathioprine in ocular manifestations of Behcet's disease: longitudinal study of up to 10 years. Int J Rheum Dis. 2014;17:444-452.
35. Durrani K, Papaliodis GN, Foster CS. Pulse IV cyclophosphamide in ocular inflammatory disease: efficacy and short-term safety. Ophthalmology. 2004; 111:960-965.
36. Kanellopoulos A, Ahmed MZ, Kishore B, Lovell R, Horgan C, Paneesha S, Lloyd R, Salhan B, Giles H, Chauhan S, Venkatadasari I, Khakwani M, Murthy V, Xenou E, Dassanayake H, Srinath S, Kaparou M, Nikolousis E. COVID-19 in bone marrow transplant recipients: reflecting on a single centre experience. Br J Haematol. 2020;190:67-70.
37. Wendling D, Paccou J, Berthelot JM, Flipo RM, Guillaume-Czitrom S, Prati C, Dernis E, Direz G, Ferrazzi V, Ristori JM; CRI. New onset of uveitis during anti-tumor necrosis factor treatment for rheumatic diseases. Semin Arthritis Rheum. 2011;41:503-510.
38. Levy-Clarke G, Jabs DA, Read RW, Rosenbaum JT, Vitale A, Van Gelder RN. Expert panel recommendations for the use of anti-tumor necrosis factor biologic agents in patients with ocular inflammatory disorders. Ophthalmology. 2014;121:785-796.
39. Sharma SM, Ramanan AV, Riley P, Dick AD. Use of infliximab in juvenile onset rheumatological disease-associated refractory uveitis: efficacy in joint and ocular disease. Ann Rheum Dis. 2007;66:840-841.
40. Ally MR, Veerappan GR, Koff JM. Treatment of recurrent Crohn's uveitis with infliximab. Am J Gastroenterol. 2008;103:2150-2151.
41. Matsuda J, Kaburaki T, Kobayashi S, Numaga J. Treatment of recurrent anterior uveitis with infliximab in patient with ankylosing spondylitis. Jpn J Ophthalmol. 2013;57:104-107.
42. Daudén E, Carretero G, Rivera R, Ferrándiz C, Llamas-Velasco M, de la Cueva P, Belinchón I, Gómez-García FJ, Herrera-Acosta E, Ruiz-Genao DP, Ferrán-Farrés M, Alsina M, Baniandrés-Rodríguez O, Sánchez-Carazo JL, Sahuquillo-Torralba A, Fernández-Freire LR, Vilar-Alejo J, García-Donoso C, Carrascosa JM, Herrera-Ceballos E, López-Estebaranz JL, Botella-Estrada R, Segovia-Muñoz E, Descalzo MA, García-Doval I; BIOBADADERM Study Group. Long-term safety of nine systemic medications for psoriasis: A cohort study using the Spanish Registry of Adverse Events for Biological Therapy in Dermatological Diseases (BIOBADADERM) Registry. J Am Acad Dermatol. 2020;83:139-150.
43. Lichtenstein GR, Feagan BG, Cohen RD, Salzberg BA, Safdi M, Popp JW, Jr., Langholff W, Sandborn WJ. Infliximab for Crohn's Disease: More Than 13 Years of Real-world Experience. Inflamm Bowel Dis. 2018;24:490-501.
44. Queiro Silva R, Armesto S, González Vela C, Naharro Fernández C, González-Gay MA. COVID-19 patients with psoriasis and psoriatic arthritis on biologic immunosuppressant therapy vs apremilast in North Spain. Dermatol Ther. 2020;33:e13961.
45. Bezzio C, Manes G, Bini F, Pellegrini L, Saibeni S. Infliximab for severe ulcerative colitis and subsequent SARS-CoV-2 pneumonia: a stone for two birds. Gut. 2020;70:623-624.
46. Din S, Kent A, Pollok RC, Meade S, Kennedy NA, Arnott I, Beattie RM, Chua F, Cooney R, Dart RJ, Galloway J, Gaya DR, Ghosh S, Griffiths M, Hancock L, Hansen R, Hart A, Lamb CA, Lees CW, Limdi JK, Lindsay JO, Patel K, Powell N, Murray CD, Probert C, Raine T, Selinger C, Sebastian S, Smith PJ, Tozer P, Ustianowski A, Younge L, Samaan MA, Irving PM. Adaptations to the British Society of Gastroenterology guidelines on the management of acute severe UC in the context of the COVID-19 pandemic: a RAND appropriateness panel. Gut. 2020;69:1769-1777.
47. Dolinger MT, Person H, Smith R, Jarchin L, Pittman N, Dubinsky MC, Lai J. Pediatric Crohn Disease and Multisystem Inflammatory Syndrome in Children (MIS-C) and COVID-19 Treated With Infliximab. J Pediatr Gastroenterol Nutr. 2020;71:153-155.
48. Suhler EB, Lowder CY, Goldstein DA, Giles T, Lauer AK, Kurz PA, Pasadhika S, Lee ST, de Saint Sardos A, Butler NJ, Tessler HH, Smith JR, Rosenbaum JT. Adalimumab therapy for refractory uveitis: results of a multicentre, open-label, prospective trial. Br J Ophthalmol. 2013;97:481-486.
49. Burmester GR, Panaccione R, Gordon KB, McIlraith MJ, Lacerda AP. Adalimumab: long-term safety in 23 458 patients from global clinical trials in rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, psoriasis and Crohn's disease. Ann Rheum Dis. 2013; 72:517-524.
50. Jaffe GJ, Dick AD, Brézin AP, Nguyen QD, Thorne JE, Kestelyn P, Barisani-Asenbauer T, Franco P, Heiligenhaus A, Scales D, Chu DS, Camez A, Kwatra NV, Song AP, Kron M, Tari S, Suhler EB. Adalimumab in Patients with Active Noninfectious Uveitis. N Engl J Med. 2016;375:932-943.
51. Valenti M, Facheris P, Pavia G, Gargiulo L, Borroni RG, Costanzo A, Narcisi A. Non-complicated evolution of COVID-19 infection in a patient with psoriasis and psoriatic arthritis during treatment with adalimumab. Dermatol Ther. 2020:e13708.
52. Tursi A, Angarano G, Monno L, Saracino A, Signorile F, Ricciardi A, Papa A. COVID-19 infection in Crohn's disease under treatment with adalimumab. Gut. 2020;69:1364-1365.
53. Tosi GM, Sota J, Vitale A, Rigante D, Emmi G, Lopalco G, Guerriero S, Orlando I, Iannone F, Frediani B, Angotti R, Messina M, Galeazzi M, Vannozzi L, Cantarini L, Fabiani C. Efficacy and safety of certolizumab pegol and golimumab in the treatment of non-infectious uveitis. Clin Exp Rheumatol. 2019;37:680-683.
54. Blauvelt A, Paul C, van de Kerkhof P, Warren RB, Gottlieb AB, Langley RG, Brock F, Arendt C, Boehnlein M, Lebwohl M, Reich K. Long-Term Safety of Certolizumab Pegol in Plaque Psoriasis: Pooled Analysis over 3 Years from Three Phase 3, Randomised, Placebo-Controlled Studies. Br J Dermatol. 2020;184:640-651.
55. Sepah YJ, Sadiq MA, Chu DS, Dacey M, Gallemore R, Dayani P, Hanout M, Hassan M, Afridi R, Agarwal A, Halim MS, Do DV, Nguyen QD. Primary (Month-6) Outcomes of the STOP-Uveitis Study: Evaluating the Safety, Tolerability, and Efficacy of Tocilizumab in Patients With Noninfectious Uveitis. Am J Ophthalmol. 2017;183:71-80.
56. Jones G, Sebba A, Gu J, Lowenstein MB, Calvo A, Gomez-Reino JJ, Siri DA, Tomsic M, Alecock E, Woodworth T, Genovese MC. Comparison of tocilizumab monotherapy versus methotrexate monotherapy in patients with moderate to severe rheumatoid arthritis: the AMBITION study. Ann Rheum Dis. 2010;69:88-96.
57. Pawar A, Desai RJ, Solomon DH, Santiago Ortiz AJ, Gale S, Bao M, Sarsour K, Schneeweiss S, Kim SC. Risk of serious infections in tocilizumab versus other biologic drugs in patients with rheumatoid arthritis: a multidatabase cohort study. Ann Rheum Dis. 2019;78:456-464.
58. Mihai C, Dobrota R, Schröder M, Garaiman A, Jordan S, Becker MO, Maurer B, Distler O. COVID-19 in a patient with systemic sclerosis treated with tocilizumab for SSc-ILD. Ann Rheum Dis. 2020;79:668-669.
59. Pérez-Sáez MJ, Blasco M, Redondo-Pachón D, Ventura-Aguiar P, Bada-Bosch T, Pérez-Flores I, Melilli E, Sánchez-Cámara LA, López-Oliva MO, Canal C, Shabaka A, Garra-Moncau N, Martín-Moreno PL, López V, Hernández-Gallego R, Siverio O, Galeano C, Espí-Reig J, Cabezas CJ, Rodrigo MT, Llinàs-Mallol L, Fernández-Reyes MJ, Cruzado-Vega L, Pérez-Tamajón L, Santana-Estupiñán R, Ruiz-Fuentes MC, Tabernero G, Zárraga S, Ruiz JC, Gutiérrez-Dalmau A, Mazuecos A, Sánchez-Álvarez E, Crespo M, Pascual J; Spanish Society of Nephrology COVID-19 Group. Use of tocilizumab in kidney transplant recipients with COVID-19. Am J Transplant. 2020;20:3182-3190.
60. Dick AD, Tugal-Tutkun I, Foster S, Zierhut M, Melissa Liew SH, Bezlyak V, Androudi S. Secukinumab in the treatment of noninfectious uveitis: results of three randomized, controlled clinical trials. Ophthalmology. 2013;120:777-787.
61. McInnes IB, Mease PJ, Ritchlin CT, Rahman P, Gottlieb AB, Kirkham B, Kajekar R, Delicha EM, Pricop L, Mpofu S. Secukinumab sustains improvement in signs and symptoms of psoriatic arthritis: 2 year results from the phase 3 FUTURE 2 study. Rheumatology (Oxford). 2017;56:1993-2003.
62. Carugno A, Gambini DM, Raponi F, Vezzoli P, Robustelli Test E, Arosio MEG, Callegaro A, Sena P. Coronavirus disease 2019 (COVID-19) rash in a

psoriatic patient treated with Secukinumab: is there a role for Interleukin 17? Dermatol Ther. 2020;33:e14011.
63. Pacha O, Sallman MA, Evans SE. COVID-19: a case for inhibiting IL-17? Nat Rev Immunol. 2020;20:345-346.
64. Sharmeen S, Elghawy A, Zarlasht F, Yao Q. COVID-19 in rheumatic disease patients on immunosuppressive agents. Semin Arthritis Rheum. 2020;50:680-686.
65. Sanchez-Piedra C, Diaz-Torne C, Manero J, Pego-Reigosa JM, Rúa-Figueroa Í, Gonzalez-Gay MA, Gomez-Reino J, Alvaro-Gracia JM; BIOBADASER study group. Clinical features and outcomes of COVID-19 in patients with rheumatic diseases treated with biological and synthetic targeted therapies. Ann Rheum Dis. 2020;79:988-990.
66. Fabiani C, Vitale A, Rigante D, Emmi G, Lopalco G, Di Scala G, Sota J, Orlando I, Franceschini R, Frediani B, Galeazzi M, Iannone F, Tosi GM, Cantarini L. The Presence of Uveitis Is Associated with a Sustained Response to the Interleukin (IL)-1 Inhibitors Anakinra and Canakinumab in Behçet's Disease. Ocul Immunol Inflamm. 2020;28:298-304.
67. Sota J, Vitale A, Insalaco A, Sfriso P, Lopalco G, Emmi G, Cattalini M, Manna R, Cimaz R, Priori R, Talarico R, de Marchi G, Frassi M, Gallizzi R, Soriano A, Alessio M, Cammelli D, Maggio MC, Gentileschi S, Marcolongo R, La Torre F, Fabiani C, Colafrancesco S, Ricci F, Galozzi P, Viapiana O, Verrecchia E, Pardeo M, Cerrito L, Cavallaro E, Olivieri AN, Paolazzi G, Vitiello G, Maier A, Silvestri E, Stagnaro C, Valesini G, Mosca M, de Vita S, Tincani A, Lapadula G, Frediani B, De Benedetti F, Iannone F, Punzi L, Salvarani C, Galeazzi M, Angotti R, Messina M, Tosi GM, Rigante D, Cantarini L; "Working Group" of Systemic Autoinflammatory Diseases of SIR (Italian Society of Rheumatology). Safety profile of the interleukin-1 inhibitors anakinra and canakinumab in real-life clinical practice: a nationwide multicenter retrospective observational study. Clin Rheumatol. 2018;37:2233-2240.
68. Monteagudo LA, Boothby A, Gertner E. Continuous Intravenous Anakinra Infusion to Calm the Cytokine Storm in Macrophage Activation Syndrome. ACR Open Rheumatol. 2020;2:276-282.
69. Calabrese LH, Calabrese C. Cytokine release syndrome and the prospects for immunotherapy with COVID-19. Part 2: The role of interleukin 1. Cleve Clin J Med. 2020.
70. Lee JH, Lee CS, Lee SC. Interferon alpha-2a treatment for refractory Behcet uveitis in Korean patients. BMC Ophthalmol. 2018;18:52.
71. Yalçindag N, Köse HC. Comparison of the Treatment Results for Behçet Uveitis in Patients Treated with Infliximab and Interferon. Ocul Immunol Inflamm. 2020;28:305-314.
72. Yalçindag N, Yanık Ö, Düzgün N. Efficacy of Infliximab in Patients with Refractory Uveitis Associated with Behcet Disease. J Clin Exp Ophthalmol. 2014;1:1-5.
73. Deuter C, Stübiger N, Zierhut M. Interferon-α therapy in noninfectious uveitis. Dev Ophthalmol. 2012;51:90-97.
74. He G, Sun W, Wu J, Cai J. Serial Computed Tomography Findings in a Child with Coronavirus Disease (COVID-19) Pneumonia. Indian Pediatr. 2020;57:467-468.
75. Chen Q, Quan B, Li X, Gao G, Zheng W, Zhang J, Zhang Z, Liu C, Li L, Wang C, Zhang G, Li J, Dai Y, Yang J, Han W. A report of clinical diagnosis and treatment of nine cases of coronavirus disease 2019. J Med Virol. 2020;92:683-687.
76. Miserocchi E, Modorati G, Berchicci L, Pontikaki I, Meroni P, Gerloni V. Long-term treatment with rituximab in severe juvenile idiopathic arthritis-associated uveitis. Br J Ophthalmol. 2016; 100:782-786.
77. Lasave AF, You C, Ma L, Abusamra K, Lamba N, Valdes Navarro M, Meese H, Foster CS. Long-term outcomes of rituximab therapy in patients with noninfectious posterior uveitis refractory to conventional immunosuppressive therapy. Retina. 2018;38:395-402.
78. Davatchi F, Shams H, Rezaipoor M, Sadeghi-Abdollahi B, Shahram F, Nadji A, Chams-Davatchi C, Akhlaghi M, Faezi T, Naderi N. Rituximab in intractable ocular lesions of Behcet's disease; randomized single-blind control study (pilot study). Int J Rheum Dis. 2010;13:246-252.
79. Lerman MA, Rabinovich CE. The Future Is Now: Biologics for Non-Infectious Pediatric Anterior Uveitis. Paediatr Drugs. 2015;17:283-301.
80. Luna G, Alping P, Burman J, Fink K, Fogdell-Hahn A, Gunnarsson M, Hillert J, Langer-Gould A, Lycke J, Nilsson P, Salzer J, Svenningsson A, Vrethem M, Olsson T, Piehl F, Frisell T. Infection Risks Among Patients With Multiple Sclerosis Treated With Fingolimod, Natalizumab, Rituximab, and Injectable Therapies. JAMA Neurol. 2019;77:184-191.
81. Nuño L, Novella Navarro M, Bonilla G, Franco-Gómez K, Aguado P, Peiteado D, Monjo I, Tornero C, Villalba A, Miranda-Carus ME, De Miguel E, Bogas P, Castilla-Plaza A, Bernad-Pineda M, García-Lorenzo E, Rodríguez-Araya T, Balsa A. Clinical course, severity and mortality in a cohort of patients with COVID-19 with rheumatic diseases. Ann Rheum Dis. 2020;79:1659-1661.
82. Schulze-Koops H, Krueger K, Vallbracht I, Hasseli R, Skapenko A. Increased risk for severe COVID-19 in patients with inflammatory rheumatic diseases treated with rituximab. Ann Rheum Dis. 2020;2021:218075.
83. Houot R, Levy R, Cartron G, Armand P. Could anti-CD20 therapy jeopardise the efficacy of a SARS-CoV-2 vaccine? Eur J Cancer. 2020; 136:4-6.
84. Maarouf A, Rico A, Boutiere C, Perriguey M, Demortiere S, Pelletier J, Audoin B; Under the aegis of OFSEP. Extending rituximab dosing intervals in patients with MS during the COVID-19 pandemic and beyond? Neurol Neuroimmunol Neuroinflamm. 2020;7:825.
85. Birolo C, Zannin ME, Arsenyeva S, Cimaz R, Miserocchi E, Dubko M, Deslandre CJ, Falcini F, Alessio M, La Torre F, Denisova E, Martini G, Nikishina I, Zulian F. Comparable Efficacy of Abatacept Used as First-line or Second-line Biological Agent for Severe Juvenile Idiopathic Arthritis-related Uveitis. J Rheumatol. 2016;43:2068-2073.
86. Alten R, Kaine J, Keystone E, Nash P, Delaet I, Genovese MC. Long-term safety of subcutaneous abatacept in rheumatoid arthritis: integrated analysis of clinical trial data representing more than four years of treatment. Arthritis Rheumatol. 2014;66:1987-1997.
87. Steingo B, Al Malik Y, Bass AD, Berkovich R, Carraro M, Fernández Ó, Ionete C, Massacesi L, Meuth SG, Mitsikostas DD, Pardo G, Simm RF, Traboulsee A, Choudhry Z, Daizadeh N, Compston DAS; CAMMS223, CAMMS03409, and TOPAZ Investigators. J Neurol. 2020;267:3343-3353.
88. Isaacs JD, Hale G, Waldmann H, Dick AD, Haynes R, Forrester JV, Watson P, Meyer PA. Monoclonal antibody therapy of chronic intraocular inflammation using Campath-1H. Br J Ophthalmol. 1995;79:1054-1055.
89. Dalla Costa G, Leocani L, Montalban X, Guerrero AI, Sørensen PS, Magyari M, Dobson RJB, Cummins N, Narayan VA, Hotopf M, Comi G; RADAR-CNS consortium. Real-time assessment of COVID-19 prevalence among multiple sclerosis patients: a multicenter European study. Neurol Sci. 2020;41:1647-1650.
90. Lu CW, Liu XF, Jia ZF. 2019-nCoV transmission through the ocular surface must not be ignored. Lancet. 2020;395:e39.
91. Choudhary R, Kapoor MS, Singh A, Bodakhe SH. Therapeutic targets of renin-angiotensin system in ocular disorders. J Curr Ophthalmol. 2017;29:7-16.
92. Ma D, Chen CB, Jhanji V, Xu C, Yuan XL, Liang JJ, Huang Y, Cen LP, Ng TK. Expression of SARS-CoV-2 receptor ACE2 and TMPRSS2 in human primary conjunctival and pterygium cell lines and in mouse cornea. Eye (Lond). 2020;34:1212-1219.
93. Seah I, Agrawal R. Can the Coronavirus Disease 2019 (COVID-19) Affect the Eyes? A Review of Coronaviruses and Ocular Implications in Humans and Animals. Ocul Immunol Inflamm. 2020;28:391-395.
94. 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.
95. 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.
96. Bostanci Ceran B, Ozates S. Ocular manifestations of coronavirus disease 2019. Graefes Arch Clin Exp Ophthalmol. 2020;258:1959-1963.
97. Casagrande M, Fitzek A, Püschel K, Aleshcheva G, Schultheiss HP, Berneking L, Spitzer MS, Schultheiss M. Detection of SARS-CoV-2 in Human Retinal Biopsies of Deceased COVID-19 Patients. Ocul Immunol Inflamm. 2020;28:721-725.

98. Marinho PM, Marcos AAA, Romano AC, Nascimento H, Belfort R, Jr. Retinal findings in patients with COVID-19. Lancet. 2020; 395:1610.
99. Vavvas DG, Sarraf D, Sadda SR, Eliott D, Ehlers JP, Waheed NK, Morizane Y, Sakamoto T, Tsilimbaris M, Miller JB. Concerns about the interpretation of OCT and fundus findings in COVID-19 patients in recent Lancet publication. Eye (Lond). 2020;34:2153-2154.
100. Bettach E, Zadok D, Weill Y, Brosh K, Hanhart J. Bilateral anterior uveitis as a part of a multisystem inflammatory syndrome secondary to COVID-19 infection. J Med Virol. 2021;93:139-140.
101. Dick AD, Rosenbaum JT, Al-Dhibi HA, Belfort R Jr, Brézin AP, Chee SP, Davis JL, Ramanan AV, Sonoda KH, Carreño E, Nascimento H, Salah S, Salek S, Siak J, Steeples L; Fundamentals of Care for Uveitis International Consensus Group. Guidance on Noncorticosteroid Systemic Immunomodulatory Therapy in Noninfectious Uveitis: Fundamentals Of Care for UveitiS (FOCUS) Initiative. Ophthalmology. 2018; 125:757-773.
102. Zierhut M, De Smet MD, Gupta V, Pavesio C, Nguyen QD, Chee SP, Cunningham ET, Agrawal R. Evolving Consensus Experience of the IUSG-IOIS-FOIS with Uveitis in the Time of COVID-19 Infection. Ocul Immunol Inflamm. 2020; 28:709-713.
103. Gupta V, Rajendran A, Narayanan R, Chawla S, Kumar A, Palanivelu MS, Muralidhar NS, Jayadev C, Pappuru R, Khatri M, Agarwal M, Aurora A, Bhende P, Bhende M, Bawankule P, Rishi P, Vinekar A, Trehan HS, Biswas J, Agarwal R, Natarajan S, Verma L, Ramasamy K, Giridhar A, Rishi E, Talwar D, Pathangey A, Azad R, Honavar SG. Indian J Ophthalmol. 2020;68:962-973.
104. Smith JR, Lai TYY. Managing Uveitis during the COVID-19 Pandemic. Ophthalmology. 2020;127:65-67.
105. Hung JCH, Li KKW. Implications of COVID-19 for uveitis patients: perspectives from Hong Kong. Eye (Lond). 2020;34:1163-1164.
106. Thng ZX, De Smet MD, Lee CS, Gupta V, Smith JR, McCluskey PJ, Thorne JE, Kempen JH, Zierhut M, Nguyen QD, Pavesio C, Agrawal R. COVID-19 and immunosuppression: a review of current clinical experiences and implications for ophthalmology patients taking immunosuppressive drugs. Br J Ophthalmol. 2020;105:306-310.
107. Stanescu-Segall D, Sales de Gauzy T, Reynolds R, Faes L, Pohlmann D, Pakzad-Vaezi K, Ting D, Saadoun D, Ambati J, Loewenstein A, Bodaghi B, de Smet MD, Touhami S. Expert opinion on the management and follow-up of uveitis patients during SARS-CoV-2 outbreak. Expert Rev Clin Immunol. 2020;16:651-657.
108. Agrawal R, Testi I, Lee CS, Tsui E, Blazes M, Thorne JE, Okada AA, Smith JR, McCluskey PJ, Kempen JH, Tappeiner C, Agarwal M, Bodaghi B, Nguyen QD, Gupta V, De Smet MD, Zierhut M, Pavesio C; COVID-19 IMT Study Group. Evolving consensus for immunomodulatory therapy in non-infectious uveitis during the COVID-19 pandemic. Br J Ophthalmol. 2020;105:639-647.
109. Landewé RB, Machado PM, Kroon F, Bijlsma HW, Burmester GR, Carmona L, Combe B, Galli M, Gossec L, Iagnocco A, Isaacs JD, Mariette X, McInnes I, Mueller-Ladner U, Openshaw P, Smolen JS, Stamm TA, Wiek D, Schulze-Koops H. EULAR provisional recommendations for the management of rheumatic and musculoskeletal diseases in the context of SARS-CoV-2. Ann Rheum Dis. 2020;79:851-858.
110. Espinosa G, Araujo O, Amaro S, Bodro M, Moreno PJ, Moreno R, Ugarte A, Cervera R. COVID-19 and Behçet's disease: clinical case series. Ann Rheum Dis. 2020;2020:217778.
111. Yurttaş B, Oztas M, Tunc A, Balkan İİ, Tabak OF, Hamuryudan V, Seyahi E. Characteristics and outcomes of Behçet's syndrome patients with Coronavirus Disease 2019: a case series of 10 patients. Intern Emerg Med. 2020;15:1567-1571.

DOI: 10.4274/tjo.galenos.2021.72662
Turk J Ophthalmol 2021;51:243-245

Case Report

Systematized Epidermal Nevus Syndrome Involving the Upper and Lower Eyelids Bilaterally

Özlem Biçer*, Ayşe Boyvat**, Melek Banu Hoşal***, Cevriye Cansız Ersöz****, Aylin Okçu Heper****

*Boğazlıyan State Hospital, Clinic of Ophthalmology, Yozgat, Turkey
**Ankara University Faculty of Medicine, Department of Dermatology, Ankara, Turkey
***Ankara University Faculty of Medicine, Department of Ophthalmology, Ankara, Turkey
****Ankara University Faculty of Medicine, Department of Pathology, Ankara, Turkey

Abstract

A 29-year-old woman presented with dark-colored raised lesions on both eyelids since early childhood. Ophthalmological examination revealed pigmented verrucous lesions on her upper and lower eyelids bilaterally. The patient had a history of generalized tonic-clonic seizures. Dermatological examination revealed hyperpigmented verrucous plaques arranged along lines of Blaschko on the neck, trunk, and arms. On the basis of these findings, the diagnosis of epidermal nevus syndrome (ENS) was made. She had surgery for debulking of the lesions. Histological analysis revealed hyperkeratosis with foci of parakeratosis, acanthosis, and papillomatosis, consistent with linear verrucous epidermal nevus. Postoperative residual lesions did not respond to oral acitretin therapy (10 mg/kg/day for 2 months). Systematized ENS can rarely cause linear verrucous nevi on the upper and lower eyelids on both sides. These patients should be investigated for accompanying systemic anomalies and followed for potential malignant transformation of the skin lesions.

Keywords: Epidermal nevus, epidermal nevus syndrome, eyelid, linear verrucous epidermal nevus

Introduction

Epidermal nevi (EN) are cutaneous hamartomatous lesions derived from the embryonic ectoderm and characterized by hyperplasia of the epidermis and adnexal structures. Epidermal nevus syndrome (ENS), first described by Schimmelpenning in 1957, is a neurocutaneous disorder characterized by the presence of EN in association with various developmental nervous, ocular, skeletal, cardiovascular, and urogenital abnormalities.[1,2] EN usually show a linear pattern along the Blashko lines and are categorized as systematized when they involve large areas on either side of the body.

Here, we report a rare case of systematized ENS causing linear verrucous EN in both upper and lower eyelids bilaterally.

Case Report

A 29-year-old woman presented with the complaint of dark-colored raised lesions on both eyelids since early childhood. At the age of 7 years, the plaques on her eyelids had become more raised, verrucous, and scaly. Her medical history was significant for generalized tonic-clonic seizures starting in early childhood. The seizures were well controlled with anti-epileptics including carbamazepine (800 mg/day) and lamotrigine (200 mg/day). There was no evidence of mental retardation in the patient. Her family history was unremarkable.

Ophthalmological examination revealed pigmented verrucous lesions on her upper and lower eyelids bilaterally (Figure 1a). Her visual acuity was 20/20 in both eyes. Slit-

Address for Correspondence: Özlem Biçer, Boğazlıyan State Hospital, Clinic of Ophthalmology, Yozgat, Turkey
E-mail: ozlembicer90@gmail.com **ORCID-ID:** orcid.org/0000-0002-7638-4739
Received: 18.10.2020 **Accepted:** 03.05.2021

Cite this article as: Biçer Ö, Bovyat A, Hoşal MB, Cansız Ersöz C, Okçu Heper A. Systematized Epidermal Nevus Syndrome Involving the Upper and Lower Eyelids Bilaterally. Turk J Ophthalmol 2021;51:243-245

lamp and fundus examinations were normal. Dermatological examination revealed hyperpigmented verrucous plaques arranged along lines of Blaschko with areas involving the neck, trunk, and arms (Figure 1b, c). No pathological findings were observed in the musculoskeletal, urogenital, and cardiovascular systems. Palliative debulking of the eyelid lesions was performed for cosmetic reasons.

Histologic examination was compatible with EN (Figure 1d). The patient was diagnosed with ENS due to the history of epilepsy accompanying the extensive EN. The patient was treated with systemic oral 10 mg/kg/day acitretin therapy but the drug was discontinued after two months because the lesion showed no reduction in size (Figure 1e).

Discussion

EN are rare hamartomas that usually appear at birth but may become clinically observable later in life.[3] EN are classified according to their clinical appearance as solitary or localized linear lesions, systematized (bilateral, parallel linear lesions), nevus unius lateralis (unilateral lesions), and ichthyosis hystrix (bilateral and symmetric involvement).[4] Our case was evaluated as systematized EN with many verrucous plaques located on the patient's neck, trunk, and extremities and oriented along the Blaschko lines. The incidence of ENS is 1 in 1,000 newborns. Sporadic cases are more common than familial ones.[3]

The prevalence of ocular involvement in ENS is estimated to be 9-70%.[5,6] EN may occur in the eyelid or conjunctiva. Associated abnormalities may include ocular coloboma, epibulbar choristomas or lipodermoids, and corneal opacities.[5,6] Other rare associations are strabismus, ptosis, microphthalmia, nystagmus, astigmatism, cataract, and bilateral tear duct obstruction.[7] Our patient had linear verrucous EN on her eyelids bilaterally without any other ocular abnormality. Bilateral EN of the eyelids have been previously described only once, in a systematized cutaneous case without any extraocular abnormalities.[8] An extensive four-eyelid blepharoplasty and anterior lamellar rotation of the eyelashes were performed for treatment.

Café-au-lait macules, cutaneous hemangiomas, acanthosis nigricans, and melanocytic nevi are other dermatological findings that can be seen in ENS.[9] Neurologic abnormalities have been described in up to 50-70% of patients with ENS and include mental retardation, seizure, hypotonia, hyperkinesia, hemiplegia, hemiparesis, and cranial nerve palsies.[9,10] Skeletal anomalies occur in approximately 50% of patients with ENS (e.g., kyphoscoliosis, congenital hip dislocation, vitamin D-resistant rickets, limb hypertrophy, syndactyly, polydactyly, clinodactyly,

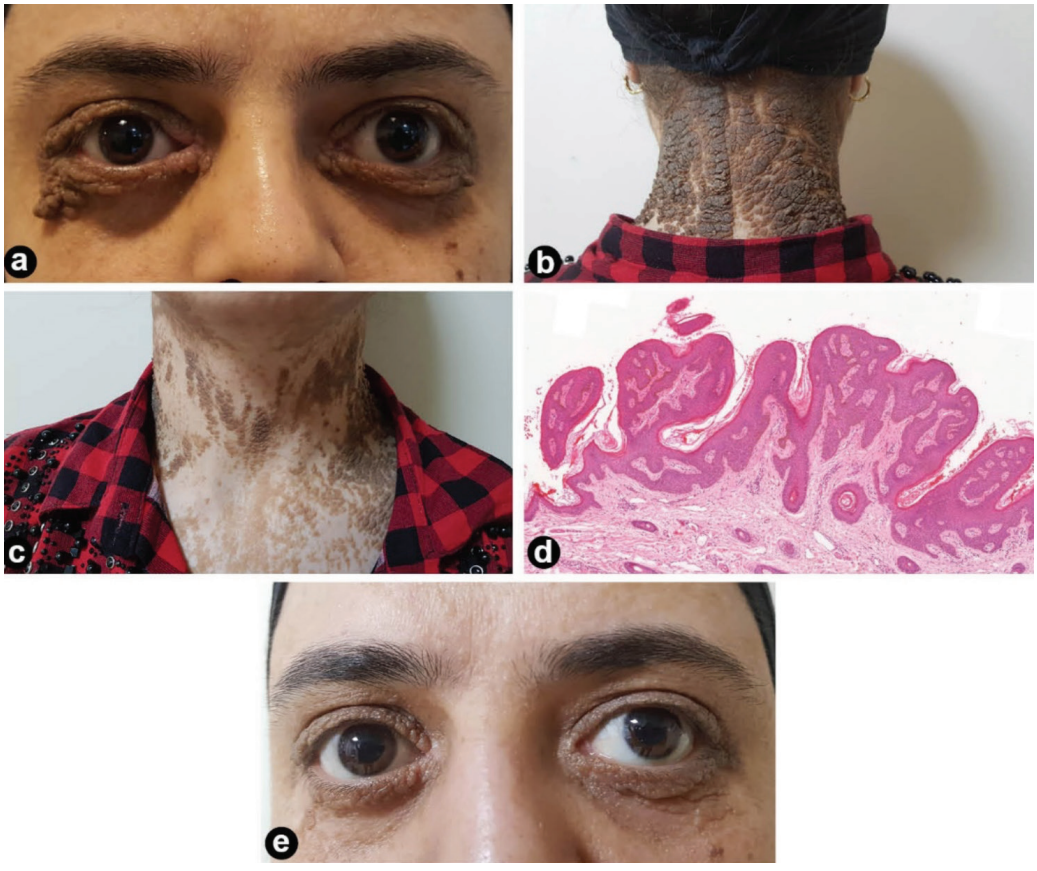

Figure 1. Pigmented verrucous lesions on the eyelids (a) and neck (b, c). d) The epidermis shows papillomatosis, hyperkeratosis, and acanthosis with marked elongation of rete ridges. Mild mononuclear cell infiltrate can be noted surrounding papillary dermal vessels; hematoxylin-eosin X40. e) Photograph taken 4 months after eyelid nevus debulking surgery

and bifid thumb).[9,10] In our case, systematized EN was associated only with generalized epilepsy.

Treatment of EN is recommended for cosmetic reasons and to prevent possible malignancy. Numerous treatment options such as excision, cryotherapy, liquid nitrogen, carbon dioxide laser, and topical or intra-lesional glucocorticoids has been used with varying success. Topical and systemic retinoids are other alternative treatment modalities. Oral acitretin therapies have been tried successfully in widespread hyperkeratotic disorders.[10] Due to the likelihood of malignant transformation in EN, long-term follow-up is suggested for patients with ENS.[11]

Ethics

Informed Consent: Obtained.

Peer-review: Externally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: M.B.H., A.B., Concept: Ö.B., M.B.H., Design: Ö.B., M.B.H., Data Collection or Processing: Ö.B., M.B.H., A.B., C.C.E., A.O.H., Analysis or Interpretation: Ö.B., A.B., M.B.H., C.C.E.,A.O.H., Literature Search: Ö.B., M.B.H., Writing: M.B.H., A.B., C.C.E., A.O.H.

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. Vidaurri-de la Cruz H, Tamayo-Sánchez L, Durán-McKinster C, de la Luz Orozco-Covarrubias M, Ruiz-Maldonado R. Epidermal nevus syndromes: clinical findings in 35 patients. Pediatr Dermatol. 2004;21:432-439.
2. Happle R. The group of epidermal nevus syndromes Part I. Well defined phenotypes. J Am Acad Dermatol. 2010;63:1-22.
3. Wolff K. Fitzpatrick's Dermatology in General Medicine. (7th ed). New York: McGraw-Hill Book Co; 2008:876-882.
4. Adams D, Athalye L, Schwimer C, Bender B. A profound case of linear epidermal nevus in a patient with epidermal nevus syndrome. J Dermatol Case Rep. 2011;5:30-33.
5. Sharma R, Singal A, Verma P, Rohatgi J, Sharma S. Epidermal nevus syndrome associated with unusual neurological, ocular, and skeletal features. Indian J Dermatol Venereol Leprol. 2012;78:480-483.
6. Insler MS, Davlin L. Ocular findings in linear sebaceous naevus syndrome. Br J Ophthalmol. 1987;71:268-272.
7. Rogers M, McCrossin I, Commens C. Epidermal nevi and the epidermal nevus syndrome. A review of 131 cases. J Am Acad Dermatol. 1989;20:476-488.
8. Loff HJ, Bardenstein DS, Levine MR. Systematized epidermal nevi: case report and review of clinical manifestations. Ophthalmic Plast Reconstr Surg. 1994;10:262-266.
9. Chatproedprai S, Wananukul S, Prasarnnaem T, Noppakun N. Epidermal nevus syndrome. Int J Dermatol. 2007;46:858-860.
10. Pandhi D, Reddy BS. A rare association of epidermal nevus syndrome and ainhum-like digital constrictions. Pediatr Dermatol. 2002;19:349-352.
11. Dubois A, Rannan-Eliya S, Husain A, Rajan N, Oliphant T. Squamous cell carcinomas in linear epidermal naevi. Clin Exp Dermatol. 2019;44:238-240.

DOI: 10.4274/tjo.galenos.2021.59558
Turk J Ophthalmol 2021;51:246-249

Case Report

Spheroidal Degeneration in Two Siblings: Clinical and Histopathological Features

Demet Yabanoğlu*, Mehmet Cem Mocan*, Murat İrkeç*, Mehmet Orhan*, Figen Söylemezoğlu**, Özlem Tanas Işıkcı**

*Hacettepe University Faculty of Medicine, Department of Ophthalmology, Ankara, Turkey
**Hacettepe University Faculty of Medicine, Department of Pathology, Ankara, Turkey

Abstract

Spheroidal corneal degeneration is predominantly seen in advanced age and hereditary predisposition to this disorder is very rare. This report describes the occurrence of bilateral band-shaped spheroidal corneal degeneration in two siblings.

Keywords: Spheroidal degeneration of the cornea and conjunctiva, band-shaped amber-colored spherules, familial predisposition, *in vivo* confocal microscopy

Introduction

Spheroidal degeneration is a slowly progressive corneal and conjunctival disorder that occurs mostly in the interpalpebral region with homogenous, band-shaped, translucent, yellow-golden globular deposits.[1,2] As corneal spherules corresponding to this clinical entity have been described under 20 different names, spheroidal degeneration is regarded as a very rare disorder in the world literature.[3] In reality, however, spheroidal degeneration is a common occurrence. Hereditary cases of this disorder are extremely rare and the pattern of inheritance is not clear.[4,5] Here, we report two cases of familial spheroidal degeneration.

Case Reports

Case 1

A 45-year-old Turkish man was evaluated for bilateral progressive loss of vision over the past 25 years. His family history was significant in that one of his sisters was diagnosed with similar corneal lesions in both eyes. His parents were not related and he had no previous history of any ocular or systemic inflammatory diseases.

Best corrected visual acuity was 20/100 in the right eye and counting fingers at 10 cm in the left eye. The ocular adnexa were normal. Slit-lamp examination revealed dilated bulbar conjunctival vasculature in both eyes and pinguecula in his left interpalpebral bulbar conjunctiva. Evaluation of both corneas revealed the presence of irregular epithelium overlying multiple amber-colored globules in the superficial stroma (Figure 1A, B). The surrounding stroma appeared hazy. Corneal thickness was measured as 1,090 µm and 1,095 µm in the right and left eyes, respectively. Although the posterior segment structures could not be visualized due to the presence of corneal lesions, ocular ultrasonography revealed attached retinas with clear vitreous. Intraocular pressures were within normal limits. The patient underwent incisional biopsy of the corneal lesions in his left eye.

Histopathology: The corneal specimen was stained with hematoxylin and eosin (H&E) (Figure 1C). On microscopic examination, the epithelium appeared normal and Bowman's layer contained small deposits that stained basophilic.

Address for Correspondence: Demet Yabanoğlu, Hacettepe University Faculty of Medicine, Department of Ophthalmology, Ankara, Turkey
E-mail: demet.aban@hacettepe.edu.tr **ORCID-ID:** orcid.org/0000-0003-4532-3543
Received: 27.10.2020 **Accepted:** 22.03.2021

Cite this article as: Yabanoğlu D, Mocan MC, İrkeç M, Orhan M, Söylemezoğlu F, Tanas Işıkcı Ö. Spheroidal Degeneration in Two Siblings: Clinical and Histopathological Features. Turk J Ophthalmol 2021;51:246-249

Confocal microscopy: The patient's corneal characteristics were evaluated using an *in vivo* laser confocal microscope, the Heidelberg Retinal Tomograph II, Rostock Cornea Module (Heidelberg Engineering GmgH, Dossenheim, Germany). A condensation of hyperreflective large globules, like hyaline accumulations, was noticed in the superficial layers of the central cornea as a consequence of protein denaturation (Figure 1D).

Case 2

The 35-year-old sister of the patient described above had bilateral progressive loss of vision and lacrimation since childhood. No ocular trauma or systemic or ocular inflammatory disorders were reported. Best corrected visual acuities were 20/125 in each eye. The ocular adnexa were normal. Biomicroscopically, band-shaped amber-colored anterior stromal globules were present in the interpalpebral cornea. The overlying epithelium appeared to be intact (Figure 2A, B). The anterior chamber was of normal depth and quiet, the iris showed normal architecture, and both eyes had moderate nuclear sclerosis. On ophthalmoscopic examination, both retinas appeared hazy due to the presence of the corneal lesions. Intraocular pressures were within normal limits. The patient underwent incisional biopsy of the corneal lesions in her right eye.

Histopathology: The corneal specimen was stained with Verhoeff-van Gieson for elastin (Figure 2C). The corneal stroma was free of deposits, but the superficial stroma lacked the normal parallel arrangement secondary to increased amount and thickness of elastic fibers as observed with Verhoeff-van Gieson staining.

Confocal microscopy: An accumulation of punctiform hyperreflective deposits was observed in confocal microscopy (Figure 2D).

Discussion

The clinical picture of spheroidal degeneration of the cornea and conjunctiva has three typical forms. Primary corneal spheroidal degeneration consists of superficial solitary or clustered spherules adjacent to the limbus, is seen especially in advanced age, is almost always bilateral, and can also be detected in normal eyes. Secondary corneal spheroidal degeneration involves single, grouped, or a solid plaque of spherules that occurs more frequently in eyes with a unilateral corneal pathology, often located in the deep stroma of the central cornea. The conjunctival type consists of conjunctival golden spherules associated with either of the corneal types and often with pinguecula, which is common in older ages.[1,2,3] However, the distinction between these forms is not sufficiently clear, and in many cases more than one form can be seen at the same time.[3]

In our report, we revealed familial band-shaped spheroidal changes with both conjunctival and corneal involvement in a family. The first patient had corneal spheroidal lesions in both eyes with intact epithelium in the subepithelium, Bowman's membrane, and superficial stroma (Figure 1A, B). In the second patient, the globules were smaller, vision was better in both eyes, and the opacity was identical in location (Figure 2A, B). Bilateral involvement and location of the spherules might indicate the diagnosis of primary corneal form. However, lesions had appeared prior to the age of 30 years. In case 1, the central plaque

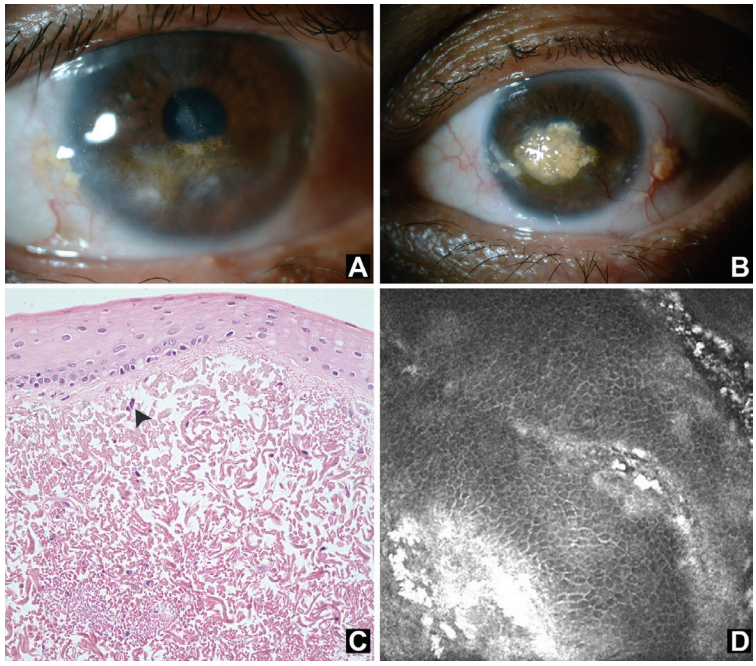

Figure 1. Clinical and histopathological characteristics of patient 1. Grade III keratopathy with spherical deposits in the central cornea.[6] The epithelium had a normal appearance on a microscopic examination. Note the subepithelial vascular invasion from the temporal and inferonasal limbus to the area of opacification (A, right eye). Grade IV keratopathy with a central plaque elevating the corneal epithelium, and pinguecula formation[6] (B, left eye). Hematoxylin and eosin (H&E) stained cornea specimen, X400. The arrow indicates basophilic stained deposits (C, left eye). *In vivo* confocal microscopy shows large hyperreflective globular deposits in the superficial layers of the central cornea (D, left eye)

was considered to be the secondary corneal form. However, the patients lacked significant signs of trauma or inflammatory diseases. The presence of pinguecula and conjunctival spherules suggested the conjunctival form. However, the patients suffered devastating corneal complications.

Based on the characteristics mentioned above, we concluded that the two siblings did not comply with the forms described.[1] With the increasing number of familial presentations, we hope that familial spheroidal degeneration might be included in the classification.

According to Johnson et al.[6], spheroidal degeneration is categorized into four grades (Grade I-IV). In our patients' right eyes, the spherules affected vision by progressing from the corneal periphery to the central zone, while the epithelium was not damaged, consistent with grade III keratopathy (Figure 1A, 2A). In the left eyes, the epithelium was raised by deposits, consistent with grade IV keratopathy, even though there were areas of clear cornea in the periphery (Figure 1B, 2B).

All forms of spheroidal degeneration are pathologically identical in both light and electron microscopy.[2] The epithelium and its basement membrane remain unaffected unless advanced degeneration is present, whereas Bowman's membrane is often disrupted. Hida et al.[5] observed changes in epithelial thickness and noted that the epithelium which was raised by spherical deposits was noticeably thinner in some areas. The spheroids, which contain proteins and are positively stained with Verhoeff's elastic stain, are characteristically found beneath the epithelium, in Bowman's layer and the superficial corneal stroma.[7] In this report, it was noted that the epithelium was not affected in the H&E-stained sections and that Bowman's membrane contained small basophilic deposits. These aggregates exhibited a positive reaction with the Verhoeff-van Gieson stain, giving the deposits a black and dark olive green appearance, and the superficial stroma lost its normal parallel pattern due to the increased amount and thickness of the elastic fibers. These hyaline corneal deposits are frequently observed in a variety of chronic ocular and corneal disorders, and as a result of exposure to climatic extremes.

Any cases of keratopathy associated with interpalpebral deposition should be considered in the differential diagnosis. Climatic conditions play a major role in climatic proteoglycan stromal keratopathy. The appearance of gray corneal opacification, central flattening, and proteoglycan accumulation differentiate it from spheroidal degeneration.[8] Mild calcific band keratopathy, in which calcium salts accumulate, differs from secondary corneal spheroidal degeneration by having a systemic or ocular inflammatory disease in the etiology.[9] Salzmann's nodular degeneration is bluish-white to grayish-yellow round lesions. Ocular surface inflammation is common. The presence of eosinophilic deposits and early destruction of epithelium can be seen in any part of the cornea, not only the interpalpebral region.

Confocal microscopy enables the clinician to evaluate microstructural corneal changes with a noninvasive approach.[11] In both of our patients, the golden spherules were observed as hyperreflective globules under the confocal microscope. These hyperreflective globules were well correlated with the histopathological specimens.

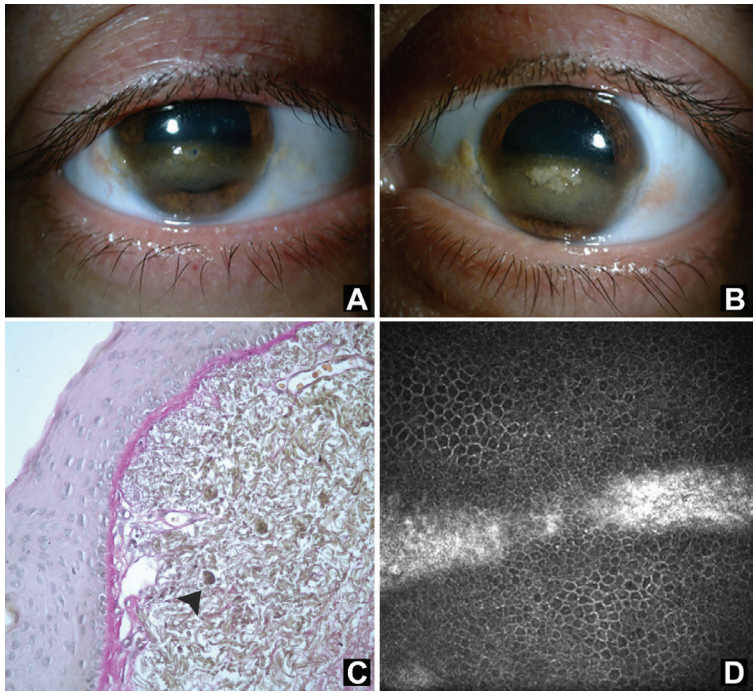

Figure 2. Clinical and histopathological characteristics of patient 2. Grade III keratopathy, characterized by band-shaped transparent amber-colored corneal spherules.[6] Note the spherules adjacent to the limbus (A, right eye). Grade IV keratopathy identified by band-shaped corneal deposits and clusters of punctiform spherules[6] (B, left eye). Cornea specimen stained with Verhoeff-van Gieson, X400. The superficial stroma lacks normal parallel arrangement. Note the bluish discoloration of the stroma. The arrow indicates dark olive green stained deposits (C, right eye). *In vivo* confocal microscopy shows punctiform hyperreflective deposits (D, right eye)

Advancing age and exposure to environmental factors or underlying ocular pathology have a major role in the etiology of spheroidal degeneration. These environmental factors include low humidity, very low temperatures, very high temperatures, microtrauma from wind blowing snow or ice particles and solar radiation from ultraviolet (UV) wavelengths. Chronic exposure to UV radiation is considered to be the primary causative factor in spheroidal degeneration. The patients in the present report were living in the province of Adana, which is the southern part of Turkey (35° 18' 49.4496'' E). It has a dry-hot summer subtropical climate. In Adana, the highest annual average temperature in summer is 40 degrees Celsius and the average daylight duration is 10 hours.[12] The average annual solar radiation in the southern part of Turkey is above 4.6 $kWhm^{-2}$.[13] In fact, chronic UV exposure may be a causative factor in our cases due to the region in which our patients live. However, in the present report our patients were rather young and had no history of preexisting ocular diseases. Although chronic exposure to UV is thought to be a causative factor, the assessment of conjunctival and corneal spheroidal degeneration with early onset in two members of the same family led us to presume a familial form of spheroidal degeneration. There are a few cases of spheroidal degeneration thought to be familial in the literature.[4,5] The limitation here is that the genetic transmission of spheroidal degeneration was not supported by concrete evidence. Spheroidal degeneration was detected in only two individuals in the same family, both in our cases and in other presumed familial cases presented in the literature. It is therefore difficult to determine the inheritance pattern of the spheroidal degeneration. With our current knowledge, it would be more accurate to interpret that there may be a familial predisposition to corneal and conjunctival microtraumas in these cases.

There is no single medical approach for treatment. In mild cases, lubrication of the ocular surface, protection from UV exposure, and appropriate ascorbic acid intake are advised. In moderate keratopathy, superficial or photorefractive keratectomy are performed.[14] In advanced cases, penetrating keratoplasty may be recommended. However, the recurrence rate is unknown.

Contrary to the relatively more common sporadic spheroidal degeneration, familial cases are bilateral, more affected by the environment, and typically symptomatic in the first decade.

In conclusion, spheroidal degeneration of the cornea and conjunctiva has mostly been reported in older subjects and most researchers did not recognize a familial tendency. This report describes bilateral band-shaped spheroidal corneal degeneration in two young siblings, which is extremely rare.

Ethics

Informed Consent: Obtained.

Peer-review: Internally and externally peer reviewed.

Authorship Contributions

Concept: M.İ., Design: M.İ., D.Y., M.C.M., M.O., Data Collection or Processing: M.İ., D.Y., M.C.M., M.O., Analysis or Interpretation: M.İ., D.Y., M.C.M., M.O., F.S., Ö.T.I., Literature Search: D.Y., Writing: D.Y., M.C.M, M.İ.

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. Fraunfelder FT, Hanna C, Parker JM. Spheroid degeneration of the cornea and conjunctiva. 1. Clinical course and characteristics. Am J Ophthalmol. 1972;74:821-828.
2. Hanna C, Fraunfelder FT. Spheroid degeneration of the cornea and conjunctiva. 2. Pathology. Am J Ophthalmol. 1972;74:829-839.
3. Fraunfelder FT, Hanna C. Spheroid degeneration of the cornea and conjunctiva: Incidences, classification, and etiology. Am J Ophthalmol. 1973;76:41-50.
4. Kloucek F. Familial band-shaped kerathopathy and spheroidal degeneration. Clinical and electron microscobic study. Albrecht Von Graefes Arch Klin Exp Ophthalmol. 1977;205:47-59.
5. Hida T, Akiya S, Kigasawa K, Hosoda Y. Familial band-shaped spheroid degeneration of the cornea. Am J Ophthalmol. 1984;97:651-652.
6. Johnson GJ, Ghosh M. Climatic droplet keratopathy. Contact Intraocul Lens Med J. 1982;8:66-75.
7. Garner A, Fraunfelder FT, Barras TC, Hinzpetert EN. Spheroidal degeneration of cornea and conjunctiva. Br J Ophthalmol. 1976;60:473-478.
8. Waring GO 3rd, Malaty A, Grossniklaus H, Kaj H. Climatic proteoglycan stromal keratopathy, a new corneal degeneration. Am J Ophthalmol. 1995;20:330-341.
9. O'Connor GR. Calcific band keratopathy. Trans Am Ophthalmol Soc. 1972;70:58-81.
10. Vannas A, Hogan MJ, Wood I. Salzmann's nodular degeneration of the cornea. Am J Ophthalmol.1975;79:211-219.
11. Bozkurt B. Irkec M. In vivo laser confocal microscopic findings in patients with epithelial basement membrane dystrophy. Eur J Ophthalmol. 2009;19:348-354.
12. https://mgm.gov.tr
13. Aksoy B. Solar radiation over Turkey and its analysis. Int J Remote Sens. 2011;32:6261-6272.
14. Elhusseiny AM, El Sheikh RH, Jamerson E, Swaify IY, Araissi AB, Saad AA. Advanced spheroidal degeneration. Digit J Ophthalmol. 2019;25:68-71.

DOI: 10.4274/tjo.galenos.2021.84484
Turk J Ophthalmol 2021;51:250-251

Letter to the Editor re: "Effects of the COVID-19 Pandemic on Turkish Ophthalmologists."

Nir Erdinest*, Naomi London**, Nadav Levinger***, Itay Lavy*

*Hadassah-Hebrew University Medical Center, Jerusalem, Israel
**Private Practice
***Enaim Refractive Surgery Center, Jerusalem, Israel

Keywords: Survey, COVID-19 anxiety, personal protective equipment use, quality of care

Dear Editor,

This letter is in regard to the article "Effects of the COVID-19 Pandemic on Turkish Ophthalmologists." authored by I.K. and M.M., which was published in volume 51, issue 2, 2021 of the *Turkish Journal of Ophthalmology*.[1]

We read this article with great interest and thank the authors for providing an excellent demonstration of how the COVID-19 pandemic has caused both a decrease in the number of patient examinations by prioritizing only the most urgent care, as well as raised anxiety among ophthalmologists in Turkey. The authors summarize and emphasize how the proximity of these professionals to patients heightens the possibility for viral contraction and how crucial proper personal protection and clear guidelines are important for all involved to prevent contagion and provide care when needed.

Understanding the distinguishing particulars causing this anxiety can help policy makers address issues specifically and appropriately and thereby rehabilitate the health care system. We similarly held a three-part survey, collecting data from eye care practitioners (ECPs) during the first wave (and coinciding with a national lockdown, though ECPs were considered essential workers), during the lull, and again during the second wave of the pandemic (pre-published, ahead of print). Even at the third stage, in July 2020, when transmission and infection modalities were better understood, a third of ECPs still refrained from providing full service, citing high levels of anxiety due to fear of contracting the virus through ocular tissue as well as, similar to the article presented here, a fear of passing the disease on to their families. Interestingly, the more novice ECPs were less reluctant and anxious than the more senior and experienced responders. As with this study, 99% of all ECPs also wore face masks throughout the survey timeframe. What was further instructive was to observe the progression of protective gear use as knowledge of transmission advanced between the stages of the pandemic and survey. For example, temperature measurement declined as it became understood that asymptomatic coronavirus disaese-2019 (COVID-19) positive patients are contagious and therefore an elevated temperature was not enough to identify and prevent disease spread. Glove usage decreased as well, with the understanding that disease transmission can be effectively prevented by thorough hand-washing (which remained high throughout all stages, at over 99%). It was sobering to note that at the end of the survey, at the second wave, still a third of the responding ECPs refrained from providing full care. It seemed that even though possible contraction of this coronavirus via ocular tissue when properly protected remains extremely low, ECPs were not sufficiently informed or receptive to that, and anxiety and subsequent substandard quality and quantity of care

Address for Correspondence: Naomi London, Private Practice
E-mail: imnl4u@gmail.com **ORCID-ID:** orcid.org/0000-0001-6935-3275
Received: 09.05.2021 **Accepted:** 30.06.2021

Cite this article as: Erdinest N, London N, Levinger N, Lavy I. Letter to the Editor re: "Effects of the COVID-19 Pandemic on Turkish Ophthalmologists.". Turk J Ophthalmol 2021;51:250-251

persisted. Although the COVID-19 pandemic has spectacularly accelerated and advanced fields such as telemedicine and brought about effective on-line consultation in ophthalmic imaging and even operations, face-to-face consultations are still often the preferred alternative.[2]

These results further support a multicenter survey conducted in Turkey in April 2020 which focused on the quality of care as well as the anxiety level of providers. The data showed that many ECPs felt the quality of their examination decreased (32.2%) as well as the quality of their intervention (38%). Telemedicine was not a prevalent alternative (62% did not use) but it is unclear if that was by choice or lack of availability. A poignant question asking "Have you missed a diagnosis during the pandemic?" was answered in the affirmative by 14.9% of responders. The authors proposed that health management organisations proactively provide mental health support, after learning 36.4% of the survey responders suffered from some level of anxiety caused by the pandemic.[3]

To conclude, the COVID-19 pandemic has disrupted all medical services across the world including ophthalmic services. In many countries, ECPs have had to independently self-educate regarding this pandemic. Seeing the results of all these studies magnifies the global significance and need for government and health care institutions' guidance, such as was provided by the Turkish Ophthalmological Association as early as April 2020,[4] but even more so, highlights the importance of continuously updated information, such as provided by the British National Health Service and British Contact Lens Association.[5] Active education of even the more experienced ECPs on how to protect themselves and their patients is paramount in order to safely rehabilitate the system as quickly as possible to pre-pandemic status.

Peer-review: Externally peer reviewed.

Authorship Contributions

Concept: N.E., N.L., Design: N.E., N.L., Data Collection or Processing: N.E., N.L., Analysis or Interpretation: N.E., N.L., Literature Search: N.E., N.L., Writing: N.E., N.L.

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. Kavadarlı I, Mutlu M. Effects of the COVID-19 Pandemic on Turkish Ophthalmologists. Turk J Ophthalmol. 2021;51:95-101.
2. Al-Sadeq DW, Nasrallah GK. The incidence of the novel coronavirus SARS-CoV-2 among asymptomatic patients: a systematic review. Int J Infect Dis. 2020;98:372-380.
3. Erdem B, Gok M, Bostan S. The evolution of the changes in the clinical course: a multicenter survey-related impression of the ophthalmologists at the peak of the COVID-19 pandemic in Turkey. Int Ophthalmol. 2021;41:1261-1269.
4. Bozkurt B, Eğrilmez S, Şengör T, Yıldırım Ö, İrkeç M. The COVID-19 pandemic: clinical information for ophthalmologists. Turk J Ophthalmol. 2020;50:59-63.
5. Association BCL. Contact Lens Wear and coronavirus (COVID-19) guidance. 2020

DOI: 10.4274/tjo.galenos.2021.65507
Turk J Ophthalmol 2021;51:252-253

Letter to the Editor re: "Effects of the COVID-19 Pandemic on Turkish Ophthalmologists."–Incremental Innovations in Clinical Ophthalmology During the COVID-19 Pandemic

Bharat Gurnani*, Kirandeep Kaur**

*Aravind Eye Hospital, Department of Cornea and Refractive Services, Pondicherry, India
**Aravind Eye Hospital, Department of Paediatric Ophthalmology and Strabismus Services, Pondicherry, India

Keywords: COVID-19, innovations, clinical ophthalmology

Dear Editor,

We read with interest the article reporting the effect of the coronavirus disease 2019 (COVID-19) pandemic on Turkish ophthalmologists, which provided intricate insights into the practice patterns in Turkey during the COVID-19 pandemic.[1] However, we have a few important potential additions based on the incremental changes and innovations across the majority of tertiary eye care hospitals in India during the pandemic. All the healthcare staff and patients underwent daily temperature screening, hand sanitization, and shoes/slippers sanitization with dilute hypochlorite solution; travel history and COVID-19 consent were obtained; and mask and personal protective equipment kits were ensured before hospital entry.[2] As highlighted in the article in terms of practitioners' reduced working hours, the healthcare staff and doctors in our country were also divided into 2-3 teams to minimize viral exposure daily to COVID patients. Patients were admitted by appointment only, limited patients were allowed on a single entry, only one attendee was allowed per patient, and during examination the attendees were not allowed inside the examination room unless deemed necessary. The patients were seated on alternate chairs with the middle chairs tied off with red ribbon to maintain social distance. Instruments such as the +90D lens, indirect ophthalmoscope with +20D lens, optical coherence tomography, fundus fluorescein angiography, keyboards, and computer screen were all cling-wrapped daily to prevent surface contamination and cross-viral infection. As perfectly highlighted in the article, during the pandemic and especially during the lockdown, elective surgeries were postponed and only emergency cases were operated on. The surgical teams followed a modified approach for ophthalmic surgery and anaesthesia to reduce COVID-19 spread via aerosols. Phacoemulsification under topical anaesthesia was the preferred surgery and a COVID-19 reverse transcription polymerase chain reaction report was mandated for long-duration surgeries like keratoplasty and vitreoretinal procedures. Peribulbar anaesthesia was avoided due to the risk of aerosol spread and subtenon's anaesthesia was preferred for COVID-19-negative patients, as positive patients can have COVID-19 in the conjunctival surface.[3] The pandemic allowed us to innovate in tough times when there was a shortage of resources like masks, sanitizers, and personal protective equipment kits. At the beginning of the pandemic when there was an acute shortage of masks, we adapted with an innovative technique of sterilizing the respirators by using hydrogen peroxide and ultraviolet rays in a closed chamber of old condemned refrigerators. This proved beneficial to safeguard all the staff during the time of shortage. Mask-induced fogging is a known phenomenon and this was taken care of by using a simple solution that was applied over the microscope eyepiece to prevent mask-induced fogging while operating on the patients. There were numerous innovations in

Address for Correspondence: Bharat Gurnani, Aravind Eye Hospital, Department of Cornea and Refractive Services, Pondicherry, India
E-mail: drgurnanibharat25@gmail.com **ORCID-ID:** orcid.org/0000-0003-0848-5172
Received: 03.06.2021 **Accepted:** 30.03.2021

Cite this article as: Gurnani B, Kaur K. Letter to the Editor re: "Effects of the COVID-19 Pandemic on Turkish Ophthalmologists."–Incremental Innovations in Clinical Ophthalmology During the COVID-19 Pandemic. Turk J Ophthalmol 2021;51:252-253

the paediatric department, like the use of disposable IV tubing to make adjustable earloops for children; using a S12C mobile vision screener to safely screen patients by employing an acrylic sheet physically separating the screener and patient to protect the examiner; implementing slit-lamp shields to prevent aerosol transmission of the virus during close-contact examination;[4] and using head loupes to examine infants and small children from a safe distance. The authors nicely elaborated the details regarding the perception of patients and doctors regarding COVID-19 and provided valuable insight into the psychological aspect and knowledge perception of patients regarding COVID-19. Similarly, we also performed a multicentric Knowledge, Attitude, and Practice (KAP) analysis regarding COVID-19 in patients presenting to our centre for a routine eye examination. We were able to demonstrate that the KAP score was high, about 80%, in our population, but elderly high-risk and illiterate patients had significantly low KAP scores. Hence, education and awareness regarding COVID-19 presentation and manifestation among the masses is the key to safeguard everyone.[5] The COVID-19 pandemic is a testing time for all of us globally. The deadly virus has challenged all of us mentally, physically, and emotionally. We have adjusted to the circumstances and learnt to adapt to unprecedented challenges. Once again we congratulate the authors for giving brilliant insights into the COVID-19 situation in Turkey. By combined efforts, we can emerge as winners and make this world Corona free.

Peer-review: Internally peer reviewed.

Authorship Contributions

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

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. Kavadarlı I, Mutlu M. Effects of the COVID-19 Pandemic on Turkish Ophthalmologists. Turk J Ophthalmol. 2021;51:95-101.
2. Gurnani B, Kaur K. Impact of the COVID-19 pandemic on clinical ophthalmology. Indian J Med Res. 2021;153:199-200.
3. Gurnani B, Kaur K. Modified drug regimen for ophthalmic anesthesia during COVID-19 pandemic: Revisiting pharmacological concepts. Indian J Pharmacol. 2021;53:178-179
4. Kaur K, Kannusamy V, Gurnani B. Incremental innovations in pediatric ophthalmology department during the COVID-19 pandemic: An experience from a tertiary eye care hospital. Indian J Ophthalmol. 2021;69:1000-1001.
5. Christy JS, Kaur K, Gurnani B, Hess OM, Narendran K, Venugopal A, Anuja J, Manohar D, Raman R, Venkatesh R. Knowledge, attitude and practise toward COVID-19 among patients presenting to five tertiary eye care hospitals in South India - A multicentre questionnaire-based survey. Indian J Ophthalmol. 2020;68:2385-2390.

DOI: 10.4274/tjo.galenos.2021.15853
Turk J Ophthalmol 2021;51:254-255

Letter to the Editor re: "Unintentional Staining of the Anterior Vitreous with Trypan Blue During Cataract Surgery"

Şaban Gönül, Serhat Eker

Selçuk University Faculty of Medicine, Department of Ophthalmology, Konya, Turkey

Dear Editor,

We have read with great interest the article by Kayıkçıoğlu et al.[1] ''Unintentional Staining of the Anterior Vitreous With Trypan Blue During Cataract Surgery''.The article describes a rare complication of phacoemulsification surgery: staining of the posterior capsule and anterior vitreous with trypan blue during phacoemulsification surgery. We thank the authors for their work and would like to make some contributions with respect to trypan blue toxicity of the retina, which can also be seen after vitrectomy with many vital dyes including trypan blue.

It has been reported that some retinal changes may occur due to the use of trypan blue at high concentrations and exposure times.[2,3] Lüke et al.[2] showed reduction of b-wave amplitudes with the use of trypan blue in their electrophysiological study. Some morphological changes in the inner retinal layers were also demonstrated due to the use of high concentrations of trypan blue solutions in a postmortem study.[3] These toxic effects may not cause any fundus abnormalities but can be detected by an electrophysiological examination such as electroretinogram. In their study, Kayıkçıoğlu et al.[1] reported that retinal toxicity was not observed in these patients. It seems that an electrophysiological test was not performed to detect possible retinal toxicity in their study, which may have caused the retinal toxicity to be overlooked. In these patients, inadvertently toxic concentrations of trypan blue may have passed into the vitreous cavity and had a toxic effect due to the long exposure time, as vitrectomy was not performed in these patients. In addition, postoperative visual acuities ranged from 0.4 to 0.9 in the patients described by the authors. None of the patients achieved a Snellen visual acuity of 1.0 or better in the postoperative period. The authors did not specify any finding that could affect the postoperative visual acuity of these patients. If there is no other finding to explain these levels of visual acuity in the postoperative period, this may also be a sign of toxic retinopathy caused by trypan blue inadvertently passing into the vitreous cavity.

As a result, electrophysiological examination should be performed to exclude retinal toxicity of any substance inadvertently applied to the vitreous cavity. We would like to congratulate the authors again for their interesting study and hope that our feedback will make a further contribution to the literature, especially in terms of retinal toxicity caused by vital dyes including trypan blue.

Peer-review: Internally peer reviewed.

Authorship Contributions

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

Address for Correspondence: Şaban Gönül, Selçuk University Faculty of Medicine, Department of Ophthalmology, Konya, Turkey
E-mail: drsabangonul@gmail.com **ORCID-ID:** orcid.org/0000-0003-0803-1197
Received: 26.12.2020 **Accepted:** 06.03.2021

Cite this article as: Gönül Ş, Eker S. Letter to the Editor re: "Unintentional Staining of the Anterior Vitreous with Trypan Blue During Cataract Surgery". Turk J Ophthalmol 2021;51:254-255

References

1. Kayıkçıoğlu ÖR, Mayalı H, Doğruya S, Alp Ş, Yılmazlar AA, Kurt E. Unintentional Staining of the Anterior Vitreous with Trypan Blue During Cataract Surgery. Turk J Ophthalmol. 2020;50:308-312.
2. Lüke C, Lüke M, Dietlein TS, Hueber A, Jordan J, Sickel W, Kirchhof B. Retinal tolerance to dyes. Br J Ophthalmol. 2005;89:1188-1191.
3. Haritoglou C, Gandorfer A, Schaumberger M, Priglinger SG, Mueller AJ, Gass CA, Kampik A. Trypan blue in macular pucker surgery: an evaluation of histology and functional outcome. Retina. 2004;24:582-590.

DOI: 10.4274/tjo.galenos.2021.49104
Turk J Ophthalmol 2021;51:256

Reply to Letter to the Editor re: "Unintentional Staining of the Anterior Vitreous with Trypan Blue During Cataract Surgery"

Özcan Kayıkçıoğlu*, Hüseyin Mayalı*, Suzan Doğruya**, Şenay Alp***, Aydın Alper Yılmazlar****, Emin Kurt*

*Celal Bayar University Faculty of Medicine, Department of Ophthalmology, Manisa, Turkey
**Uşak Training and Research Hospital, Clinic of Ophthalmology, Uşak, Turkey
***Adıyaman Training and Research Hospital, Clinic of Ophthalmology, Adıyaman, Turkey
****Aydın State Hospital, Aydın, Turkey

Dear Editor,

We thank the authors for their contribution to our study. Unfortunately, we did not have chance to look for toxicity using electrophysiological tests, which might be more sensitive to detect subtle changes in function before morphologically observable derangements. It is probable that a small portion of the trypan dye injected into the anterior chamber reached the anterior vitreous cavity and theoretically was later diluted in about 4.5 cc of vitreous cavity fluid. Although vitrectomy was not performed, on clinical examination this dye disappeared quickly postoperatively. The cases were not routine cataract cases, so we attributed the acuity loss either to primary coexistent disease or difficulty in surgery.

We did not encounter significant retinal changes in fundus examinations and optical coherence tomography postoperatively; however, we cannot completely rule out toxic effects of trypan blue on the retinal cells without electrophysiological tests. This may be a possible cause of the moderate visual acuity levels reached by the patients, as the contributors justifiably mentioned.

Peer-review: Internally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: Ö.K., Concept: Ö.K., H.M., S.D., Ş.A., A.A.Y., E.K., Design: Ö.K., H.M., S.D., Ş.A., A.A.Y., E.K., Data Collection or Processing: Ö.K., S.D., Ş.A., A.A.Y., Analysis or Interpretation: Ö.K., H.M., S.D., Ş.A., A.A.Y., E.K., Literature Search: Ö.K., S.D., Ş.A., A.A.Y., Writing: S.D., Ö.K.

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

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

Address for Correspondence: Suzan Doğruya, Uşak Training and Research Hospital, Clinic of Ophthalmology, Uşak, Turkey
E-mail: sdogruya@hotmail.com **ORCID-ID:** orcid.org/0000-0002-6822-9077
Received: 12.01.2021 **Accepted:** 06.03.2021

Cite this article as: Kayıkçıoğlu Ö, Mayalı H, Doğruya S, Alp Ş, Yılmazlar AA, Kurt E. Reply to Letter to the Editor re: "Unintentional Staining of the Anterior Vitreous with Trypan Blue During Cataract Surgery". Turk J Ophthalmol 2021;51:256