www.oftalmoloji.org

E-ISSN: 2149-8709

TURKISH JOURNAL OF OPHTHALMOLOGY

TURKISH JOURNAL OF OPHTHALMOLOGY TJO

Research Articles

Review

Case Reports

September
October
2020
50 Volume
Issue 5

galenos

TURKISH JOURNAL OF OPHTHALMOLOGY

TJO

www.oftalmoloji.org

Publishing House
Molla Gürani Mah. Kaçamak Sokak No: 21,
34093 Fındıkzade-İstanbul-Turkey
Publisher Certificate Number: 14521
Phone: +90 212 621 99 25 **Fax:** +90 212 621 99 27
E-mail: info@galenos.com.tr
Online Publishing Date: October 2020
International scientific journal published bimonthly.
E-ISSN: 2149-8709

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

On Behalf of Turkish Ophthalmological Association Owner

İzzet CAN
Private Practice, Ankara, Turkey

TURKISH JOURNAL OF OPHTHALMOLOGY

TJO

www.oftalmoloji.org

ABOUT US

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

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

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

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

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

Open Access Policy

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

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

Subscription Information

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

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

Membership Procedures

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

Correspondence Address

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

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

Permissions

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

Advertisement

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

Publisher Corresponding Address

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

Instructions for Authors

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

Material Disclaimer

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

The journal is printed on acid-free paper.

TURKISH JOURNAL OF OPHTHALMOLOGY

TJO

www.oftalmoloji.org

INSTRUCTIONS TO AUTHORS

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

GENERAL GUIDELINES

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

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

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

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

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

REFERENCES

Authors are solely responsible for the accuracy of all references.

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

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

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

TURKISH JOURNAL OF OPHTHALMOLOGY

TJO

www.oftalmoloji.org

INSTRUCTIONS TO AUTHORS

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

Reference Format

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

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

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

TABLES, GRAPHICS, FIGURES, AND IMAGES

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

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

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

BIOSTATISTICS

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

MANUSCRIPT TYPES

Original Articles

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

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

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

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

Case Reports

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

Review Articles

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

Letters to the Editor

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

CORRESPONDENCE

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

TURKISH JOURNAL OF OPHTHALMOLOGY

TJO

www.oftalmoloji.org

CONTENTS

TURKISH JOURNAL OF OPHTHALMOLOGY

TJO

www.oftalmoloji.org

EDITORIAL

2020 Issue 5 at a Glance;

This issue of our journal begins with a eulogy written by Turkish Ophthalmology Association president Professor İzzet Can, MD in memory of Professor M. Erol Turaçlı, MD, the doyen of our professional community who we lost due to COVID-19. This is followed by 6 original research articles, 1 review, and 5 case reports.

Infectious keratitis is a condition characterized by uncontrolled inflammation associated with the proliferation of bacteria, viruses, fungi, or parasites in the cornea due to impaired defense mechanisms for various reasons. Bacterial keratitis can result in severe vision loss and therefore, empirical antibiotherapy should be initiated early, without waiting for culture and smear results. Dikmetaş et al. retrospectively evaluated the medical records of 31 patients who were hospitalized and treated for bacterial keratitis. Of these, 20 patients (64.5%) received fortified cephalosporin (50 mg/mL cefazolin) and aminoglycoside (14 mg/mL gentamicin) combination therapy after nonresponse to initial treatment with fourth-generation fluoroquinolone (5 mg/mL moxifloxacin), while 11 patients (35.5%) received fortified therapy as first-line treatment. Superficial lesions showed faster response to treatment (p=0.037) and moderate correlations were observed between response to treatment and time to treatment initiation (r=0.527, p=0.184) and initial best corrected visual acuity (BCVA) (r=0.517, p=0.120). The authors noted that patients with initially low BCVA show poorer response to treatment and emphasized that fortified antibiotics still have a place in the treatment of bacterial keratitis and remain the best alternative to fluoroquinolone therapy (See pages 258-263).

Yılmaz et al. investigated the consistency between optical coherence tomography (OCT) (Spectralis, Heidelberg Engineering, Heidelberg, Germany) images and OCT angiography (OCTA) (AngioVue, Optovue Inc., Fremont, CA, USA) images for the measurement of retinal nerve fiber layer thickness (RNFLT) in patients with primary open angle glaucoma (POAG). Intraclass correlation coefficients used to test the agreement between the two devices indicated excellent agreement in the global average and the superior, inferior, and temporal quadrants and good agreement in the nasal quadrant. In contrast, in Bland-Altman analysis there was poor agreement in all measurements due to the wide limits of agreement and statistically significant proportional bias (p>0.05), while linear regression analysis models showed strong association between peripapillary vessel density (VD) and RNFLT measured by both devices. The authors concluded that data obtained from the two devices should not be used interchangeably but stated that due to the strong correlation between VD and RNFL values with both devices, the AngioVue could be used in glaucoma management for the measurement of RNFLT as well as VD (See pages 264-270).

Uzlu et al. conducted a study evaluating the relationship between body position and intraocular pressure (IOP) values measured by rebound tonometry (RT) in healthy children. In the study, IOP values of 49 eyes of 49 healthy pediatric patients with normal ophthalmic examination findings were measured with RT in standing, sitting, and supine positions and there was no statistically significant difference between the measurements (p=0.846, p=0.751, p=0.606). However, there was a statistically significant correlation between corneal thickness and IOP values in all measurements (See pages 271-274).

A prospective study by Barış et al. aimed to determine the frequency of inadequate response to intravitreal (IV) anti-vascular endothelial growth factor (anti-VEGF) treatment in active neovascular age-related macular degeneration (nvAMD) and to define subgroups of poor responding eyes. A total of 235 eyes of 202 treatment-naive patients received ranibizumab and those with recurrence, persistence, or worsening despite treatment were classified as "poor responders." The authors found that 78 eyes (33.2%) showed poor response and that the frequency of pigment epithelial detachment (PED) and occult choroidal neovascularization (CNV) was statistically significantly higher in eyes that responded poorly to treatment (p<0.001). This finding emphasizes that determining eyes' pre-treatment characteristics and performing subgroup analysis will be beneficial to modify and improve treatment strategies in such cases (See pages 275-282).

Yılmaz Tuğan et al. analyzed changes in the reflectivity of the retinal pigment epithelium (RPE), ellipsoid zone (EZ), and outer limiting membrane (OLM) in OCT images and evaluated the relationship between reflectivity change and visual acuity improvement in 24 eyes of 24 patients with idiopathic full-thickness macular holes closed after vitrectomy. They observed significant increases in EZ reflectivity (absolute and relative) at postoperative 12 months compared to postoperative 1 month and a significant positive correlation between the increase in EZ reflectivity and BCVA, and concluded that EZ reflectivity could be an indicator of functional and anatomical improvement after macular hole surgery (See pages 283-287).

Kalaycı evaluated the causes and frequency of blindness in the adult population of Somalia according to the criteria of the World Health Organization. Based on data from 2605 patients over the age of 18, the overall blindness rate was 9.8% and the most common causes in the monocular blindness group were trauma complication (23.6%), cataract (19%), and diabetic retinopathy (13.2%), while the most common causes in the bilateral blind group were cataract (26.9%), diabetic retinopathy (21.1%), and glaucoma (15.4%). It was noted that trauma is the most important cause of blindness in Somalia due to security conditions in the country (See pages 288-292).

Primary melanoma of the eye can occur in 4 different anatomical structures of the eye: the orbit, eyelids, conjunctiva, and uvea. Conjunctival melanoma is a rare disease that accounts for about %5 of all ocular melanomas. It can occur de novo or arise from a conjunctival nevus or primary acquired melanosis. In this issue's review,

TURKISH JOURNAL OF OPHTHALMOLOGY

TJO

www.oftalmoloji.org

EDITORIAL

Koç and Kıratlı address the clinical findings, differential diagnosis, diagnostic tools, and staging of conjunctival melanoma. They explain to the readers that biomicroscopic examination is indispensible in the diagnosis, identification of additional features, and follow-up of the disease while other imaging methods can be used as auxiliary tools, albeit with their own limitations (See pages 293-303).

Viral endotheliitis is endothelial inflammation and damage characterized by corneal edema, keratic precipitates (KPs), mild anterior chamber reaction, and elevated IOP. The main causes are herpes simplex virus (HSV), varicella zoster virus (VZV), mumps virus, and cytomegalovirus (CMV). CMV-associated endotheliitis can occur de novo or secondary to ocular surgery in immunocompetent individuals. Çelik Büyüktepe and Yalçındağ report a patient who was using local and systemic immunosuppressive agents due to graft rejection following penetrating keratoplasty and presented with localized corneal edema, coin-shaped KPs, and elevated IOP on examination at postoperative 4 years. CMV-DNA was detected by polymerase chain reaction analysis of an aqueous humor sample, and the patient was started on oral valganciclovir 900 mg twice a day, topical dexamethasone drops 5 times a day, ganciclovir gel 5 times a day, and topical dorzolamide-timolol drops twice a day. The patient's graft edema and anterior chamber reaction resolved within 2 months of follow-up and IOP was controlled with topical therapy. The authors point out the fact that local or systemic immunosuppressants used after keratoplasty may trigger CMV reactivation, that CMV should be considered among the causes of viral endotheliitis, and ganciclovir therapy should be initiated immediately in cases with coin-shaped KPs (See pages 304-307).

Kayıkçıoğlu et al. present 6 cases in which the trypan blue dye used to stain the anterior capsule migrated into the vitreous cavity and stained the posterior capsule and anterior vitreous during phacoemulsification and intraocular lens (IOL) implantation surgery. The IOL was implanted in the capsular bag with no problems in 5 of the patients, while the other patient had trauma-induced iris and zonular defects and a sutured IOL was implanted in the same session. With this case report, the authors emphasize that trypan blue staining of the posterior capsule and anterior vitreous can occur during phacoemulsification in eyes with risk factors related to cataract surgery as well as in eyes with no zonular pathology, and that the migration of trypan blue to the posterior segment can impair visualization of the posterior capsule and capsulorhexis and thereby increase the risk of operative complications (See pages 308-312).

Leber's hereditary optic neuropathy (LHON) is a maternally inherited mitochondrial DNA-related disease. Characteristic findings in patients with asymptomatic and early-stage disease include optic disc hyperemia, vascular tortuosity, and peripapillary telangiectatic vessels. The increase in capillary vessel size and tortuosity in the optic disc suggests that the disease is a neurovascular disorder. In 2 male LHON patients aged 28 and 8 years, OCTA revealed capillary dropout areas and reduced radial peripapillary capillary density in the quadrants that showed reduced RNFLT on OCT. Progressive decrease in radial peripapillary capillary density and RNFLT were demonstrated in the patients' 12- and 30-month follow-up. Bingöl Kızıltunç et al. note the importance of OCTA imaging in the evaluation of changes in LHON patients and asymptomatic carriers (See pages 313-316).

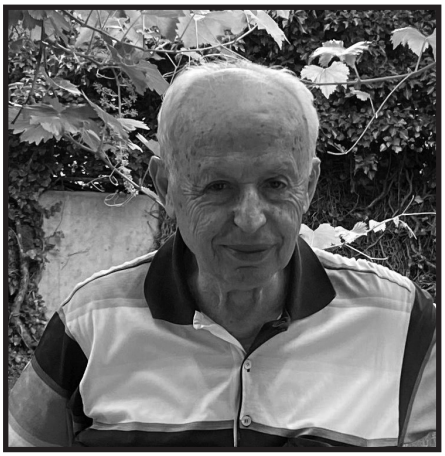
Koçer et al. describe a 12-year-old boy under follow-up for amblyopia who presented with low vision in his left eye and was found to have BCVA of 1.0 in the right eye and 0.3 in the left eye. Increased horizontal cup-to-disc ratio was observed in both optic discs on dilated fundus examination, RNFLT measurement showed diffuse nerve fiber loss, and bitemporal hemianopsia was detected in visual field test. Magnetic resonance imaging revealed a lesion that filled and widened the sella and suprasellar cistern and compressed the optic chiasm, and the patient underwent surgery via transcranial approach. The pathologic diagnosis was craniopharyngioma. The authors recommended using additional tests before making a diagnosis of amblyopia in children with suspicious examination findings and inadequate cooperation (See pages 317-320).

Foveal hypoplasia is defined as the underdevelopment of the fovea and is characterized by nystagmus with low visual acuity. It is usually associated with optic nerve hypoplasia, familial exudative vitreoretinopathy (FEVR), Stickler syndrome, albinism, aniridia, and microphthalmia. It can also be isolated, occurring in the absence of any other pathology. Değirmenci et al. examined a 19-year-old young man who presented with the complaint of nonprogressive visual impairment but exhibited no marked anterior or posterior segment pathology except for low visual acuity and bilateral latent nystagmus. On OCT imaging, they found that the foveal pit was absent in both eyes, OCTA showed that the foveal avascular zone and central black gap were absent, and there was no hypoautofluorescence in the area corresponding to the fovea in fundus autofluorescence images. The authors diagnosed the patient as having foveal hypoplasia based on these findings and emphasized the importance of evaluating patients with low visual acuity using multimodal imaging methods (See page 321-323).

We hope you will find the articles featured in our fifth issue this year interesting and guiding in your professional practice.

Respectfully on behalf of the Editorial Board,

Özlem Yıldırım, MD



In Memory of Professor M. Erol Turaçlı, MD

On October 5, 2020, Turkish ophthalmology lost Professor M. Erol Turaçlı MD, the doyen and honorary president of the Turkish Ophthalmology Association (TOA). Having reached the highest and most respected position in our association, he leaves behind an indelible legacy.

Prof. Turaçlı was born in 1939 in Niksar, Turkey. He completed his elementary, middle, and high school education in Ankara, graduated from Ankara University Faculty of Medicine in 1964, and started his specialty training in ophthalmology in the same year. He completed his specialization and became an ophthalmologist in 1967. From 1969 to 1971, he worked as a researcher at Glasgow University in Scotland and later at the University of Amsterdam in the Netherlands. He became an associate professor in 1974 and achieved professorship in 1979. Our esteemed teacher expressed his pioneering status in the clinic with the following statement at his retirement ceremony in 2006: "In the new Ophthalmology Department and Eye Bank of Ankara University Faculty of Medicine, opened in 1963, and under the late Professor Cahit Örgen, I was his first resident, first specialist, first associate professor, and first professor." After retiring, Prof. Turaçlı worked until 2015 as a founding faculty member and head of the ophthalmology department of Ufuk University Faculty of Medicine. He is survived by his wife and two children.

Prof. Turaçlı was a leader in the advancement of glaucoma diagnosis and treatment in Turkey. While still a resident in 1966, he established the glaucoma unit in the Ankara Faculty of Medicine. During the creation of the TOA training subsocieties, he established the glaucoma society and became the chair of its first executive board. He would hold that office until 2006. With his numerous academic activities both in Turkey and abroad, he became a source of pride for our country in this field. Prof. Turaçlı has more than 200 national and international publications, authored book chapters, and served as editor or advisory board member for many ophthalmology books and journals. In addition, he undertook the role of organizing as well as making major scientific contributions at numerous national and international congresses and meetings.

He was physician to our late President Süleyman Demirel and the late President of Azerbaijan Heydar Aliyev, whose ocular diseases he followed up and treated for many years.

His most important contributions to ophthalmology in our country were realized within the TOA. He served as TOA Ankara Regional Branch Chair for 5 terms and as TOA President for 3 terms. In 1981, while serving as the Ankara Branch Chair, he started the TOA Ankara Regional Branch National April courses, a tradition that will be held for the 40th time next year. Publishing the lectures presented at these courses in book form has also become a tradition and continues to have a substantial role in promoting ophthalmology education in our country.

Prof. Turaçlı is one of the key figures cultivated by the Republic of Turkey. He was a public-minded person. The aid he sent to earthquake-affected areas and the eponymous science high school he funded in his hometown of Niksar in the Tokat province also serve as examples of his philanthropic contributions to our country.

Turkish ophthalmology will not forget its revered teacher and honorary president, lost due to the COVID-19 pandemic while still professionally active. To keep the memory of Prof. M. Erol Turaçlı alive, the TOA Administrative Board has decided to hold a memorial conference in his name each year during the April courses he founded.

We offer our sincerest condolences to the entire community and to his colleagues and family. His contributions to our country, our association, and all ophthalmologists will never be forgotten.

On behalf of the TOA,
Professor İzzet Can, MD
TOA President

DOI: 10.4274/tjo.galenos.2020.37346
Turk J Ophthalmol 2020;50:258-263

Original Article

The Value of Fortified Aminoglycoside/ Cephalosporin Treatment as First-Line Treatment and in Fluoroquinolone-Resistant Bacterial Keratitis

Özlem Dikmetaş*, Yağmur Deniz*, Sibel Kocabeyoğlu*, Merve Başol**, Murat İrkeç*

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

Abstract

Objectives: Topical application of fluoroquinolone antibiotics is thought to be as effective as fortified antibiotics. The aim of this study was to evaluate the efficacy of fluoroquinolones as an alternative to fortified antibiotic therapies.

Materials and Methods: The medical records of 31 patients who were hospitalized in our department due to bacterial keratitis were retrospectively reviewed. Fluoroquinolone was started as the first treatment for 20 (64.5%) patients and upon no response fortified antibiotic was initiated, and 11 (35.5%) patients were started with fortified treatment. Cultures and smears were recorded before treatment. Lesions were evaluated as superficial or deep according to their depth. Treatment response was evaluated based on reduction of infiltrate depth and size, change in visual acuity, and regression of hypopyon.

Results: Central, paracentral, and peripheral location were detected in 9 (29.0%), 10 (32.2%) and 12 (38.7%) eyes, respectively. According to lesion depth, 15 (48.3%) were deep and 16 (51.6%) were superficial. Response of superficial lesions was found to be statistically earlier (p=0.037). Culture was positive in 9 (29.0%) eyes. The initial best corrected visual acuity (BCVA) was 0.5±0.7 logMAR (-0.1-2.3) and 0.3±0.3 logMAR (-0.1-0.9) after treatment. Treatment response showed moderate but statistically nonsignificant correlation with time to treatment initiation and initial BCVA (r=0.527, p=0.184; r=0.517, p=0.120).

Conclusion: Although fluoroquinolones are the first choice for the treatment of bacterial keratitis, fortified antibiotics have been shown to be effective in patients who do not respond to treatment. Fortified therapy should be kept in mind in the treatment of bacterial keratitis.

Keywords: Bacterial keratitis, topical treatment, fortified antibiotics

Introduction

Infectious keratitis is a condition characterized by uncontrolled inflammation associated with the proliferation of bacteria, viruses, fungi, or parasites in the cornea due to impaired defense mechanisms for various reasons.[1,2,3] If not diagnosed accurately and treated early, it can result in severe vision loss.[3] The annual incidence is 6.3-710 per 100,000, with higher rates among contact lens users.[1,4,5,6,7,8] Although culture and smear are frequently used in the diagnosis of keratitis, accurate and rapid diagnosis is currently made with polymerase chain reaction and *in vivo* confocal microscopy.[7]

Bacterial keratitis is infectious keratitis caused by bacteria. *Staphylococcus aureus* and *Streptococcus pneumoniae,* which are frequently associated with eyelid and tear film problems, and *Pseudomonas aeruginosa*, which is frequently seen as a result of

Address for Correspondence: Özlem Dikmetaş, M.D., Hacettepe University Faculty of Medicine, Department of Ophthalmology, Ankara, Turkey
Phone:+90 535 470 08 29 E-mail: ozlemdikmetas@gmail.com **ORCID-ID:** orcid.org/0000-0001-5670-2384
Received: 20.01.2020 **Accepted:** 06.04.2020

Cite this article as: Dikmetaş Ö, Deniz Y, Kocabeyoğlu S, Başol M, İrkeç M. The Value of Fortified Aminoglycoside/Cephalosporin Treatment as First-Line Treatment and in Fluoroquinolone-Resistant Bacterial Keratitis. Turk J Ophthalmol. 2020;50:258-263

contact lens use, are common causative agents.[1] Hospitalization of the patient may be preferable because the condition requires fast and effective treatment after diagnosis. In particular, it is more appropriate to hospitalize patients who have central corneal involvement, rapid progression, clinical signs of virulent bacteria, and those who are unlikely to have adequate care at home.[9] The aim of treatment is to eliminate the causative agent and ensure minimal structural damage.[9] Treatment should be started immediately after obtaining a corneal sample. Due to the possibility of rapid progression and poor prognosis, empirical antibiotic therapy should be initiated in patients those pathogen is undetermined.

Numerous antibiotics can be used in the treatment of keratitis. These antibiotics should be bactericidal and have low toxicity to ocular tissues. Therefore, fortified antibiotic combination therapies are used after analyzing their effectiveness against gram-positive and gram-negative bacteria.[9] First-generation cephalosporins (especially cefazolin), glycopeptides (vancomycin), aminoglycosides, and fluoroquinolones are used for gram-positive bacteria, while aminoglycosides and fluoroquinolones are used for gram-negative bacteria.[10,11] Fluoroquinolones have also been used because they act against both gram-positive and gram-negative bacteria and provide high treatment success with a single drug.[10,11] However, although the probability of developing resistance was expected to be lower than other bacteria, resistance develops more rapidly. The most important disadvantage of fluoroquinolones was their low activity against gram-positive bacteria, especially streptococci, but this activity was improved with the development of fourth-generation fluoroquinolones.[10,11]

The current study aimed to demonstrate the effectiveness of fortified antibiotic combination therapy, which is now less preferred than fluoroquinolones.[12] The objective was to evaluate the efficacy of this treatment in cases of bacterial keratitis initially treated with fourth-generation fluoroquinolone therapy or with fortified aminoglycoside/cephalosporin therapy.

Materials and Methods

This study was performed after obtaining approval from the Hacettepe University Faculty of Medicine Ethics Committee (no. GO 17/264) and adhered to the principles of the Declaration of Helsinki. The medical data of patients who presented to the Cornea Unit of the Hacettepe University Faculty of Medicine Department of Ophthalmology were evaluated retrospectively. Of these patients, those who had previously started treatment, those treated at another center, those with systemic comorbidity, contact lens users, and those with other ocular surface diseases were excluded. Causes of keratitis include bullous keratopathy, recurrent corneal epithelial defect, trauma-induced epithelial defect, and blepharitis. A total of 31 patients who presented directly to our hospital, had not been treated previously, and were treated in our clinic were included in the study.

Treatment with a fourth-generation fluoroquinolone (5 mg/mL moxifloxacin) or fortified cephalosporin (50 mg/mL cefazolin) and aminoglycoside (14 mg/mL gentamicin) combination therapy was initiated. Fortified antibiotics were prepared daily for use. All patients received 1 drop every 15 minutes for the first 6 hours, hourly day and night for 48 hours, hourly during the day for the next 3 days, and tapered thereafter depending on the clinical course. Patients who did not respond to fluoroquinolone within the first 72 hours were switched to fortified antibiotic therapy.[13] This applied to all cases. The patients were given no other treatment before these medical treatments. None of the patients received steroid therapy.

The patients' best corrected visual acuity (BCVA), intraocular pressure, and anterior and posterior segment examination findings were evaluated. In addition, culture and smear results were analyzed. Deep and superficial corneal infiltration were differentiated based on the involvement of half or more of the full corneal thickness in the biomicroscopic examination.[14] Treatment response was evaluated based on the reduction in the depth and size of the corneal infiltrate, regression of corneal edema, change in visual acuity, anterior chamber inflammation, and regression of hypopyon.[15] Patients with infiltrates located in the central cornea and larger than 2 mm and all patients started on fortified antibiotic treatment were hospitalized for treatment.

Statistical Analysis

For descriptive statistics, continuous variables were expressed as mean and standard deviation, and categorical variables as number and percentage. Categorical variables (lesion depth, hypopyon, lesion localization) were compared using chi-square test. Relationships between categorical variables and numerical variables were analyzed using eta correlation coefficient. The level of significance was accepted as $p<0.05$. Analyses were performed using IBM SPSS version 21.0.

Results

At diagnosis, the mean age of the patients (18 males and 13 females) was 49.1±24.2 (3-88) years. Mean BCVA was 0.5±0.7 (-0.1-2.3) logMAR (logarithm of the minimum angle of resolution) before treatment and 0.3±0.3 logMAR (-0.1-0.9) after treatment. Subgroup analysis based on 4 age groups (0-16, 17-50, 51-80, and >81 years) revealed no significant correlation between age and initial or final BCVA ($r=0.325$, $p=0.074$; $r=-0.254$, $p=0.201$). There were no significant differences in initial or final BCVA among the age groups ($p=0.695$, $p=0.096$). Mean treatment duration was 3.2±0.3 (1-10) weeks. Three patients had short follow-up periods and it was noted that these patients had peripheral and superficial infiltrates. In these patients' final follow-up examination, their BCVA was perfect and the lesions had resolved. The general demographic and clinical characteristics of the patients are summarized in Table 1.

For 64.5% (20/31) of the patients, fourth-generation fluoroquinolone therapy was used as first-line treatment and fortified aminoglycoside/cephalosporin treatment was initiated after no response was obtained. Of these 20 eyes, infiltrates were peripheral in 12 (60%) and paracentral in 8 (40%); none had central lesions. BCVA in these eyes was 0.3±0.2

(-0.1-0.7) logMAR before treatment and 0.2±0.3 (-0.1-0.9) logMAR after treatment. The mean follow-up period for these patients was 3.5±0.3 (3-6) weeks. In the entire study group, treatment response showed moderate but statistically nonsignificant correlation with time to treatment initiation and initial BCVA (r=0.527, p=0.184; r=0.517, p=0.120). Earlier initiation of treatment was associated with better treatment response. Patients with low initial BCVA had lower final BCVA and poor treatment response in terms of corneal infiltrates.

When corneal smear and culture results were examined, microorganisms were detected in the smears of 6 eyes (19.3%) and culture was positive in 9 eyes (29%). Of the microorganisms demonstrated, 6 (66.6%) were gram-positive bacteria and 3 (33.3%) were gram-negative bacteria; no fungi or parasites were detected (Table 2). The most common pathogen was *Staphylococcus epidermidis,* followed by *Streptococcus mitis, P. aeruginosa, Klebsiella pneumoniae,* and *Haemophilus influenzae.* According to culture results, *S. aureus* keratitis was seen in only 1 patient, whose final BCVA was lower than the initial level.

Keratitis foci were located centrally, paracentrally, and peripherally in 9 (29%), 10 (32.2%), and 12 (38.7%) of the eyes, respectively, and hypopyon was detected in 5 eyes (16.1%). Presence of hypopyon in the anterior chamber was found to be associated with poor treatment response (p=0.001). According to lesion depth, 15 (48.3%) of the lesions were deep and 16 (51.6%) were superficial. Superficial lesions showed significantly faster response to treatment (p=0.037). Three patients (9.6%) who did not respond to treatment underwent amniotic membrane transplantation. These 3 patients had BCVA of 2.3, 2.3, and 0.9 logMAR before treatment and 0.9, 0.9, and 0.9 logMAR after treatment, respectively.

Discussion

This study demonstrated the effectiveness of fortified aminoglycoside/cephalosporin combination therapy in eyes with bacterial keratitis when used as first-line treatment or after non-response to fourth-generation fluoroquinolone therapy. Of the patients included in the study, 64.5% (20/31) were first treated with fourth-generation fluoroquinolone, while 35.5% (11/31) received fortified aminoglycoside/cephalosporin combination therapy as first-line treatment. Patients in the fluoroquinolone group who did not respond to treatment were treated with fortified aminoglycoside/cephalosporin. In total, 90.3% (28/31) of the patients responded to treatment, while 9.6% (3/31) did not. These 3 non-responders underwent amniotic membrane transplantation and their visual acuity remained stable. As

Table 1. Demographic and clinical characteristics

	Fortified aminoglycoside/cephalosporin therapy after 4th-gen FQ (n=20)	**First-line fortified aminoglycoside/ cephalosporin therapy (n=11) (mean ± SD, range)**
Sex (male/female) (mean ± SD, range)	13/7	5/6
Mean age (years) (mean ± SD, range)	46.9±22.3 (3-80)	50.3±20.4 (8-88)
Initial VA (logMAR) (mean ± SD, range) <0.7 (n, %) 0.25-0.7 (n, %) >0.25 (n, %)	0.3±0.2 (-0.1-0.7) 12 (60) 7 (35) 1 (5)	0.9±0.7 (-0.1-2.3) 7 (63.7) 0 (0) 4 (36.3)
Final VA (logMAR) (mean ± SD, range)	0.2±0.3 (-0.1-0.9)	0.3±0.3 (-0.1-0.9)
Treatment duration (weeks)	3.5±0.3 (3-6)	4.6±1.5 (1-10)
Keratitis location (n, %) Central Paracentral Peripheral	 0 (0) 8 (40) 12 (60)	 9 (81.8) 2 (18.2) 0 (0)
Lesion depth Deep (n, %) Superficial (n, %)	 4 (20) 16 (80)	 11 (100) 0 (0)
Culture isolate (n, %)	7 (35) *Haemophilus influenzae, Klebsiella pneumoniae, Staphylococcus epidermidis, Staphylococcus aureus*	2 (18.1) *Pseudomonas aeruginosa, Streptococcus mitis*
Antibiogram	1 patient resistant to piperacillin and imipenem, 3 patients sensitive to cephalosporins, aminoglycosides, and fluoroquinolones, 3 patients sensitive to cephalosporins and aminoglycosides	2 patients sensitive to cephalosporins, aminoglycosides, and fluoroquinolones

FQ: Fluoroquinolone, SD: Standard deviation, VA: Visual acuity, LogMAR: Logarithm of minimal angle of resolution, n: number, %: percentage

Table 2. Culture results	
Pathogen	**n (%)**
Gram-negative bacteria	3 (33.3)
Pseudomonas aeruginosa	1 (3.2)
Haemophilus influenzae	1 (3.2)
Klebsiella pneumoniae	1 (3.2)
Gram-positive bacteria	6 (66.6)
Staphylococcus epidermidis	4 (12.9)
Staphylococcus aureus	1 (3.2)
Streptococcus mitis	1 (3.2)
Negative culture	22 (70.9)
n: number, %: percentage	

for the reasons for nonresponse to treatment, deep lesions and presence of hypopyon were found to be significant in our study.

Similar to our study, Karalezli et al.[16] administered fluoroquinolone or aminoglycoside/cephalosporin combination therapy separately to both groups and compared their efficacy, and they did not detect any statistically significant differences between these two antibiotic groups. Unlike other studies, in the present study we evaluated the outcomes of patients who were first treated with fourth-generation fluoroquinolone and switched to fortified aminoglycoside/cephalosporin combination therapy after non-response to treatment, compared to patients who used fortified aminoglycoside/cephalosporin combination as first-line treatment.

Because bacterial keratitis can result in severe vision loss, empirical antibiotic treatment should be initiated early, without waiting for culture and smear results.[15] Although the culture positivity rate in keratitis varies in studies conducted worldwide, the mean rate is around 30-50%.[17,18] In our study, the positive culture rate was 29% (9/31).

Broad-spectrum antibiotic monotherapy has gained popularity due both to its practicality and the notion that administering a single drug will reduce adverse effects. Fourth-generation fluoroquinolones are frequently used for this purpose. Fluoroquinolone formulations are also preferred as monotherapy due to their broad-spectrum activity, stability at room temperature, convenience for patients, low cost, and solution stability features.[19] Fluoroquinolones are therapeutic agents with very good tissue penetration and the least ocular toxicity.[20] The main problem with drugs applied to the ocular surface is being able to reach the effective dose in the cornea. Topical agents may have low bioavailability for this reason. The mucoadhesive polymeric hydrogel formulations used with fluoroquinolones facilitate the drug reaching the therapeutic dose in the cornea.[21] They exert their effect by inhibiting bacterial DNA synthesis.[10]

While first-generation fluoroquinolones mainly act against gram-negative bacteria, new-generation fluoroquinolones have increased activity against gram-positive bacteria, but their effectiveness against *Pseudomonas* strains could not be increased. At present, the most effective fluoroquinolone against *Pseudomonas* strains is ciprofloxacin, a second-generation fluoroquinolone.[22] Kowalski et al.[23] showed that moxifloxacin and gatifloxacin, both fourth-generation fluoroquinolones, were more effective against gram-positive and gram-negative bacteria, respectively, compared to other generations of fluoroquinolones.

Previous studies show that despite their effectiveness, the development of resistance against fluoroquinolones has become an important problem.[24,25] With this group of antibiotics, sufficient gram-positive/gram-negative activity cannot be achieved against all microorganisms when administered alone and resistance may develop quickly.[26] Due to differing effects of fluoroquinolones against gram-negative and gram-positive bacteria and the important problem of antibiotic resistance, the known effectiveness of fortified aminoglycoside/cephalosporin combination antibiotics is still preferable, as our study also suggests.

Aminoglycosides are mainly effective against gram-negative bacteria and inhibit protein synthesis by binding to the 30S subunit of bacterial ribosomes.[27] Although gentamicin is frequently used, tobramycin and amikacin may be preferred in case of resistance. Tobramycin in particular is an important option from the aminoglycoside group of drugs that is preferred for its marked effectiveness against *P. aeruginosa*.[27] Aminoglycosides are often combined with beta-lactam antibiotics to increase their bactericidal activity.[27] Cephalosporins are a group of antibiotics related to beta-lactams that show a dose-dependent effect by inhibiting cell wall synthesis.[28] They act against both gram-positive and gram-negative bacteria. Fourth-generation cephalosporins in particular have a broad spectrum of activity and may be preferable in patients with antibiotic resistance.

Hanet et al.[11] conducted a literature review analyzing 8 randomized and 5 nonrandomized studies and in their comparison of fluoroquinolones and fortified antibiotics, they demonstrated fluoroquinolones is appropriate as an alternative, second-line treatment option to fortified antibiotics. Constantinou et al.[29] found that fortified antibiotic treatment and second-generation fluoroquinolone-derivative antibiotics were similarly effective. Unlike our study, these studies directly compare two different treatment methods. However, in our study we evaluated the effectiveness of fortified aminoglycoside/cephalosporin after nonresponse to fluoroquinolones in one group. Based on this, fortified antibiotics may be a preferable option, especially to prevent the problem of antibiotic resistance.

In our study, we also observed that most keratitis patients who did not respond to initial treatment with fluoroquinolone responded to fortified antibiotics. Patients whose treatment was started early had better final visual acuity and corneal infiltrate response to treatment. This may be related to the fact that in patients who presented earlier, corneal lesions induced less inflammatory response during this period.

Sharma et al.[30] also compared the efficacy of gatifloxacin and tobramycin-cefazolin fortified antibiotic therapy in keratitis eyes and reported that they were equally effective and not substantially different in cost in developed countries. However, despite the equal effectiveness in these studies, the preference of new generation fluoroquinolone-derivative agents as first-line

treatment should be limited due to resistance. Our study showed that fortified therapy was effective in cases of bacterial keratitis that were unresponsive to fourth-generation fluoroquinolones and those initially treated with fortified aminoglycoside/cephalosporin combination. In patients who do not respond to fluoroquinolones, fortified antibiotic therapy should be considered as an option.

Study Limitations

The main limitations of this study are its retrospective design, absence of a control group, low culture positivity rate, inability to evaluate treatment adherence in patients not hospitalized during fluoroquinolone treatment, and not performing drug stability assessment.

Conclusion

In light of the studies in the literature, we conclude that fortified antibiotics still have a place in the treatment of bacterial keratitis and remain the best alternative to fluoroquinolone therapy. This study emphasizes that fortified antibiotic therapy must be kept in mind and its effectiveness not forgotten.

Ethics

Ethics Committee Approval: This study was performed after obtaining approval from the Hacettepe University Faculty of Medicine Ethics Committee (no. GO 17/264) and adhered to the principles of the Declaration of Helsinki.

Informed Consent: Obtained.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Ö.D., S.K., M.İ., Concept: S.K., M.İ., Design: S.K., M.İ., Data Collection or Processing: Ö.D., Y.D., S.K., Analysis or Interpretation: Ö.D., M.B., Y.D., S.K., M.İ., Literature Search: Ö.D., Y.D., Writing: Ö.D., S.K., 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. Bourcier T, Thomas F, Borderie V, Chaumeil C, Laroche L. Bacterial keratitis: predisposing factors, clinical and microbiological review of 300 cases. Br J Ophthalmol. 2003;87:834-838.
2. Thomas PA, Geraldine P. Infectious keratitis. Curr Opin Infect Dis. 2007;20:129-141.
3. Gümüş MK. Bakteriyel Keratitler. Turkiye Klinikleri Ophthalmology-Special Topics. 2012;5:41-46.
4. Lakhundi S, Siddiqui R, Khan NA. Pathogenesis of microbial keratitis. Microb Pathog. 2017;104:97-109.
5. Kam KW, Yung W, Li GKH, Chen LJ, Young AL. Infectious keratitis and orthokeratology lens use: a systematic review. Infection. 2017;45:727-735.
6. Sızmaz S, Bingöllü S, Erdem E, Kibar F, Koltaş S, Yağmur M, Ersöz R. Polymicrobial Infection of the Cornea Due to Contact Lens Wear. Turk J Ophthalmol. 2016;46:83-86.
7. Ung L, Bispo PJM, Shanbhag SS, Gilmore MS, Chodosh J. The persistent dilemma of microbial keratitis: Global burden, diagnosis, and antimicrobial resistance. Surv Ophthalmol. 2019;64:255-271.
8. Organization WH. Guidelines for the management of corneal ulcer at primary, secondary and tertiary care health facilities in the South-East Asia region. 2004. http://www.who.int/iris/handle/10665/205174.
9. Austin A, Schallhorn J, Geske M, Mannis M, Lietman T, Rose-Nussbaumer J. Empirical treatment of bacterial keratitis: an international survey of corneal specialists. BMJ Open Ophthalmol. 2017;2:e000047.
10. Chan T, Bunce PE. Fluoroquinolone antimicrobial drugs. CMAJ. 2017;189:638.
11. Hanet MS, Jamart J, Chaves AP. Fluoroquinolones or fortified antibiotics for treating bacterial keratitis: systematic review and meta-analysis of comparative studies. Can J Ophthalmol. 2012;47:493-499.
12. Hsu HY, Nacke R, Song JC, Yoo SH, Alfonso EC, Israel HA. Community opinions in the management of corneal ulcers and ophthalmic antibiotics: a survey of 4 states. Eye Contact Lens. 2010;36:195-200.
13. Shah VM, Tandon R, Satpathy G, Nayak N, Chawla B, Agarwal T, Sharma N, Titiyal JS, Vajpayee RB. Randomized clinical study for comparative evaluation of fourth-generation fluoroquinolones with the combination of fortified antibiotics in the treatment of bacterial corneal ulcers. Cornea. 2010;29:751-757.
14. Karaca I, Barut Selver O, Palamar M, Egrilmez S, Aydemir S, Yagci A. Contact Lens-Associated Microbial Keratitis in a Tertiary Eye Care Center in Turkey. Eye Contact Lens. 2020;46:110-115.
15. Lin A, Rhee MK, Akpek EK, Amescua G, Farid M, Garcia-Ferrer FJ, Varu DM, Musch DC, Dunn SP, Mah FS; American Academy of Ophthalmology Preferred Practice Pattern Cornea and External Disease Panel. Bacterial Keratitis Preferred Practice Pattern(R). Ophthalmology. 2019;126:1-55.
16. Karalezli A, Nurözler AB, Telek H, Duman S. Bakteriyel Keratit Tedavisinde Kullanılan Antibiyotiklerin Etkinliğinin Karşılaştırılması ve Etyolojide Rol Oynayan Faktörler. Turkiye Klinikleri J Ophthalmol. 2008;17:238-244.
17. Ferreira CS, Figueira L, Moreira-Goncalves N, Moreira R, Torrao L, Falcao-Reis F. Clinical and Microbiological Profile of Bacterial Microbial Keratitis in a Portuguese Tertiary Referral Center-Where Are We in 2015? Eye Contact Lens. 2018;44:15-20.
18. Palamar M, Masaroğulları M, Eğrilmez S, Aydemir Ş, Yağcı A. Our microbiological analysis results in microbial contact lens keratitis. Turk J Ophthalmol. 2010;40:349-353.
19. Khokhar S, Sindhu N, Mirdha BR. Comparison of topical 0.3% ofloxacin to fortified tobramycin-cefazolin in the therapy of bacterial keratitis. Infection. 2000;28:149-152.
20. Blondeau JM. Fluoroquinolones: mechanism of action, classification, and development of resistance. Surv Ophthalmol. 2004;49(Suppl 2):73-78.
21. Gade SK, Shivshetty N, Sharma N, Bhatnagar S, Garg P, Venuganti VVK. Effect of Mucoadhesive Polymeric Formulation on Corneal Permeation of Fluoroquinolones. J Ocul Pharmacol Ther. 2018;34:570-578.
22. Grillon A, Schramm F, Kleinberg M, Jehl F. Comparative Activity of Ciprofloxacin, Levofloxacin and Moxifloxacin against Klebsiella pneumoniae, Pseudomonas aeruginosa and Stenotrophomonas maltophilia Assessed by Minimum Inhibitory Concentrations and Time-Kill Studies. PLoS One. 2016;11:e0156690.
23. Kowalski RP, Dhaliwal DK, Karenchak LM, Romanowski EG, Mah FS, Ritterband DC, Gordon YJ. Gatifloxacin and moxifloxacin: an in vitro susceptibility comparison to levofloxacin, ciprofloxacin, and ofloxacin using bacterial keratitis isolates. Am J Ophthalmol. 2003;136:500-505.
24. Goldstein MH, Kowalski RP, Gordon YJ. Emerging fluoroquinolone resistance in bacterial keratitis: a 5-year review. Ophthalmology. 1999;106:1313-1318.
25. Miller D, Chang JS, Flynn HW, Alfonso EC. Comparative in vitro susceptibility of besifloxacin and seven comparators against ciprofloxacin- and methicillin-susceptible/nonsusceptible staphylococci. J Ocul Pharmacol Ther. 2013;29:339-344.
26. Karlowsky JA, Hoban DJ, Decorby MR, Laing NM, Zhanel GG. Fluoroquinolone-resistant urinary isolates of Escherichia coli from outpatients are frequently multidrug resistant: results from the North American Urinary Tract Infection Collaborative Alliance-Quinolone Resistance study. Antimicrob Agents Chemother. 2006;50:2251-2254.

27. Becker B, Cooper MA. Aminoglycoside antibiotics in the 21st century. ACS Chem Biol. 2013;8:105-115.
28. Chaudhry SB, Veve MP, Wagner JL. Cephalosporins: A Focus on Side Chains and beta-Lactam Cross-Reactivity. Pharmacy (Basel). 2019;7:103.
29. Constantinou M, Daniell M, Snibson GR, Vu HT, Taylor HR. Clinical efficacy of moxifloxacin in the treatment of bacterial keratitis: a randomized clinical trial. Ophthalmology. 2007;114:1622-1629.
30. Sharma N, Goel M, Bansal S, Agarwal P, Titiyal JS, Upadhyaya AD, Vajpayee RB. Evaluation of moxifloxacin 0.5% in treatment of nonperforated bacterial corneal ulcers: a randomized controlled trial. Ophthalmology. 2013;120:1173-1178.

DOI: 10.4274/tjo.galenos.2020.18488
Turk J Ophthalmol 2020;50:264-270

Original Article

Agreement Between Standard Optical Coherence Tomography and Optical Coherence Tomography-Based Angiography in Estimating Retinal Nerve Fiber Layer Thickness

Hayati Yılmaz*, Mehmet Talay Köylü**, Alper Can Yılmaz**, Ali Hakan Durukan**, Yusuf Uysal**

*University of Health Sciences Turkey, Ümraniye Training and Research Hospital, Clinic of Ophthalmology, İstanbul, Turkey
**University of Health Sciences Turkey, Gülhane Medical Faculty, Department of Ophthalmology, Ankara, Turkey

Abstract

Objectives: To investigate the agreement between optical coherence tomography (OCT) and OCT-based angiography in estimating retinal nerve fiber layer thickness (RNFLT) and evaluate the associations between peripapillary vessel density (VD) and RNFLT measurements obtained with both devices.

Materials and Methods: The AngioVue (Optovue Inc., Fremont, CA, USA) and Spectralis (Heidelberg Engineering, Heidelberg, Germany) images of 325 patients were screened retrospectively. RNFLT values were recorded using both devices. The intraclass correlation coefficient (ICC) and Bland-Altman plots were obtained to investigate the agreement between the devices. Age- and intraocular pressure-corrected associations between VD and RNFLT measured by the two devices were analyzed using linear regression models.

Results: ICC revealed excellent agreement for global, superior, inferior, and temporal RNFLT and good agreement for the nasal quadrant (ICC=0.895, 0.936, 0.923, 0.887, and 0.614, respectively). The Bland-Altman plots showed poor agreement for all measurements with a large span of limits of agreement and significant proportional bias ($p<0.05$). VD was found to be strongly associated with the RNFLT measurements of both devices ($p<0.001$).

Conclusion: The disagreement between the devices should be considered in clinical practice, and the data should not be used interchangeably. The association of the peripapillary VD with RNFLT using both devices indicated that RNFLT assessed by the AngioVue could be used in glaucoma management along with VD.

Keywords: Glaucoma, optical, coherence, angiography, agreement

Introduction

Optical coherence tomography (OCT), first invented in 1991, allows imaging and analysis of the retinal nerve fiber layer (RNFL).[1] Given the fact that functional visual field loss cannot be detected until up to 40% RNFL loss, analysis of the RNFL has great importance for the early detection of glaucoma.[2,3,4,5,6]

With technological advances, time domain OCT, which has a scanning speed of 400 A-scans/s, has been replaced by spectral domain OCT (SD-OCT), with an improved scanning speed

Address for Correspondence: Hayati Yılmaz, M.D., University of Health Sciences Turkey, Ümraniye Training and Research Hospital, Clinic of Ophthalmology, İstanbul, Turkey Phone:+90 541 282 36 19 E-mail: dr.hyilmaz@hotmail.com **ORCID-ID:** orcid.org/0000-0001-5051-5713
Received: 16.02.2020 **Accepted:** 06.04.2020

Cite this article as: Yılmaz H, Köylü MT, Yılmaz AC, Durukan AH, Uysal Y. Agreement Between Standard Optical Coherence Tomography and Optical Coherence Tomography-Based Angiography in Estimating Retinal Nerve Fiber Layer Thickness. Turk J Ophthalmol. 2020;50:264-270

of 29,000 to 55,000 A-scans/s, in ophthalmological practice.[7] Recently, the advent of OCT angiography (OCTA) has enabled the noninvasive visualization of the retinal and peripapillary vessels, as well as analysis of structural parameters such as RNFL thickness (RNFLT) in the same scan.[8,9] Using OCTA, the reduction of vessel density (VD) and blood flow index in glaucomatous eyes has been well documented in numerous studies.[10,11] Furthermore, it was established by previous studies that OCT and OCTA both have excellent repeatability and reproducibility.[12,13,14,15,16]

There are limited data about the structural measurements of peripapillary parameters such as RNFLT using the OCTA scanning module. It is very important for clinicians to determine whether OCTA could be used only for the vascular network assessment of the retina and optic nerve head (ONH) and whether this can replace traditional OCT for monitoring glaucoma patients. Therefore, the aim of the present study was to investigate the agreement between SD-OCT scans and SD-OCT-based OCTA system scans for RNFLT measurement in subjects with primary open-angle glaucoma (POAG).

Materials and Methods

The present study was conducted after receiving the approval of the Institutional Non-interventional Research Ethics Committee of The Health Sciences University and was conducted in agreement with the principles of the Declaration of Helsinki. The study was designed retrospectively, and patients with a diagnosis of POAG or glaucoma suspect (GS) who visited our glaucoma clinics between January 2018 and August 2019 and underwent OCT and OCTA scans during this visit were identified from the hospital records. The exclusion criteria were as follows: age under 18 years, refractive error greater than ±3 diopters, presence of any other ophthalmological pathology that could confound the assessment results (e.g., diabetes or hypertensive retinal diseases, amblyopia, optic nerve anomalies, optic neuropathies other than glaucoma, and age-related macular degeneration), SD-OCT signal strength <20 for Spectralis, and OCTA signal strength <70 for AngioVue.

Assessment of RNFLT Using SD-OCT

Spectralis OCT (version 4.0) (Heidelberg Engineering, Heidelberg, Germany) was used for the measurement of RNFLT. This device has an A-scan rate of 40,000/s using a light source of 820 nm. An en face image focusing on the ONH was generated using a confocal scanning laser ophthalmoscope, and after a 3.4-mm circle was centered on the ONH, 15 images were acquired under high resolution settings and averaged automatically by the built-in software. After the scan was completed, global and quadrantal RNFLT values were recorded in accordance with the temporal-superior-nasal-inferior-temporal (TSNIT) chart.

Assessment of RNFLT Using OCTA

OCTA scan acquisition was performed using an AngioVue OCTA system (Optovue Inc., Fremont, CA, USA) with an A-scan rate of 70,000/s using a light source of 840 nm. En face images were acquired focusing on the ONH (4.5 mm x 4.5 mm) using the Angio Disc QuickVue module. Each scan contained 400x400 A-scans with two following B-scans at each fixed location. To reduce motion artifacts, each image consisted of one orthogonal horizontal and vertical scan.

OCTA provides RNFLT and peripapillary VD data in the same scan. After the scanning was completed, in addition to the VD of the global retinal peripapillary capillary plexus (RPCP), global and quadrantal RNFLT values were recorded in accordance with the TSNIT chart.

Statistical Analyses

Quantitative variables were expressed as mean and standard deviation (SD), and qualitative variables as percentages. The paired t-test was used to compare the results of the two devices. The magnitude of the disagreement between the Spectralis and the AngioVue data was estimated as the mean absolute difference of the global and quadrantal RNFLT values. The agreement between the corresponding Spectralis and AngioVue data was calculated using intraclass correlation coefficient (ICC). Absolute ICCs based on the mixed model analysis of variance were used in the present study. An ICC value less than 0.4 was considered to indicate poor agreement, 0.4 to 0.75 as fair to good agreement, and a value greater than 0.75 as excellent agreement.[17] ICC calculations were performed before and after the subjects were divided into the POAG and GS groups. The Shapiro-Wilk test was used to determine whether the differences in corresponding Spectralis and AngioVue data were normally distributed. Bland-Altman plots were used to assess the agreement between Spectralis and AngioVue in terms of RNFLT measurements. One-sample t-test was performed to reveal the differences before the Bland-Altman plots were created.[18] Then, the linear regression analyses of the Bland-Altman plots were performed to determine the significance of the proportional biases. Age- and intraocular pressure (IOP)-corrected linear regression models were created to analyze the associations between RNFLT data and the small VD of the RPCP. The results of the regression results were obtained with coefficients (B), 95% confidence intervals (CI), and p values. All statistical analyses were undertaken using IBM SPSS Statistics version 21 (IBM Corp., Armonk, NY, USA). A p value less than 0.05 was considered statistically significant.

Results

Of the 386 patients that met the inclusion criteria, a total of 325 patients (52% female, mean age 61.4±18.7 years) were included in the study, and only 1 eye of each patient (with better SD-OCT and OCTA quality) was included in the statistical analysis. Of these 325 eyes, 218 were diagnosed as having POAG and 107 as GS.

Table 1 presents the mean global and quadrantal RNFLT values obtained with AngioVue and Spectralis, the mean differences between the measurements of the two devices, and the results of the paired t-test. The devices significantly differed in all RNFLT parameters ($p<0.001$). AngioVue tended to measure

RNFLT thicker than Spectralis in all quadrants. The global, superior, nasal, inferior, and temporal RNFLT measurements of the two devices were all positively and strongly correlated (R=0.948, 0.908, 0.764, 0.920, and 0.824, respectively).

The mean small VD of the RPCP was 47.97% for the whole sample, 45.84% for the POAG patients, and 51.24% for the GS patients. VD was significantly lower in the POAG group compared to the GS group (p<0.001, Student's t-test).

Agreement Between SD-OCT and OCTA

The results of the ICC analyses are presented in Table 2. There was excellent agreement between the two devices for all RNFLT measurements (ICC=0.895 for global RNFLT, 0.936 for superior, 0.923 for inferior, and 0.887 for temporal) except the nasal quadrant, for which the agreement was good (ICC=0.614). The rates of agreement were higher for the POAG patients than GS cases (Table 2).

Figure 1 presents the scatter plot of AngioVue versus Spectralis in terms of global, superior, nasal, inferior, and temporal RNFLT along with the Bland-Altman plots of these parameters. The Bland-Altman plots showed that the mean bias ± SD between the measurements of AngioVue and Spectralis was 10.74±6.56 for global RNFLT, and 6.35±12.47, 21.39±12.78, 10.53±11.91, and 4.29±9.86 for superior, nasal, inferior, and temporal RNFLT, respectively. The limits of agreement (LOA) were -2.11 -23.59 for global RNFLT, -18.09 -30.79 for superior, -3.67 -46.45 for nasal, -12.99 -33.69 for inferior and -15.03 -23.61 for temporal RNFLT. The Bland-Altman plots revealed the slope of the regression line as 0.13, 0.11, 0.18, 0.12, and -0.04 for global, superior, nasal, inferior, and temporal RNFLT, respectively, indicating that AngioVue tended to provide thicker RNFLT values than Spectralis except for the temporal quadrant, where the opposite result was obtained. The linear regression analyses of the proportional bias were all statistically significant except for the temporal quadrant (p<0.001 for global, inferior, and nasal RNFLT, p=0.014 for superior RNFLT and p=0.407 for temporal RNFLT). The wide spans of LOA and the statistically significant proportional biases suggested poor agreement between AngioVue and Spectralis. However, for the temporal quadrant, the disagreement between the two devices seemed to be much more tolerable.

Table 1. Mean values of the AngioVue and spectralis OCT measurements of the RNFLT and the paired t-test results

	AngioVue (SD)	Spectralis (SD)	Difference (SD)	p
Global (mm)	93.02 (20.13)	82.27 (17.70)	10.74 (6.56)	<0.001
Superior (mm)	106.32 (29.69)	99.97 (26.69)	6.35 (12.47)	<0.001
Nasal (mm)	83.27 (16.33)	61.87 (19.83)	21.39 (12.78)	<0.001
Inferior (mm)	112.28 (30.34)	102.81 (26.97)	10.53 (11.91)	<0.001
Temporal (mm)	69.96 (16.33)	65.67 (16.87)	4.29 (9.86)	<0.001

RNFLT: Retinal nerve fiber layer thickness, SD: Standard deviation, OCT: Optical coherence tomography

Table 2. Intraclass correlation coefficient (ICC) values between AngioVue and spectralis measurements

		ICC	95% CI (lower/upper bounds)	p
Global	Total	0.895	0.876/0.962	<0.001
	POAG	0.900	0.894/0.944	<0.001
	GS	0.756	0.521/0.872	<0.001
Superior	Total	0.936	0.646/0.969	<0.001
	POAG	0.949	0.711/0.968	<0.001
	GS	0.758	0.617/0.952	<0.001
Nasal	Total	0.614	0.465/0.859	<0.001
	POAG	0.603	0.400/0.851	<0.001
	GS	0.553	0.274/0.846	<0.001
Inferior	Total	0.923	0.646/0.969	<0.001
	POAG	0.926	0.711/0.968	<0.001
	GS	0.840	0.617/0.952	<0.001
Temporal	Total	0.887	0.814/0.927	<0.001
	POAG	0.888	0.818/0.927	<0.001
	GS	0.848	0.628/0.928	<0.001

CI: Confidence interval, POAG: Primer open angle glaucoma, GS: Glaucoma suspect

Associations with RPCP VD

The results of the regression models are given in Table 3. Global and all quadrantal RNFLT values obtained by both AngioVue and Spectralis were strongly and independently associated with the small VD of the RPCP. Global RNFLT had the closest relation with the small VD of the RPCP (B=0.327 for AngioVue and 0.382 for Spectralis).

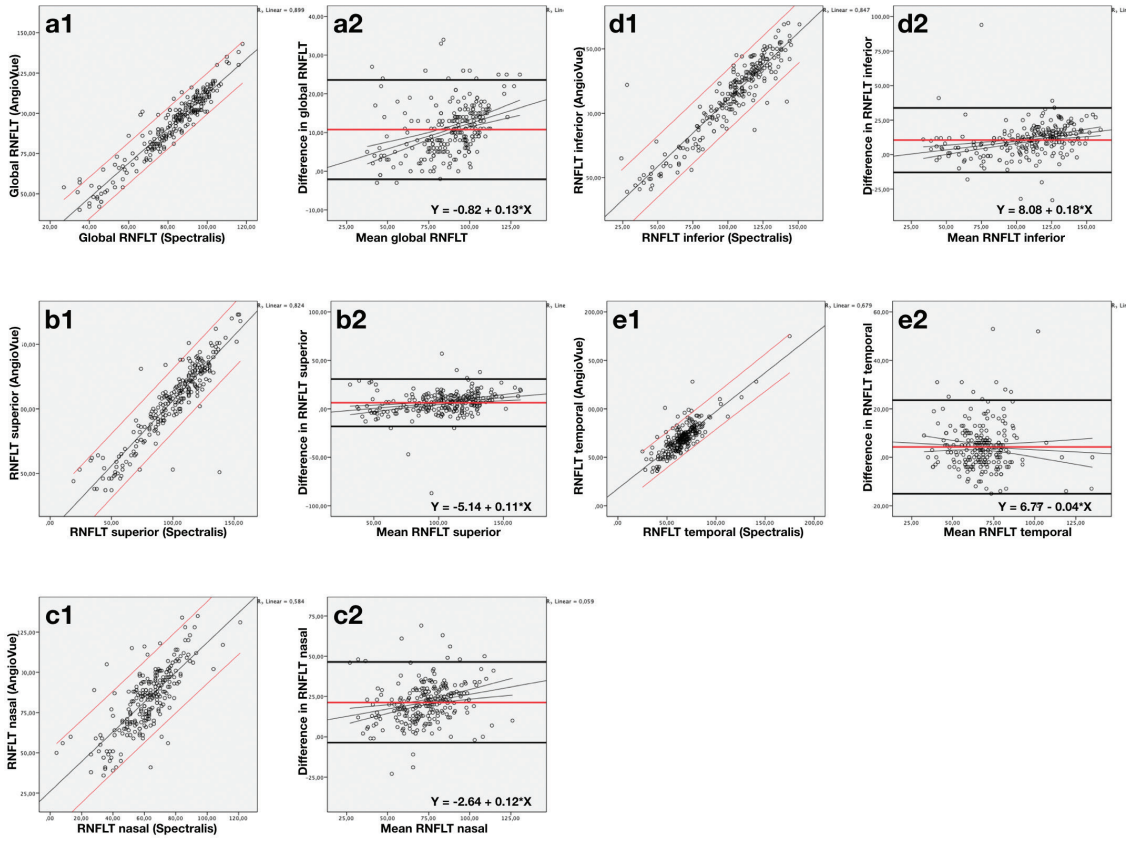


Figure 1. Scatter plots of AngioVue versus Spectralis OCT for RNFLT (column 1) and the Bland-Altman plots for the agreement between AngioVue and Spectralis for the RNFLT (column 2). Scatter plots were given with the regression line (black line) and the 95% limits of agreements (red lines). Bland-Altman plots were given with the mean of the difference (red bold line), 1.96 SDs (black bold lines), and the regression lines (black thin lines). RNFLT scatter and Bland-Altman plots for global (a1,a2), superior (b1,b2), nasal (c1,c2), inferior (d1,d2), temporal (e1,e2) RNFLT values

OCT: Optical coherence tomography, RNFLT: Retinal nerve fiber layer thickness, SD: Standard deviation

Table 3. The linear regression models for the RPCP small VD

RNFLT	Device	B	95% CI (lower/upper bounds)	p
Global	AngioVue	0.327	0.302/0.353	<0.001
	Spectralis	0.382	0.353/0.411	<0.001
Superior	AngioVue	0.213	0.193/0.232	<0.001
	Spectralis	0.243	0.221/0.264	<0.001
Nasal	AngioVue	0.288	0.254/0.322	<0.001
	Spectralis	0.301	0.253/0.350	<0.001
Inferior	AngioVue	0.198	0.178/0.218	<0.001
	Spectralis	0.232	0.210/0.255	<0.001
Temporal	AngioVue	0.199	0.141/0.258	<0.001
	Spectralis	0.186	0.130/0.242	<0.001

RPCP: Retinal peripapillary capillary plexus, VD: Vessel density, RNFLT: Retinal nerve fiber layer thickness, B: Coefficient, CI: Confidence interval

Discussion

The present study investigated the agreement between two different SD-OCT scanning systems, Spectralis OCT and AngioVue, in terms of RNFLT measurements. Although these devices use similar technologies to measure RNFLT and they are both systems based on SD-OCT, the differences in their built-in algorithms caused important differences, indicating that the data should not be used interchangeably. Age- and IOP-controlled associations of the peripapillary VD with RNFLT measurements assessed by these devices were also evaluated in this study. The RNFLT measurements of both devices were found to be strongly associated with the small VD of the RPCP.

Previous studies assessing the agreement between OCT devices similar to our study found better agreement for global thickness.[19,20,21] The better agreement for global RNFLT compared to quadrant thicknesses may be related to the small centralization errors around the ONH. It has been shown that quadrantal measurements may result in greater errors in noncentered scans.[22] Hong et al.[23] compared RNFLT measurements assessed by swept-source OCT (SS-OCT, Triton, Topcon) with SD-OCT (3D-OCT-2000, Topcon). They found that the agreement between these devices was excellent; however, they suggested that the clinician should be aware of measurement errors, especially in patients with retinal diseases. Koh et al.[24] investigated the agreement between SD-OCT (Cirrus HD-OCT, Carl Zeiss Meditec) and OCT/scanning laser ophthalmoscopy (OCT/SLO, OPKO/OTI) and found differences in RNFLT measurements; however, they also suggested that the devices were similar in terms of the detection of glaucomatous damage. Similarly, Mwanza et al.[25] compared 3 different SD-OCT devices (Cirrus HD-OCT, Spectralis OCT and RTVue) and reported different RNFLT values but noted that the dynamic range and the number of steps to the RNFL floor were similar between the devices. Leite et al.[19] also compared the same 3 devices and concluded that these devices could not be used interchangeably.

The only study which investigated the agreement in RNFLT measurements between the traditional OCT system (Cirrus HD-OCT, Carl Zeiss Meditec) and OCTA (Plex Elite 9000, Carl Zeiss Meditec) as in our study was that of Tan et al.[9], who found excellent agreement in terms of the global, superior, and inferior quadrants and good agreement in the temporal and nasal quadrants. The authors concluded that RNFLT could be sufficiently extracted from wide-field OCTA scans. In our study, the agreement was also excellent for the global, superior, inferior, and temporal RNFLT and good for the nasal quadrant.

While investigating the agreement between instruments, the intra-subject repeatability of measurements should also be considered. Previous studies investigated the repeatability of measurements for numerous commercially available OCT devices and the intra-test variability was found to be approximately 5 µm.[21,26,27] With an intra-test variability of 5 µm for each device, even if the instruments have perfect agreement, an error of approximately 10 µm (±5 µm) in the agreement could be expected.[19] In the present study, the span of the LOA of the global RNFLT was approximately 25 µm, more than twice the expected error. The spans of the LOA of the quadrants were even wider than that of the global RNFLT, again indicating that the AngioVue and Spectralis data could not be used interchangeably.

There were fixed biases between the measurements in all corresponding parameters. The AngioVue measurements were consistently thicker than those of Spectralis. There were also proportional biases, indicating that the differences in the RNFLT measurements between the instruments varied according to the actual thickness of RNFL. AngioVue consistently measured RNFLT thicker than Spectralis in all quadrants, but this difference was even greater where the RNFL was thicker. AngioVue and Spectralis seemed to agree more in cases with a thinner RNFL. This was also supported by the much higher ICCs of the POAG patients compared to the GS subjects. Similar proportional biases were observed in previous studies.[19,23,24,28,29] However, no assumption can be made regarding the accuracy of the measurements without a direct comparison to histologic measurements.

The differences between AngioVue and Spectralis were greatest in measurements of the nasal quadrant. There were strong correlations between the corresponding measurements of the two devices; however, the correlation of the nasal quadrant measurements was the weakest. In addition, ICCs revealed good agreement for the nasal quadrant but excellent agreement for all the remaining quadrants, which is consistent with the findings of previous studies.[9,19,20,30] The reason for the greater difference in the nasal quadrant measurements might be the use of different incidence angle of the laser beam by different devices.[19]

Small VD in the RPCP was found to be associated with RNFLT in all quadrants for both AngioVue and Spectralis. She et al.[31] showed that the peripapillary VD was closely related to RNFLT and concluded that OCTA could be valuable for detecting glaucomatous damage. In contrast to She et al.[31], Holló[32,33] conducted a 2-year follow-up study and reported that peripapillary VD did not support glaucomatous progression; however, after removing the large vessels, peripapillary VD could be helpful in detecting progression. The built-in software of AngioVue automatically removes the large vessels and calculates only small VD. The associations of the RNFLT measurements of both devices with RPCP VD were nearly the same. This indicates that RNFLT assessed with OCTA is adequate for use in the management of glaucoma.

Conclusion

In conclusion, even with the excellent agreement revealed by ICC, the wide spans of LOA and the significant proportional biases suggest poor agreement between AngioVue and Spectralis, and therefore the data obtained from these instruments should not be used interchangeably. However, given the fact that VD in the peripapillary area is highly associated with glaucomatous damage and that the results of the present study revealed strong correlations between RNFLT and peripapillary VD for both AngioVue and Spectralis measurements, the RNFLT values of

OCTA could be used for monitoring RNFLT in addition to VD in patients with glaucoma.

Ethics

Ethics Committee Approval: The present study was conducted after receiving the approval of the Institutional Non-interventional Research Ethics Committee of The Health Sciences University and was conducted in agreement with the principles of the Declaration of Helsinki.

Informed Consent: Retrospective.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: H.Y., Design: H.Y., M.T.K., Data Collection or Processing: A.C.Y., Analysis or Interpretation: H.Y., M.T.K., A.H.D., Y.U., Literature Search: H.Y., Writing: H.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. Huang D, Swanson EA, Lin CP, Schuman JS, Stinson WG, Chang W, Hee MR, Flotte T, Gregory K, Puliafito CA, et al. Optical coherence tomography. Science. 1991;254:1178-1181.
2. Zhang Y, Wu LL, Yang YF. Potential of stratus optical coherence tomography for detecting early glaucoma in perimetrically normal eyes of open-angle glaucoma patients with unilateral visual field loss. J Glaucoma. 2010;19:61-65.
3. Kanamori A, Nakamura M, Escano MF, Seya R, Maeda H, Negi A. Evaluation of the glaucomatous damage on retinal nerve fiber layer thickness measured by optical coherence tomography. Am J Ophthalmol. 2003;135:513-520.
4. Yoo YC, Park KH. Comparison of optical coherence tomography and scanning laser polarimetry for detection of localized retinal nerve fiber layer defects. J Glaucoma. 2010;19:229-236.
5. Kim TW, Park UC, Park KH, Kim DM. Ability of stratus OCT to identify localized retinal nerve fiber layer defects in patients with normal standard automated perimetry results. Invest Ophthalmol Vis Sci. 2007;48:1635-1641.
6. Quigley HA, Addicks EM, Green WR. Optic Nerve Damage in Human Glaucoma: III. Quantitative Correlation of Nerve Fiber Loss and Visual Field Defect in Glaucoma, Ischemic Neuropathy, Papilledema, and Toxic Neuropathy. Arch Ophthalmol. 1982;100:135-146.
7. Mumcuoglu T, Wollstein G, Wojtkowski M, Kagemann L, Ishikawa H, Gabriele ML, Srinivasan V, Fujimoto JG, Duker JS, Schuman JS. Improved Visualization of Glaucomatous Retinal Damage Using High-speed Ultrahigh-Resolution Optical Coherence Tomography. Ophthalmology. 2008;115:782-789.
8. Koustenis A Jr, Harris A, Gross J, Januleviciene I, Shah A, Siesky B. Optical coherence tomography angiography: An overview of the technology and an assessment of applications for clinical research. Br J Ophthalmol. 2017;101:16-20.
9. Tan B, Chua J, Harish T, Lau A, Gan ATL, Tan YL, Wong DWK, Chong RS, Ang M, Husain R, Schmetterer L. Comparison of a commercial spectral-domain OCT and swept-source OCT based on an angiography scan for measuring circumpapillary retinal nerve fibre layer thickness. Br J Ophthalmol. 2020;104:974-979.
10. Bojikian KD, Chen PP, Wen JC. Optical coherence tomography angiography in glaucoma. Curr Opin Ophthalmol. 2019;30:110-116.
11. Yarmohammadi A, Zangwill LM, Diniz-Filho A, Suh MH, Manalastas PI, Fatehee N, Yousefi S, Belghith A, Saunders LJ, Medeiros FA, Huang D, Weinreb RN. Optical coherence tomography angiography vessel density in healthy, glaucoma suspect, and glaucoma eyes. Invest Ophthalmol Vis Sci. 2016;57:451-459.
12. Lee SY, Bae HW, Kwon HJ, Seong GJ, Kim CY. Repeatability and Agreement of Swept Source and Spectral Domain Optical Coherence Tomography Evaluations of Thickness Sectors in Normal Eyes. J Glaucoma. 2017;26:46-53.
13. Matlach J, Wagner M, Malzahn U, Göbel Winfried. Repeatability of peripapillary retinal nerve fiber layer and inner retinal thickness among two spectral domain optical coherence tomography devices. Invest Ophthalmol Vis Sci. 2014;55:6536-6546.
14. Carpineto P, Mastropasqua R, Marchini G, Toto L, Di Nicola M, Di Antonio L. Reproducibility and repeatability of foveal avascular zone measurements in healthy subjects by optical coherence tomography angiography. Br J Ophthalmol. 2016;100:671-676.
15. Al-Sheikh M, Tepelus TC, Nazikyan T, Sadda SVR. Repeatability of automated vessel density measurements using optical coherence tomography angiography. Br J Ophthalmol. 2017;101:449-452.
16. Coscas F, Sellam A, Glacet-Bernard A, Jung C, Goudot M, Miere A, Souied EH. Normative data for vascular density in superficial and deep capillary plexuses of healthy adults assessed by optical coherence tomography angiography. Investig Ophthalmol Vis Sci. 2016;57:211-223.
17. Everitt BS, Fleiss JL. Statistical Methods for Rates and Proportions. Biometrics. 1981;37:867.
18. Doğan NÖ. Bland-Altman analysis: A paradigm to understand correlation and agreement. Turkish J Emerg Med. 2018;18:139-141.
19. Leite MT, Rao HL, Weinreb RN, Zangwill LM, Bowd C, Sample PA, Tafreshi A, Medeiros FA. Agreement among spectral-domain optical coherence tomography instruments for assessing retinal nerve fiber layer thickness. Am J Ophthalmol. 2011;151:85-92.
20. Vizzeri G, Weinreb RN, Gonzalez-Garcia AO, Bowd C, Medeiros FA, Sample PA, Zangwill LM. Agreement between spectral-domain and time-domain OCT for measuring RNFL thickness. Br J Ophthalmol. 2009;93:775-781.
21. González-García AO, Vizzeri G, Bowd C, Medeiros FA, Zangwill LM, Weinreb RN. Reproducibility of RTVue Retinal Nerve Fiber Layer Thickness and Optic Disc Measurements and Agreement with Stratus Optical Coherence Tomography Measurements. Am J Ophthalmol. 2009;147:1067-1074.
22. Vizzeri G, Bowd C, Medeiros FA, Weinreb RN, Zangwill LM. Effect of improper scan alignment on retinal nerve fiber layer thickness measurements using stratus optical coherence tomograph. J Glaucoma. 2008;17:341-349.
23. Hong EH, Ryu SJ, Kang MH, Seong M, Cho H, Yeom JH, Shin YU. Comparison of repeatability of swept-source and spectral-domain optical coherence tomography for measuring inner retinal thickness in retinal disease. PLoS One. 2019;14:e0210729.
24. Koh KM, Jin S, Hwang YH. Cirrus high-definition optical coherence tomography versus spectral optical coherence tomography/scanning laser ophthalmoscopy in the diagnosis of glaucoma. Curr Eye Res. 2014;39:62-68.
25. Mwanza JC, Kim HY, Budenz DL, Warren JL, Margolis M, Lawrence SD, Jani PD, Thompson GS, Lee RK. Residual and dynamic range of retinal nerve fiber layer thickness in glaucoma: Comparison of three OCT platforms. Invest Ophthalmol Vis Sci. 2015;56:6344-6351.
26. Leung CK, Cheung CY, Weinreb RN, Qiu Q, Liu S, Li H, Xu G, Fan N, Huang L, Pang CP, Lam DS. Retinal Nerve Fiber Layer Imaging with Spectral-Domain Optical Coherence Tomography. A Variability and Diagnostic Performance Study. Ophthalmology. 2009;116:1257-1263.
27. Garas A, Vargha P, Holló G. Reproducibility of Retinal Nerve Fiber Layer and Macular Thickness Measurement with the RTVue-100 Optical Coherence Tomograph. Ophthalmology. 2010;117:738-746.
28. Faghihi H, Hajizadeh F, Hashemi H, Khabazkhoob M. Agreement of two different spectral domain optical coherence tomography instruments for retinal nerve fiber layer measurements. J Ophthalmic Vis Res. 2014;9:31-37.
29. Seibold LK, Mandava N, Kahook MY. Comparison of retinal nerve fiber layer thickness in normal eyes using time-domain and spectral-domain optical coherence tomography. Am J Ophthalmol. 2010;150:807-814.
30. Ozkok A, Akkan JC, Tamcelik N, Erdogan M, Comlekoglu DU, Yildirim R. Comparison of retinal nerve fiber layer and macular thickness measurements

with Stratus OCT and OPKO/ OTI OCT devices in healthy subjects. Int J Ophthalmol. 2015;8:98-103.

31. She X, Guo J, Liu X, Zhu H, Li T, Zhou M, Wang F, Sun X. Reliability of vessel density measurements in the peripapillary retina and correlation with retinal nerve fiber layer thickness in healthy subjects using optical coherence tomography angiography. Ophthalmologica. 2018;240:183-190.
32. Holló G. Comparison of Peripapillary OCT Angiography Vessel Density and Retinal Nerve Fiber Layer Thickness Measurements for Their Ability to Detect Progression in Glaucoma. J Glaucoma. 2018;27:302-305.
33. Holló G. Influence of Removing the Large Retinal Vessels-related Effect on Peripapillary Vessel Density Progression Analysis in Glaucoma. J Glaucoma. 2018;27:137-139.

DOI: 10.4274/tjo.galenos.2020.57702
Turk J Ophthalmol 2020;50:271-274

Original Article

Effect of Body Position on Intraocular Pressure Measured by Rebound Tonometer in Healthy Children

Dilek Uzlu*, Nurettin Akyol*, Adem Türk*, Nurcan Gürsoy*, Ahmet Mehmet Somuncu*, Yavuz Oruç**

*Karadeniz Technical University Faculty of Medicine, Department of Ophthalmology, Trabzon, Turkey
**University of Health Sciences Turkey, Fethi Sekin City Hospital, Clinic of Ophthalmology, Elazığ, Turkey

Abstract

Objectives: To evaluate the effect of body position on intraocular pressure (IOP) measurement in the pediatric age group.

Materials and Methods: Children whose general condition was healthy and ophthalmic examination was within normal limits were included. Forty-nine eyes of 49 pediatric patients were included in the study. IOP was measured with an ICARE rebound tonometer (ICARE PRO; ICARE, Helsinki, Finland) while patients were in standing, sitting, and supine positions. Differences between the consecutive measurements were compared statistically.

Results: Twenty-two of the 49 patients were female, 27 were male. The mean age was 9.61±2.66 (5-15) years. Mean IOP values in the standing, sitting, and supine positions were 18.81±2.97 (11.6-26.2) mmHg, 18.88±3.44, (12-28.2) mmHg, and 19.01±2.8 (13.5-25.9) mmHg, respectively. There were no statistically significant differences in pairwise comparisons of the measurements taken in the different positions (p=0.846, p=0.751, p=0.606). There was a statistically significant correlation between corneal thickness and intraocular pressure values in all measurements (p=0.001, r=0.516).

Conclusion: IOP values measured with the ICARE rebound tonometer in healthy children are not affected by body position.

Keywords: Child, intraocular pressure, body position, ocular tonometry

Introduction

As in adult patients, the accurate measurement of intraocular pressure (IOP) plays an important role in the diagnosis, treatment, and follow-up of pediatric glaucoma. IOP is still the only modifiable risk factor for preventing glaucoma progression.[1,2] Evaluation of IOP in pediatric patients may vary based on the patient's age and compliance.

The rebound tonometer (RT) is a portable tonometer that does not require topical anesthesia. In previous studies it was reported that RT is easy to use and provides reliable results in the pediatric age group.[3,4] RT measurements strongly correlate with those obtained with a Goldmann applanation tonometer (GAT).[3,4,5] Because evaluating changes such as visual field and retinal nerve fiber losses is difficult is in the follow-up of glaucoma in pediatric patients, it is important for IOP measurements to be accurate and reliable. During examination in outpatient clinics, IOP measurements are often obtained from infants while recumbent and from children while standing or sitting. In the literature it is reported that body position affects IOP and that IOP measurements made in supine position are higher in adult patients. In previous studies, changes in IOP due to body position were found to differ by 0.2-5.9 mmHg in measurements with different tonometers.[6,7,8,9,10] There is

Address for Correspondence: Dilek Uzlu, M.D., Karadeniz Technical University Faculty of Medicine, Department of Ophthalmology, Trabzon, Turkey
Phone:+90 554 793 56 40 E-mail: dilenkh@hotmail.com **ORCID-ID:** orcid.org/0000-0002-7882-9076
Received: 03.02.2020 **Accepted:** 07.04.2020

Cite this article as: Uzlu D, Akyol N, Türk A, Gürsoy N, Somuncu AM, Oruç Y. Effect of Body Position on Intraocular Pressure Measured by Rebound Tonometer in Healthy Children. Turk J Ophthalmol. 2020;50:271-274

little information in the literature about how IOP changes with body position in children. Determining IOP changes associated with body position is important in terms of standardizing IOP measurements in the follow-up of pediatric patients.

In this study, we aimed to evaluate the relationship between IOP values measured with an RT in different body positions in healthy children.

Materials and Methods

The study included 49 eyes of 49 healthy children under the age of 15 years who presented to the ophthalmology outpatient clinic for routine eye screening between September 2019 and December 2019. Children with no ocular disease other than refractive errors were included in the study. Exclusion criteria were high myopia or hypermetropia (>6.00 D), corneal astigmatism >2.5 D, any known ocular disease (glaucoma, ocular hypertension, uveitis, corneal pathology), history of ocular surgery, contact lens use, use of any systemic or ocular medication that might affect IOP, and non-compliance with measurements. The study was carried out in accordance with the principles of the Declaration of Helsinki and ethics committee approval was obtained. Before the study, written informed consent was obtained from the parents of the participating children. All of the children underwent a full ophthalmologic examination in which best corrected visual acuity levels and slit-lamp anterior and posterior segment examination findings were recorded in detail. Corneal thickness measurements were performed using an optical biometry device (NIDEK, AL-SCAN, Japan).

IOP measurements were performed by the same experienced researcher using an RT (ICARE PRO; ICARE, Helsinki, Finland) in the morning between 9:00 and 12:00. When the children arrived in the outpatient clinic for examination, their IOP was first measured with the ICARE RT after they remained standing for 5 minutes. They were then instructed to sit for 5 minutes, after which the second IOP measurements were obtained. Finally, after 5 minutes lying in supine position with no pillow, the third IOP measurement was performed. Measurements were made with the ICARE RT at an appropriate distance from the central cornea while the children's eyes were open and looking straight ahead, without use of a speculum or manual intervention to open the eyelids. Children who did not open their eyelids voluntarily, squinted their eyes, tried to open their eyelids with their hands, cried during measurement, did not comply with any of the measurement positions, or did not complete all of the measurements were not included in the study. For each body position, at least 6 consecutive measurements were made and the average IOP value was recorded. The ICARE tonometer displays results in green when the variation between measurements is within normal range, yellow when at the upper limit, and red when high. Because green results are reliable, only measurements displayed in green were used for statistical analysis.

Statistical Analysis

Numerical data were expressed as mean ± standard deviation (SD). Statistical analysis was performed using SPSS software (SPSS, version 13.0.1, Chicago, IL, USA; license: 9069728). Comparisons between the 3 consecutive measurements were made using repeated measures analysis of variance (ANOVA). Kolmogorov-Smirnov test was used to determine whether the data were normally distributed. $P<0.05$ was accepted as the limit of significance. The relationship between central corneal thickness (CCT) and mean IOP measurements was evaluated using Pearson's correlation test.

Results

A total of 49 healthy children, 22 girls (44.9%) and 27 boys (55.1%), were included in the study. The mean age of the study group was 9.61±2.66 (5-15) years. Their mean Snellen best corrected visual acuity level was 0.97±0.08 (0.7-1). Mean IOP values in the right eye were 18.81±2.97 (11.6-26.2) mmHg in standing position, 18.88±3.44 (12.0-28.2) mmHg in sitting position, and 19.01±2.80 (13.5-25.9) mmHg in supine position. There was a difference of -0.067±0.34 mmHg in IOP measurements between standing and sitting position, -0.129±0.4 mmHg between sitting and supine positions, and -0.196±0.37 mmHg between standing and supine positions. The comparison of IOP values measured in different body positions can be seen in Table 1. The mean CCT value of the eyes in which IOP was measured was 552.93±29.04 (499-606) µm.

There was a statistically significant positive correlation between the mean IOP and CCT values obtained in the 3 different positions ($p=0.001$, $r=0.516$).

Discussion

IOP remains the only modifiable risk factor in the prevention of glaucoma progression. Therefore, it is extremely important to measure IOP accurately and reliably. Although postural changes in IOP are common, the mechanisms underlying these IOP fluctuations are not fully understood. Looking at the literature, most previous studies were conducted in adults and compared IOP measurements obtained in sitting and recumbent positions.[7,8,9,10] In most studies, higher IOP was reported in the supine position, but in other studies IOP did not change or decreased in the supine position.[7,8,9,10,11,12,13] IOP elevation in the recumbent position has been attributed to an increase in

Table 1. Comparison of intraocular pressure values measured in different body positions

	Intraocular pressure (mmHg)	p
Standing	18.81±2.97	Standing vs sitting p=0.846
Sitting	18.88±3.44	Sitting vs supine p=0.751
Supine	19.01±2.8	Standing vs supine p=0.606

episcleral venous pressure.[14,15,16] In glaucoma patients, postural IOP changes are greater in magnitude.[17,18,19,20]

Because children are not tall enough to sit at the instruments in outpatient clinics, measurements are frequently performed in the supine or standing position. The ICARE RT is a recently introduced tonometer that provides rapid, repeatable, and highly reliable IOP measurements. Although contact with the eye causes children anxiety when using the ICARE RT, its ability to obtain measurements faster than the blink reflex allows it to be used comfortably in the pediatric age group. There are few studies in the literature that examine postural changes in IOP measurements in children. Dosunmu et al.[21] compared IOP measurements in sitting and supine position with the ICARE RT and Tonopen in pediatric patients with and without glaucoma and reported an increase in supine IOP of +0.9±2.3 mmHg with ICARE RT and +0.7±1.8 mmHg with the Tonopen. In our study, there was a difference of 0.13 mmHg between sitting and supine position, but it was not statistically significant. The smaller IOP elevation in our study compared to that observed by Dosunmu et al.[21] may be explained by the fact that our study group consisted of only healthy pediatric patients.

In our study, no statistically significant difference was observed in IOP measurements performed in healthy pediatric patients in standing, sitting, and supine positions. The postural increase in IOP observed in the children in our study was less than that of adults. This smaller increase in the pediatric age group may be related to children's smaller body mass and smaller episcleral venous pressure change. Sultan and Blondeau[14] evaluated seated and recumbent episcleral venous pressures in young adults and elderly patients and reported that the elderly group had higher episcleral venous pressure compared to the younger age group.

Changes in CCT with different body positions have been demonstrated in previous studies. Maslin et al.[22] showed that CCT decreased in the supine position in open-angle glaucoma patients and healthy subjects, with similar changes in both groups. Fogagnolo et al.[23,24] reported that IOP and CCT exhibited diurnal variation and that IOP fluctuations in different body positions were independent of fluctuations in CCT. Because CCT measurements in different body positions were not evaluated in our study, comparisons could not be made.

One of the weaknesses of our study was the inability to measure with a GAT, which is the gold standard for IOP measurement. Because IOP measurements cannot be obtained from children in the recumbent and standing positions with the GAT, the ICARE RT was used as the measurement method. The small number of patients is another weakness of our study. In addition, we did not include the children's blood pressure measurements or body mass index values in the study. In order to standardize the measurements made in our study, IOP measurements were performed first in standing position, then sitting, and finally in supine position. We cannot rule out the possibility that changing this order would yield different results. Our study included healthy pediatric cases; further studies are needed to examine IOP associated with different body positions in pediatric glaucoma patients, who may show larger postural IOP changes.

Conclusion

In conclusion, in this study it was determined that IOP measurements performed with the ICARE RT in healthy children in different body positions did not vary significantly. In the pediatric age group, the ICARE RT can be used to obtain IOP measurements either in supine position under general anesthesia or in supine or standing position in outpatient clinic examinations. Further research is needed to understand the effect of postural changes on IOP in pediatric glaucoma patients.

Ethics

Ethics Committee Approval: Karadeniz Technical University Faculty of Medicine Presidentship of Ethics Committee approved this study. The approval number is 24237859-146.

Informed Consent: Before the study, informed consent was taken from the parents of the children who participate.

Peer-review: Externally and internally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: D.U., N.G., A.M.S., Concept: D.U., Y.O., N.G., Design: D.U., N.A., A.T., Data Collection or Processing: N.G., A.M.S., Analysis or Interpretation: D.U., A.T., N.A., Literature Search: D.U., Y.O., Writing: D.U., A.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. Heijl A, Leske MC, Bengtsson B, Hyman L, Bengtsson B, Hussein M; Early Manifest Glaucoma Trial Group. Reduction of intraocular pressure and glaucoma progression: results from the Early Manifest Glaucoma Trial. Arch Ophthalmol. 2002;120:1268-1279.
2. Leske MC, Heijl A, Hussein M, Bengtsson B, Hyman L, Komaroff E; Early Manifest Glaucoma Trial Group. Factors for glaucoma progression and the effect of treatment: the early manifest glaucoma trial. Arch Ophthalmol. 2003;121:48-56.
3. Pakrou N, Gray T, Mills R, Landers J, Craig J. Clinical comparison of the ICare tonometer and Goldmann applanation tonometry. J Glaucoma. 2008;17:43-47.
4. Brusini P, Salvetat ML, Zeppieri M, Tosoni C, Parisi L. Comparison of ICare tonometer with Goldmann applanation tonometer in glaucoma patients. J Glaucoma. 2006;15:213-217.
5. Iliev ME, Goldblum D, Katsoulis K, Amstutz C, Frueh B. Comparison of rebound tonometry with Goldmann applanation tonometry and correlation with central corneal thickness. Br J Ophthalmol. 2006;90:833-835.
6. Malihi M, Sit AJ. Effect of Head and Body Position on Intraocular Pressure. Ophthalmology. 2012;119:987-991.
7. Barkana Y. Postural change in intraocular pressure: comparison of measurement with a Goldmann tonometer, Tonopen XL, Pneumatonometer, and HA-2. J Glaucoma. 2014;23:23-28.
8. Krieglstein G, Langham ME. Influence of body position on the intraocular pressure of normal and glaucomatous eyes. Ophthalmologica. 1975;171:132-145.

9. Lee JY, Yoo C, Jung JH, Hwang YH, Kim YY. The Effect of Lateral Decubitus Position on Intraocular Pressure in Healthy Young Subjects. Acta Ophthalmol. 2012;90:68-72.
10. Mansouri K, Weinreb RN, Liu JHK. Effects of aging on 24-hour intraocular pressure measurements in sitting and supine body positions. Invest Ophthalmol Vis Sci. 2012;53:112-116.
11. Barkana Y, Gutfreund S. Measurement of the difference in intraocular pressure between the sitting and lying body positions in healthy subjects: direct comparison of the Icare Pro with the Goldmann applanation tonometer, Pneumatonometer and Tonopen XL. Clin Exp Ophthalmol. 2014;42:608-614.
12. De Bernardo M, Borrelli M, Cembalo G, Rosa N. Intraocular Pressure Measurements in Standing Position with a Rebound Tonometer. Medicina (Kaunas). 2019;55:701.
13. Mayalı H, Tekin B, Kayıkçıoğlu ÖR, Kurt E, İlker SS. Evaluation of the Effect of Body Position on Intraocular Pressure Measured with Rebound Tonometer. Turk J Ophthalmol. 2019;28:49:6-9.
14. Sultan M, Blondeau P. Episcleral venous pressure in younger and older subjects in the sitting and supine positions. J Glaucoma. 2003;12:370-373.
15. Arora N, Mclaren JW, Hodge DO, Sit AJ. Effect of Body Position on Episcleral Venous Presssure in Healthy Subjects. Invest Ophthalmol Vis Sci. 2017;58:5151-5156.
16. Blondeau P, Tetrault JP, Papamarkakis C. Diurnal variation of episcleral venous pressure in healthy patients: a pilot study. J Glaucoma. 2001;10:18-24.
17. Kothe AC. The effect of posture on intraocular pressure and pulsatile ocular blood flow in normal and glaucomatous eyes. Surv Ophthalmol. 1994;38(Suppl):191-197.
18. Moster SJ, Fakhraie G, Venketesh R, Moster ML, Zhao Y, Moster MR. Relationship of central corneal thickness to postural IOP changes in patients with and without glaucoma in southern India. Int Ophthalmol. 2012;32:307-311.
19. Prata TS, De Moraes CGV, Kanadani FN, Ritch R, Paranhos A Jr. Posture-induced intraocular pressure changes: considerations regarding body position in glaucoma patients. Surv Ophthalmol. 2010;55:445-453.
20. Kiuchi T, Motoyama Y, Oshika T. Postural response of intraocular pressure and visual field damage in patients with untreated normal-tension glaucoma. J Glaucoma. 2010;19:191-193.
21. Dosunmu EO, Marcuss I, Tung I, Thiamthat W, Freedman SF. Intraocular Pressure In Children: The Effect of Body Position as Assessed by Icare and Tono-Pen Tonometers. Am J Ophthalmol. 2014;158:1348-1352.
22. Maslin J, Teng CC, Chadha N, Liu J. Effect Of Supine Body Position on Central Corneal Thickness. Clin Exp Ophthalmol. 2016;44:678-683.
23. Fogagnolo P, Rossett L, Mazzolani F, Orzalesi N. Circadian variations in central corneal thıckness and intraocular pressure in patients with glaucoma. Br J Ophthalmol. 2006;90:24-28.
24. Fogagnolo P, Capizzi F, Orzalesi N, Figus M, Ferreras A, Rossetti L. Can mean central corneal thickness and ıts 24-hour fluctuation influence fluctuation of intraocular presure? J Glaucoma. 2010;19:418-423.

DOI: 10.4274/tjo.galenos.2020.38488
Turk J Ophthalmol 2020;50:275-282

Original Article

Subgroups and Features of Poor Responders to Anti-Vascular Endothelial Growth Factor Treatment in Eyes with Neovascular Age-Related Macular Degeneration

Mine Esen Barış, Jale Menteş, Filiz Afrashi, Serhad Nalçaçı, Cezmi Akkın

Ege University Faculty of Medicine, Department of Ophthalmology, İzmir, Turkey

Abstract

Objectives: This study aimed to determine the incidence of poor response to intravitreal (IV) anti-VEGF treatment in neovascular age-related macular degeneration (nvAMD) and to define subgroups of poor responders.

Materials and Methods: A total of 235 treatment-naive eyes of 202 patients completed this prospective study. Patients younger than 50 years of age and those with a contraindication for anti-VEGF therapy were excluded. All eyes were treated with IV ranibizumab. Poor response was defined as recurrence, persistence, or worsening despite treatment. Poor responders were classified into subgroups based on progression patterns.

Results: Of the 235 eyes, 78 (33.2%) showed poor response. Pigment epithelial detachment (PED) and occult choroidal neovascularization (CNV) were more common among poor responders ($p<0.001$) and 5 subgroups were identified.

Conclusion: Poor response to anti-VEGF treatment is not uncommon and occult CNV and PED are frequently seen in these eyes. Various subgroups can be defined based on clinical features.

Keywords: Anti-vascular endothelial growth factor, neovascular age-related macular degeneration, treatment response

Introduction

Intravitreal (IV) injection of anti-vascular endothelial growth factors (anti-VEGF) is accepted as a standard treatment method for neovascular age-related macular degeneration (nvAMD).

Of the many multicenteric clinical trials, MARINA (Minimally Classic/Occult Trial of Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration) and ANCHOR (Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in AMD) were seminal trials of monthly ranibizumab (Lucentis; Genentech, San Francisco, CA, USA) therapy in eyes with minimally classic and occult nvAMD and predominantly classic nvAMD, respectively. While the 2-year results of these trials demonstrated improved or preserved visual acuity in approximately 90-95% of treated eyes compared to control eyes, vision loss of at least 15 letters (3 lines) despite continued monthly anti-VEGF therapy was also reported in 5-10% of eyes.[1,2,3,4,5] It has also been noted that eyes showing inadequate or no treatment response and persistent disease activity are those with better baseline visual acuity compared to the group with the greatest letter gains.[6,7]

Identifying eyes with good or poor anatomic response to anti-VEGF drugs, distinguishing different subgroups if present, and knowing the baseline lesion characteristics of eyes with nvAMD are believed to be important for predicting treatment outcomes and determining the causes of resistance.

Address for Correspondence: Mine Esen Barış, M.D., Ege University Faculty of Medicine, Department of Ophthalmology, İzmir, Turkey
Phone:+90 506 751 62 84 E-mail: mine.baris@yahoo.com **ORCID-ID:** orcid.org/0000-0003-1341-6737
Received: 23.12.2019 **Accepted:** 23.03.2020

Cite this article as: Barış ME, Menteş J, Afrashi F, Nalçacı S, Akkın C. Subgroups and Features of Poor Responders to Anti-Vascular Endothelial Growth Factor Treatment in Eyes with Neovascular Age-Related Macular Degeneration. Turk J Ophthalmol. 2020;50:275-282

Therefore, the aim of this prospective clinical trial was to characterize responses to anti-VEGF therapy with ranibizumab in eyes with active nvAMD, to analyze subgroups within the good and poor response groups, and to evaluate their baseline clinical features.

Materials and Methods

This prospective cohort study included 297 eyes of 245 consecutive patients diagnosed with active nvAMD and treated with IV anti-VEGF therapy in the Retina Unit of the Ege University Medical Faculty Department of Ophthalmology.

Patients less than 50 years of age, those who had previously been treated for nvAMD, those with a contraindication for anti-VEGF therapy or developed complications that might alter the Optical Coherence Tomography (OCT) parameters during treatment, and those who did not follow the treatment protocol were excluded from the study. As a result, 235 eyes of 202 patients completed the study and were included in the evaluation.

An informed voluntary consent form was obtained from each patient, ethical board approval was obtained from the Ege University Clinical Research Ethics Committee (decision no. 12-2/47, 2013) and the Ministry of Health Turkish Pharmaceuticals and Medical Devices Agency (transaction no. 1135321/06.03.2013). The study was conducted in adherence to the principles of the Declaration of Helsinki.

All patients underwent a complete ophthalmologic examination, including best corrected visual acuity (BCVA) determined by Snellen chart, intraocular pressure (IOP) measurement, and biomicroscopic examination of the anterior and posterior segments. Prior to treatment, each patient underwent a spectral domain optic coherence tomography (SD-OCT) scan with a Topcon SD-OCT (Topcon Medical Systems, Paramus, NJ, USA) and Heidelberg Spectralis HRA + OCT (Heidelberg Engineering, Heidelberg, Germany) device, in addition to fluorescein angiography (FA) with a Topcon TRC.50IX device (Topcon Medical Systems, Paramus, USA). Neovascularization (nv) type was assessed based on the presence, type and location of increased central retinal thickness (CRT), subretinal fluid (SRF), intraretinal cysts (IRC), and pigment epithelial detachment (PED) on SD-OCT. CRT evaluations were made based on irregularities in retinal thickness in the central 6x6 mm^2 area at the posterior pole. The types of nv based on the staining properties of the lesions, as well as dye leakage in late phases, were recorded with FA. Well-demarcated areas of intense hyperfluorescence appearing early and showing progressive leakage were accepted as classical choroidal neovascularization (CNV), whereas fibrovascular PEDs and late leakage of undetermined source were evaluated as occult CNV. In case of mixed types, the lesion was considered predominantly classical if more than 50% consisted of classical component and minimally classical if it comprised 1-50% classical component. Types of nv based on location on SD-OCT images were also noted as type 1 (sub-retinal pigment epithelium [RPE]), type 2 (subretinal), and type 3 (intraretinal).

Eyes exhibiting fresh hemorrhage in clinical examination, findings of SRF, IRC, or sub-RPE fluid on SD-OCT, and leakage on FA were classified as having active nvAMD. These eyes were treated with IV ranibizumab (0.5 mg/0.05 mL ranibizumab, Lucentis; Genentech Inc., San Francisco, CA, USA) under fully sterile operating room conditions.

Follow-up examinations were performed 4-6 weeks after treatment. BCVA and SD-OCT findings were reevaluated and IV ranibizumab injections were repeated for eyes with signs of persistent activity (fresh hemorrhage, SRF, IRC, or sub-RPE fluid).

Eyes that showed full regression or resorption in follow-up examinations before or after completing the 6 injections were classified as "good responders" (Figure 1), while eyes with recurrence, persistence, or progressive worsening after 6 injections were classified as "poor responders". Visual acuity was not considered as a parameter in our definitions of response or poor response. The differences in baseline features between eyes in the two groups were statistically analyzed. Treatment was stopped in eyes that showed total regression of activation signs before completing 6 injections and these eyes were considered good responders. These patients were seen in regular follow-up visits and injections started again if they showed any sign of activation. Patients who still needed anti-VEGF treatment after 6 injections continued to receive treatment as long as they needed.

Poor responders were divided into 5 subgroups by analyzing anatomical findings and response characteristics:

1. True nonresponders: Eyes with no change in signs of activity (SRF, IRF, sub-RPE fluid, fresh hemorrhage) during treatment;

2. Partial nonresponders: Eyes exhibiting partial improvement (e.g., minimal regression in SRF and/or IRF) in signs of activity during treatment (Figure 2);

3. Anti-VEGF dependents: Eyes that showed complete regression of signs of activity with treatment but were unable

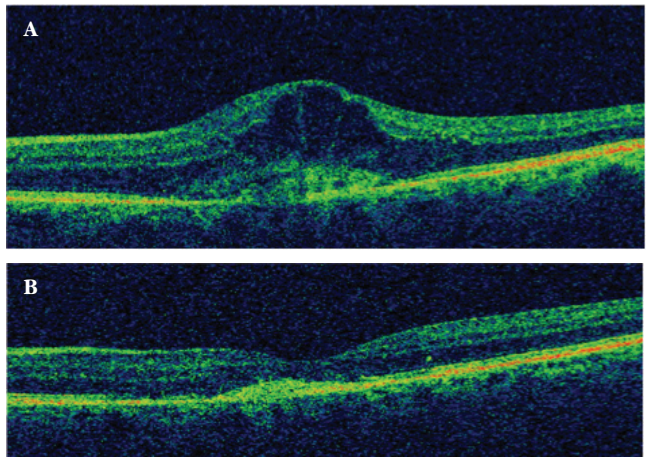


Figure 1. Spectral domain optical coherence tomography (SD-OCT) images of an eye that showed good response to intravitreal anti-VEGF injections. A) Initial image shows intraretinal cysts and increased central retinal thickness. B) SD-OCT image after 6 consecutive injections

to tolerate intervals longer than 4-6 weeks between injections without showing recurrence (increase in SRF/IRF, sub-RPE fluid or PED size);

4. Worsening: Eyes with progression of anatomic findings, with exudate or hemorrhage, despite treatment (Figure 3);

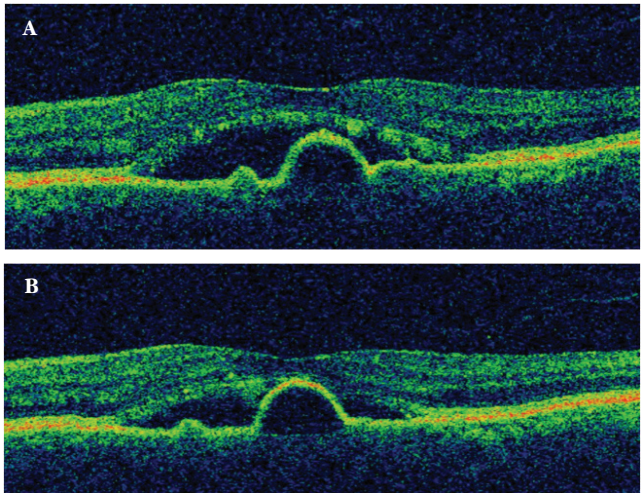


Figure 2. An eye with partial nonresponse to treatment A) before treatment and B) after 6 injections. There was only a minimal change in spectral domain optical coherence tomography findings despite treatment

5. Nonresponse over time: Eyes that initially responded well to treatment but became unresponsive over time due to reduction in drug effectiveness with continued treatment (Figure 4).

Statistical Analysis

SPSS 15.0 package software was used for statistical analyses. Independent samples t-test, chi-square test, and Fisher's Exact test were used to evaluate the findings, with p values <0.05 were accepted as statistically significant.

Results

Of the 202 patients, 102 (50.5%) were male and 100 (49.5%) were female; 33 (16.3%) had bilateral nvAMD, and the mean age was 74.03±7.8 (56-89) years.

Of the 235 eyes, treatment response to anti-VEGF therapy with IV ranibizumab was evaluated as good in 157 eyes (66.8%) and poor in 78 eyes (33.2%). Of the 33 bilateral patients, 17 showed good response and 7 showed poor response to treatment, while 9 patients had 1 eye in each group.

The demographic characteristics, lens status, pre- and post-treatment BCVA, number of injections, and follow-up periods pertaining to the eyes with good and poor treatment responses are shown in Table 1. There were no statistically significant differences between the groups in terms of age and gender distribution (p=0.22 and p=0.48, respectively; t-test and chi-square test). The groups were also statistically comparable in

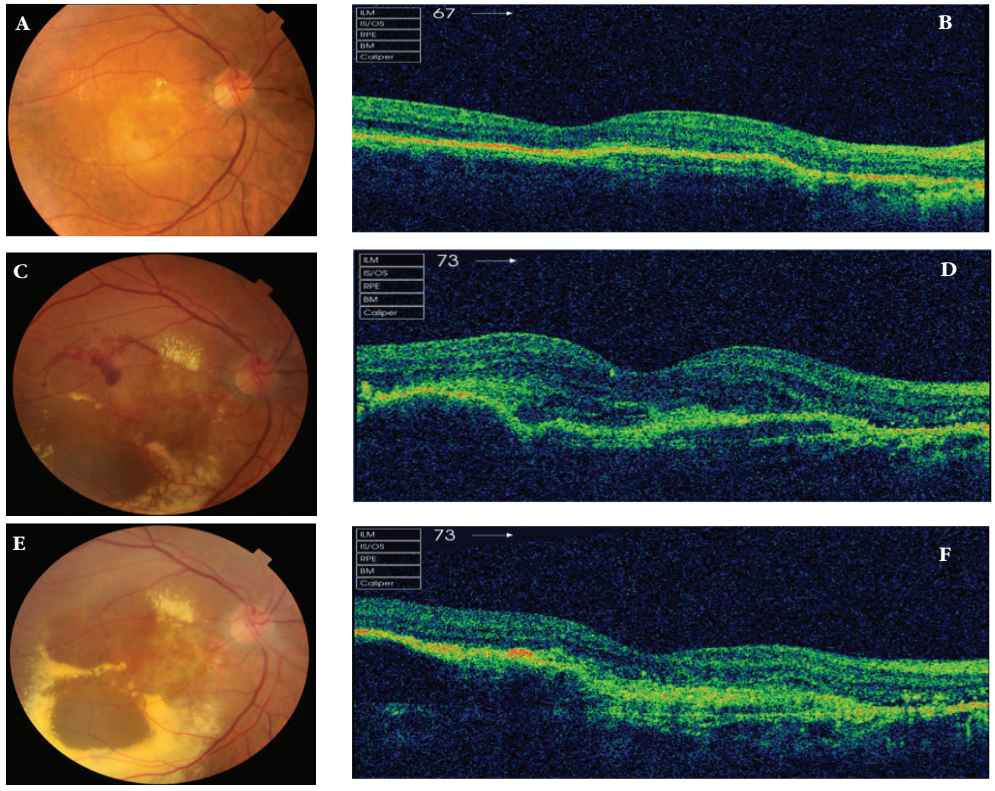


Figure 3. An example from the "worsening" subgroup. A) Fundus photograph and B) spectral domain optical coherence tomography image at the time of initial examination. C and D) Images obtained after 6 injections show increased central retinal thickness, subretinal fluid, increased exudation, and a fresh hemorrhage. E and F) After 9 injections, there is a marked increase in exudation

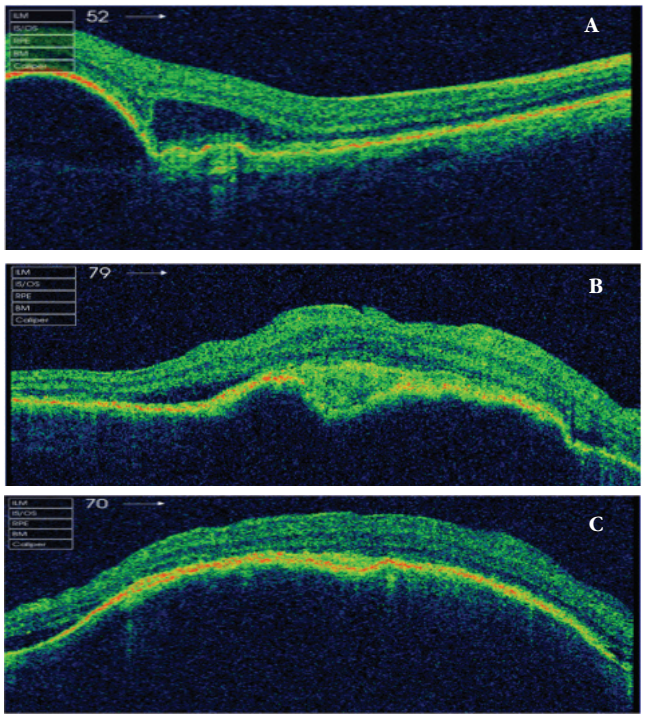


Figure 4. Spectral domain optical coherence tomography images of an eye in the "non-response over time" subgroup. A) Before treatment. B), Pigment epithelial detachment (PED) height and subretinal fluid amount were reduced after 6 injections. C) Images obtained after 9 injections show the PED returned to pretreatment height despite ongoing treatment

terms of lens status (pseudophakic or phakic) (p=0.8; Fisher's Exact test). Comparison of BCVA between the groups revealed no statistically significant differences either pre- or posttreatment (p=0.38 and p=0.06 respectively; t-test and Fisher's Exact test). Eyes with poor treatment response had significantly higher mean number of injections and longer follow-up period compared to eyes with good response (p<0.001 and p<0.001; t-test).

Twenty-one eyes (26.9%) were categorized as true nonresponders, 29 eyes (37.2%) as partial nonresponders, 13 eyes (16.7%) as anti-VEGF dependents, 11 eyes (14.1%) as worsening, and 4 eyes (5.1%) as showing nonresponse over time.

The baseline SD-OCT and FA features of the eyes in both groups are shown in Table 2. The number of eyes with increased CRT and IRC in the good responders group was significantly higher compared to the poor responders group, while there was no significant difference in terms of SRF (p=0.02, p=0.004, p=0.4; Fisher's Exact test). Absence of PED was significantly more common among good responder eyes compared to poor responders (p<0.001; chi-square test). Poor responder eyes had an initial PED rate of 88.5% and a significantly higher prevalence of fibrovascular PED (77%) compared to good responders (39.5%) (p<0.001; chi-square test). Comparison of the nv types based on SD-OCT location between the two groups showed that type 2 nv (subretinal) was significantly more common in good responders, while type 1 nv (sub-RPE) was significantly more common in poor responders (p=0.03 and p=0.04, respectively; chi-square test).

In terms of baseline lesion characteristics on FA, predominantly classic nv (53.5%) was significantly more

Table 1. Demographic characteristics, lens status, best corrected visual acuity, number of injections, and follow-up periods of good and poor responder eyes

Characteristic	Good responders number (%)	Poor responders number (%)	p value
All eyes	157 (66.8)	78 (33.2)	
Bilateral eyes*	26 (61.9)	16 (38.0)	0.37**
Gender Female Male	 71 (50.7) 69 (49.3)	 34 (47.9) 37 (52.1)	0.48**
Age, years (mean ± SD) (min-max)	74.5±7.6 (57-87)	73.1±8.0 (56-89)	0.22†
Lens status Phakic Pseudophakic	 108 (68.8) 49 (31.2)	 54 (69.2) 24 (30.8)	0.8†
Pretreatment BCVA, Mean ± SD (Snellen)	0.25±0.20 (20/80±20/100)	0.28±0.20 (20/70±20/100)	0.34†
Posttreatment BCVA, Mean ± SD (Snellen)	0.20±0.20 (20/100±20/100)	0.32±0.25 (20/63±20/80)	0.06††
Number of injections Mean ± SD (min-max)	4.40±0.12 (2-15)	6.42±1.14 (6-12)	<0.001†
Follow-up time, Months mean (min-max)	11.3 (6-24)	21.7 (15-24)	

SD: Standard deviation, min: minimum, max: maximum, BCVA: Best corrected visual acuity
*Of the 33 bilateral patients, 9 patients had 1 eye in both the good and poor treatment response groups,**Chi-square test, †t-test, ††Fisher's Exact test

Table 2. Baseline optical coherence tomography and fluorescein angiography characteristics in the good and poor responder groups

	Eyes with good treatment response number (%)	Eyes with poor treatment response number (%)	P value
Central retinal thickness			
Increased	141 (89.8)	61 (78.2)	
Normal	16 (10.2)	17 (21.8)	0.02*
Subretinal fluid			
Yes	122 (77.7)	65 (83.3)	0.02*
No	35 (22.3)	13 (16.7)	
Intraretinal fluid			
Yes	89 (56.7)	28 (35.9)	
No	68 (43.3)	50 (64.1)	0,04
PED			
Yes	74 (47.1)	69 (88.5)	
Serous	12 (7.6)	8 (10.2)	
Fibrovascular	55 (35.0)	42 (53.9)	<0.0001**
Hemorrhagic	0	(1.3)	
Serous + fibrovascular	2 (1.3)	18 (23.1)	
Fibrovascular + hemorrhagic	5 (3.2)	0	
No	83 (52.9)	9 (11.5)	<0.0001**
OCT nv type			
Type 1	99 (63.0)	60 (76.9)	0.04**
Type 2	46 (29.3)	8 (10.3)	0.03**
Type 3	12 (7.7)	10 (12.8)	
FA nv type			
Pure classic	15 (9.5)	5 (6.5)	
Predominantly classic	84 (53.5)	2 (2.5)	<0.001**
Minimally classic	6 (3.8)	3 (3.8)	
Occult	47 (30.0)	55 (70.5)	<0.001**
Undeterminable	3 (1.9)	5 (6.5)	
No nv findings	2 (1.3)	8 (10.2)	

PED: Pigment epithelium detachment, OCT: Optical coherence tomography, nv: Neovascularization, FA: Fluorescein angiography, *Fisher's Exact test, **Chi-square test

common in the good responders group, while occult nv (70.5%) was significantly more common among poor responders (p<0.001 for both; chi-square test).

The baseline SD-OCT and FA features of the poor responder subgroups are shown in Table 3. There was no statistically significant difference between the subgroups in terms of increased CRT or presence of SRF, IRC, or presence and type of PED (p=0.82, p=0.78, p=0.62, and p=0.94, respectively; chi-square test). There was also no difference between the subgroups in terms of the nv types identified via SD-OCT and FA (p=0.33; chi-square test).

Discussion

In this prospective clinical trial, 235 eyes with nvAMD received consecutive doses of IV ranibizumab therapy at intervals of 4-6 weeks, and treatment response was defined as good in 157 eyes (66.8%) and poor in 78 eyes (33.2%). Criteria for poor response in this trial included persistent, recurrent, or progressive signs of nvAMD activity in clinical examination or SD-OCT performed 1 month after 6 doses of IV ranibizumab.

Although IV injection of anti-VEGF agents is currently accepted as a standard treatment method for active nvAMD, the rate of unresponsiveness to treatment reported in different trials varies widely (7.5-68.1%).[8,9] The main reason for these differences is the use of different criteria when assessing treatment response. There is still no consensus among clinicians as to whether regression of signs of activity or improvement in visual acuity should be accepted as the primary criterion of treatment response, or after how many doses response should be evaluated.[10] Treatment response was defined according to changes in BCVA in the MARINA and ANCHOR trials, which were the first trials to demonstrate the efficacy of ranibizumab. In these trials, preserved or improved (15 letters or more) BCVA was reported for 90% of the patients who received monthly anti-VEGF therapy for 24 months, and losses of more than 15 letters were reported for the other 10% of patients. In clinical practice, however, there are few studies in which BCVA is accepted as the treatment response criterion.[9,11,12,13] Most clinicians evaluate response and decide to repeat treatment based on signs of activity detected on examination and SD-OCT (in other words, based

Table 3. Baseline optical coherence tomography and fluorescein angiography characteristics in subgroups of poor responders

	True non-responders number (%)	Partial responders number (%)	Anti-VEGF dependents number (%)	Worsening number (%)	Non-response over time number (%)	P value
Eyes	21 (26.9)	29 (37.2)	13 (16.7)	11 (14.1)	4 (5.1)	-
Central retinal thickness						
Increased	16 (76.2)	21 (72.4)	11 (84.6)	10 (90.9)	3 (75)	
Normal	5 (23.8)	8 (27.6)	2 (15.4)	1 (9.1)	1 (25)	0.82*
Subretinal fluid						
Yes	18 (85.7)	25 (86.2)	10 (76.9)	8 (72.8)	4 (100)	
No	3 (14.3)	4 (13.8)	3 (23.1)	3 (27.2)	0	0.78*
Intraretinal fluid						
Yes	7 (33.3)	13 (44.8)	4 (30.8)	4 (36.4)	0	
No	14 (66.7)	16 (55.2)	9 (69.2)	7 (63.6)	4 (100)	0.62*
PED						
Yes	19 (90.5)	26 (89.7)	10 (76.9)	10 (90.9)	4 (100)	-
Serous	2 (9.5)	4 (13.8)	1 (7.7)	0	1 (25.0)	-
Fibrovascular	11 (52.4)	12 (41.4)	9 (69.2)	7 (63.6)	3 (75.0)	-
Hemorrhagic	0	1 (3.4)	0	0	0	-
Serous + fibrovascular	6 (28.6)	9 (31.1)	0	3 (27.3)	0	-
No	2 (9.5)	3 (10.3)	3 (23.1)	1 (9.1)	0	-
OCT nv type						
Type 1	16 (76.2)	23 (79.3)	11 (84.6)	6 (54.5)	4 (100)	-
Type 2	2 (9.5)	1 (3.5)	1 (7.7)	4 (36.4)	0	-
Type 3	3 (14.3)	5 (17.2)	1 (7.7)	1 (9.1)	0	-
FA NV type						
Pure classic	4 (19)	1 (3.5)	0	0	0	-
Predominantly classic	0	1 (3.5)	0	1 (9.1)	0	-
Minimally classic	1 (4.8)	0	1 (7.7)	1 (9.1)	0	-
Occult	16 (76.2)	19 (65.5)	8 (61.5)	9 (81.8)	3 (75.0)	-
Undeterminable	0	3 (10.3)	1 (7.7)	0	1 (25.0)	-
No nv findings	0	5 (17.2)	3 (23.1)	0	0	-

SD: Standard deviation, PED: Pigment epithelium detachment, OCT: Optical coherence tomography, nv: Neovascularization, FA: Fluorescein angiography
*Chi-square test

on anatomic findings rather than an increase in BCVA), with regression or complete resolution of these findings considered good treatment response.[8,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28]

In a retrospective study involving 218 eyes, Otsuji et al.[13] considered eyes with no increase in BCVA and/or no reduction in CRT despite 3 consecutive doses of IV ranibizumab therapy administered at 4-week intervals as unresponsive to treatment, reporting the rate of unresponsiveness as 10.1%. Shin et al.[8] retrospectively evaluated 267 nvAMD cases and determined that 7.5% were unresponsive to anti-VEGF therapy (ranibizumab and bevacizumab). In their study, persistent and/or increased intraretinal or subretinal exudate despite 3 consecutive IV injections was accepted as the criterion for unresponsiveness. Byun et al.[9] analyzed treatment response in 113 consecutive eyes with nvAMD that received IV bevacizumab injections for 1 year, describing eyes that showed less than 7-11 ETDRS letters improvement in BCVA as unresponsive (68.1%).

Slakter[14] suggested that BCVA may not increase and may even decrease despite complete regression of signs of activity and remission of disease in good responders to anti-VEGF therapy. He attributed this to changes that occur secondarily to nvAMD such as subretinal fibrosis and scar formation or RPE and photoreceptor atrophy, stating that for these reasons BCVA is not a reliable criterion for determining responsiveness or unresponsiveness to treatment. In the present study, we used the regression of signs of nvAMD activity to define response to ranibizumab therapy. There were no statistically significant differences in BCVA between good and poor responders in our study. As indicated by Slakter, we believe this is due to secondary changes that occurred in some eyes that showed good treatment response.

There is also no consensus regarding when to evaluate treatment response among clinical trials. Assessments were done after 3 or 6 consecutive injections in the vast majority of trials [8,9,13,26] while in some trials this number is reported as 9, 12, or more.[23] In the present trial, the eyes were re-evaluated 1 month after receiving the last of 6 consecutive ranibizumab injections. Eyes showing a poor response received a significantly higher mean number of injections and had a significantly longer mean follow-up period compared to eyes with good treatment response.

In our study, the prevalence of predominantly classic nv was higher among good responders, while occult nv was more common among poor responders, and this difference was found to be statistically significant. Previously published studies have differed on this point. Lux et al.[12] detected no difference in nv type between responsive and unresponsive eyes, but reported that the unresponsive group had significantly larger baseline nv area. Otsuji et al.[13] determined that occult nv was more prevalent than classic nv among poor responders, whereas response/nonresponse was not associated with baseline nv dimensions. Hörster et al.[29] reported that predominantly classic and minimally classic nv required more injections than occult nv. However, these data have not been supported by the results of other studies. Veritti et al.[30] stated that less satisfactory outcomes were achieved when treating eyes with occult nv associated with nvAMD compared to other types of nv.

In our study, increased CRT and presence of IRC were significantly more common among good responders compared to poor responders, while the groups showed no difference in terms of SRF presence. Shin et al.[8] divided non-responders into two groups those who had SRF only and those who had predominantly IRC and found that the eyes with SRF were less responsive to treatment compared to eyes with IRC. Guber et al.[31] also reported that eyes with IRC responded better to treatment than those with SRF or PED and showed a more pronounced reduction in CRT. Tannan et al.[32] reported that pretreatment SRF was associated with longer duration of anti-VEGF therapy.

In our study, there was a significant difference between good and poor responder eyes in terms of baseline PED presence (47.1% and 88.5%, respectively). In addition, the prevalence of fibrovascular PED was significantly higher in poor responders (77%) compared to good responders (39.5%). Inoue et al.[33] observed a greater BCVA improvement in eyes with baseline serous PED compared to eyes with fibrovascular PED. Punjabi et al.[34] categorized PEDs as empty, solid, or mixed based on their appearance on OCT, reporting the rate of complete or partial regression with treatment to be 3% for solid PEDs and 46% for empty PEDs.

Our evaluation of poor responders to anti-VEGF therapy with ranibizumab based on clinical response and SD-OCT findings revealed 5 distinct subgroups. The most common pattern was partial non-response (37.2%), which was characterized by partial improvement in signs of activity during treatment. Furthermore, some eyes responded well to treatment but required another injection every month and could not tolerate treatment intervals longer than 4-6 weeks. These eyes were referred to as "anti-VEGF dependent" (16.7%). Approximately 5% of the eyes showed good initial response but became unresponsive due to diminished effect of the drug over time, and these were classified in the "non-response over time" group. Publications on tachyphylaxis, defined as a reduction in the effectiveness of a drug on tissue after repeated administration, have reported that this phenomenon occurs after at least 5 consecutive anti-VEGF injections, with an incidence of 2%.[21] A search of the literature did not yield any studies on the development of tolerance to anti-VEGF drugs.

In his 2010 review, Slakter[14] stated that there are many patients who do not exhibit the desired response to ranibizumab therapy and whose exudative findings persist or progress; he referred to these patients as "anti-VEGF nonresponders" and described 5 subgroups within this group. The article does not provide data on the prevalence and baseline clinical features of the subgroups, but 3 of the described subgroups are similar to those in our study. To the best of our knowledge, ours is the first clinical study to determine subgroups of poor responders to anti-VEGF therapy and evaluate their prevalence.

Conclusion

The value of anti-VEGF drugs as effective and safe therapies for the treatment of nvAMD is undisputable. However, poor response or nonresponse to anti-VEGF drugs in some eyes is an important issue in clinical practice. In addition to determining the prevalence of these suboptimal responses in clinical studies, our results suggest that identifying baseline features of these eyes and conducting subgroup analysis will be beneficial in order to investigate the causes of unresponsiveness and to modify and improve treatment strategies in such cases.

Ethics

Ethics Committee Approval: An informed voluntary consent form was obtained from each patient, ethical board approval was obtained from the Ege University Clinical Research Ethics Committee (decision no. 12-2/47, 2013) and the Ministry of Health Turkish Pharmaceuticals and Medical Devices Agency (transaction no. 1135321/06.03.2013). The study was conducted in adherence to the principles of the Declaration of Helsinki.

Informed Consent: An informed voluntary consent form was obtained from each patient.

Peer-review: Externally peer reviewed.

Authorship Contributions

Data Collection or Processing: F.A., S.N., C.A., Analysis or Interpretation: M.E.B., J.M., Writing: F.A., S.N., C.A., M.B., J.M.

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

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

References

1. Kaiser PK, Brown DM, Zhang K, Hudson HL, Holz FG, Shapiro H, Schneider S, Acharya NR. Ranibizumab for predominantly classic neovascular age-related macular degeneration: subgroup analysis of first-year ANCHOR results. Am J Ophthalmol. 2007;144:850-857.
2. Brown DM, Michels M, Kaiser PK, Heier JS, Sy JP, Ianchulev T; ANCHOR Study Group. Ranibizumab versus verteporfin photodynamic therapy for neovascular age-related macular degeneration: two-year results of the ANCHOR study. Ophthalmology. 2009;116:57-65.
3. Bressler NM, Chang TS, Suñer IJ, Fine JT, Dolan CM, Ward J, Ianchulev T; MARINA and ANCHOR Research Groups. Vision related function after

ranibizumab treatment by better- or worse-seeing eye: clinical trial results from MARINA and ANCHOR. Ophthalmology. 2010;117:747-756.
4. CATT Research Group, Martin DF, Maguire MG, Ying GS, Grunwald JE, Fine SL, Jaffe GJ. Ranibizumab and bevacizumab for neovascular age-related macular degeneration.N Engl J Med. 2011;364:1897-1908.
5. Mitchell P, Korobelnik JF, Lanzetta P, Holz FG, Prünte C, Schmidt-Erfurth U, Tano Y, Wolf S. Ranibizumab (lucentis) in neovascular age-related macular degeneration: evidence from clinical trials. Br J Ophthalmol. 2010;94:2-13.
6. Rosenfeld PJ, Shapiro H, Tuomi L, Webster M, Elledge J, Blodi B; MARINA and ANCHOR Study Groups. Characteristics of patients losing vision after 2 years of monthly dosing in the phase III ranibizumab clinical trials. Ophthalmology. 2011;118:523-530.
7. Mariani A, Deli A, Ambresin A, Mantel I. Characteristics of eyes with secondary loss of visual acuity receiving variable dosing ranibizumab for neovascular age-related macular degeneration. Graefes Arch Clin Exp Ophthalmol. 2011;249:1635-1642.
8. Shin JY, Woo SJ, Ahn J, Park KH. Anti-VEGF-refractory exudative age-related macular degeneration: differential response according to features on optical coherence tomography. Korean J Ophthalmol. 2013;27:425-432.
9. Byun YJ, Lee SJ, Koh HJ. Predictors of response after intravitreal bevacizumab injection for neovascular age-related macular degeneration. Jpn J Ophthalmol. 2010;54:571-577.
10. Amoaku WM, Chakravarthy U, Gale R, Gavin M, Ghanchi F, Gibson J, Harding S, Johnston RL, Kelly SP, Lotery A, Mahmood S, Menon G, Sivaprasad S, Talks J, Tufail A, Yang Y. Defining response to anti-VEGF therapies in neovascular AMD. Eye (London). 2015;29:721-731.
11. Cohen SY, Mimoun G, Oubraham H, Zourdani A, Malbrel C, Queré S, Schneider V; LUMIERE Study Group. Changes in visual acuity in patients with wet age-related macular degeneration treated with intravitreal ranibizumab in daily clinical practice: the LUMIERE study. Retina. 2013;33:474-481.
12. Lux A, Llacer H, Heussen FM, Joussen AM. Non-responders to bevacizumab (Avastin) therapy of choroidal neovascular lesions. Br J Ophthalmol. 2007;91:1318-1322.
13. Otsuji T, Nagai Y, Sho K, Tsumura A, Koike N, Tsuda M, Nishimura T, Takahashi K. Initial non-responders to ranibizumab in the treatment of age-related macular degeneration (AMD). Clin Ophthalmol. 2013;7:1487-1490.
14. Slakter JS. What to do when anti-VEGF therapy fails. Retin Physician 2010.
15. Keane PA, Liakopoulos S, Ongchin SC, Heussen FM, Msutta S, Chang KT, Walsh AC, Sadda SR. Quantitative subanalysis of optical coherence tomography after treatment with ranibizumab for neovascular age-related macular degeneration. Invest Ophthalmol Vis Sci. 2008;49:3115-3120.
16. Ying GS, Huang J, Maguire MG, Grunwald JE, Jaffe GJ, Martin DF; CATT Research Group. Baseline predictors of visual acuity response to ranibizumab and bevacizumab in the comparison of AMD treatment trial (CATT). Invest Ophthalmol Vis Sci. 2012;53:3681.
17. Binder S. Loss of reactivity in intravitreal anti-VEGF therapy: tachyphylaxis or tolerance? Br J Ophthalmol. 2012;96:1-2.
18. Gasperini JL, Fawzi AA, Khondkaryan A, Lam L, Chong LP, Eliott D, Walsh AC, Hwang J, Sadda SR. Bevacizumab and ranibizumab tachyphylaxis in the treatment of choroidal neovascularisation. Br J Ophthalmol. 2012;96:14-20.
19. Lalwani GA, Rosenfeld PJ, Fung AE, Dubovy SR, Michels S, Feuer W, Davis JL, Flynn HW Jr, Esquiabro M. A Variable-dosing regimen with ıntravitreal ranibizumab for neovascular age-related macular degeneration: year 2 of the PrONTO study. Am J Ophthalmol. 2009;148:43-58.
20. Jang L, Gianniou C, Ambresin A, Mantel I. Refractory subretinal fluid in patients with neovascular age related macular degeneration treated with intravitreal ranibizumab: visual acuity outcome. Graefes Arch Clin Exp Ophthalmol 2015;253:1211-1216
21. Eghoj MS, Sorensen TL. Tachyphylaxis during treatment of exudative age-related macular degeneration with ranibizumab. Br J Ophthalmol. 2012;96:21-23.
22. Kovach JL, Schwartz SG, Flynn HW Jr, Scott IU. Anti-VEGF treatment strategies for wet AMD. J Ophthalmol. 2012;2012:786870.
23. Krebs I, Glittenberg C, Ansari-Shahrezaei S, Hagen S, Steiner I, Binder S. Non-responders to treatment with antagonists of vascular endothelial growth factor in age related macular degeneration. Br J Ophthalmol. 2013;97:1443-1446.
24. Wang VM, Rosen RB, Meyerle CB, Kurup SK, Ardeljan D, Agron E, Tai K, Pomykala M, Chew EY, Chan CC, Tuo J. Suggestive association between PLA2G12A single nucleotide polymorphism rs2285714 and response to anti-vascular endothelial growth factor therapy in patients with exudative age related macular degeneration. Mol Vis. 2012;18:2578-2585.
25. Wykoff CC, Clark WL, Nielsen JS, Brill JV, Greene LS, Heggen CL. Optimizing anti-VEGF treatment outcomes for patients with neovascular age related macular degeneration. J Manag Care Spec Pharm. 2018;24(2-a Suppl):3-15.
26. Rich RM, Rosenfeld PJ, Puliafito CA, Dubovy SR, Davis JL, Flynn HW Jr, Gonzalez S, Feuer WJ, Lin RC, Lalwani GA, Nguyen JK, Kumar G. Short-term safety and efficacy of intravitreal bevacizumab (Avastin) for neovascular age-related macular degeneration. Retina. 2006;26:495-511.
27. Schaal S, Kaplan HJ, Tezel TH. Is there tachyphylaxis to intravitreal anti-vascular endothelial growth factor pharmacotherapy in age-related macular degeneration? Ophthalmology. 2008;115:2199-2205.
28. Forooghian F, Cukras C, Meyerle CB, Chew EY, Wong WT. Tachyphylaxis after intravitreal bevacizumab for exudative age-related macular degeneration. Retina. 2009;29:723-731.
29. Hörster R, Ristau T, Sadda SR, Liakopoulos S. Individual recurrence intervals after anti-VEGF therapy for age-related macular degeneration. Graefes Arch Clin Exp Ophthalmol. 2011;249:645-652.
30. Veritti D, Macor S, Menchini F, Lanzetta P. Effects of VEGF inhibition on retinal morphology, neovascular network size, and visual acuity in patients with vascularized pigment epithelium detachment because of occult choroidal neovascularization. Retina. 2013;33:982-989.
31. Guber J, Henrich PB, Guber I, Cybulska A, Flammer J, Josifova T. Predictive factors for poor central retinal thickness response to ranibizumab in wet AMD. Invest Ophthalmol Vis Sci. 2012;53:51-55.
32. Tannan A, Li C, Stevens TS. Predicting treatment outcomes in patients with newly diagnosed exudative age-related macular degeneration based on initial presentation. Invest Ophthalmol Vis Sci. 2010;51:907.
33. Inoue M, Arakawa A, Yamane S, Kadonosone K. Variable response of vascularized pigment epithelial detachments to ranibizumab based on lesion subtypes, including polypoidal choroidal vasculopathy. Retina. 2013;33:990-997.
34. Punjabi OS, Huang J, Rodriguez L, Lyon AT, Jampol LM, Mirza RG. Imaging characteristics of neovascular pigment epithelial detachments and their response to anti-vascular endothelial growth factor therapy. Br J Ophthalmol. 2013;97:1024-1031.

DOI: 10.4274/tjo.galenos.2020.21456
Turk J Ophthalmol 2020;50:283-287

Original Article

Correlation of Visual Recovery and Increased Ellipsoid Zone Reflectivity After Successful Macular Hole Surgery

Büşra Yılmaz Tuğan*, Levent Karabaş*, Fatih Yenihayat**, Sevgi Subaşı*, Enes Kesim***, Berna Özkan****

*Kocaeli University Faculty of Medicine, Department of Ophthalmology, Kocaeli, Turkey
**Dünyagöz Kocaeli Hospital, Clinic of Ophthalmology, Kocaeli, Turkey
***Tuzla State Hospital, Clinic of Ophthalmology, İstanbul, Turkey
****Acıbadem Mehmet Ali Aydınlar University Faculty of Medicine, Department of Ophthalmology, İstanbul, Turkey

Abstract

Objectives: To assess changes in reflectivity of the retinal pigment epithelium (RPE), ellipsoid zone (EZ), and external limiting membrane (ELM) on spectral domain-optical coherence tomography (SD-OCT) images and the effects of reflectivity changes on visual acuity improvement after vitrectomy in macular hole patients.

Materials and Methods: Twenty-four eyes of 24 patients with idiopathic full-thickness macular hole closed after vitrectomy were retrospectively reviewed. The "plot profile" function of the medical imaging software was used by a single masked physician to analyze RPE, EZ, and ELM reflectivity on OCT images at postoperative 1 month and 12 months.

Results: Absolute and relative EZ reflectivity showed highly significant increases at postoperative 12 months compared to 1 month ($p<0.001$ and $p<0.001$, respectively). Absolute and relative EZ reflectivity changes from postoperative month 1 to month 12 after macular hole surgery were significantly correlated with best corrected visual acuity improvement ($p=0.012$ and $p=0.020$, respectively).

Conclusion: EZ reflectivity can be a predictor of functional and anatomical improvement after macular hole surgery.

Keywords: Absolute and relative reflectivity, ellipsoid zone reflectivity, macular hole, vitrectomy

Introduction

Idiopathic macular hole (MH) is a full-thickness anatomical defect of the neural retina at the fovea that can lead to central vision loss. Edema and detachment of the sensory retina may lead to the progression of hole enlargement, retinal pigment epithelium (RPE) atrophy, and decrease in visual acuity.[1]

Kelly and Wendel[2] first introduced vitrectomy and intraocular gas tamponade for MH surgery. Later, with progress in surgical instrumentation and techniques, anatomical closure rates reached over 90%.[3] Large numbers of associated factors lead to variation in visual outcomes despite anatomical closure. Recent improvements in the resolution of optical coherence tomography (OCT) have enabled ophthalmologists to observe retinal structures more precisely. Researchers have suggested that maximal visual recovery may take a year or more and is linked to photoreceptor layer status.[4,5,6,7] Furthermore, recent studies

Address for Correspondence: Büşra Yılmaz Tuğan, M.D., Kocaeli University Faculty of Medicine, Department of Ophthalmology, Kocaeli, Turkey
Phone:+90 533 351 33 99 E-mail: busrayilmaz87@hotmail.com **ORCID-ID:** orcid.org/0000-0001-6660-1608
Received: 24.12.2019 **Accepted:** 14.04.2020

Cite this article as: Yılmaz Tuğan B, Karabaş L, Yenihayat F, Subaşı S, Kesim E, Özkan B. Correlation of Visual Recovery and Increased Ellipsoid Zone Reflectivity After Successful Macular Hole Surgery. Turk J Ophthalmol. 2020;50:283-287

using spectral-domain OCT (SD-OCT) support the suggestion that delayed visual recovery may be related to the reorganization of the photoreceptor layer.[8,9]

Current literature emphasizes that structural or functional impairment in related retinal layers causes lower reflectivity.[10,11,12]

In this study, we intended to observe the effects of vitrectomy on RPE, ellipsoid zone (EZ), and external limiting membrane (ELM) reflectivity using image processing computer software (ImageJ 1.47v, Wayne Rasband, National Institutes of Health, USA, http://imagej.nih.gov/ij) in MH patients.[13] In addition, we analyzed the association between visual recovery and retinal layer integrity and reflectivity after vitrectomy.

Materials and Methods

Twenty-four eyes of 24 patients with idiopathic full-thickness MH closed after vitrectomy between January 2015 and June 2016 were included in this retrospective study. The local ethics committee approved this study, and we followed the tenets of the Declaration of Helsinki. All patients were diagnosed with stage 2 or 3 idiopathic MH according to Gass classification system and were followed for at least 12 months postoperatively.[14] Patients with full-thickness MH that closed successfully after vitrectomy confirmed by SD-OCT examinations (Spectralis OCT; Heidelberg Engineering, Heidelberg, Germany) were included. Patients with previous retinal surgery, macular degeneration, diabetic retinopathy, inflammatory ocular diseases, retinal vascular occlusions, hypertensive retinopathy, MH associated with other pathology, lamellar MH, or pseudo-MH were excluded. Reactive gliosis (glial healing) is a complex process that is considered to promote retinal repair following pathological insult or surgery. Therefore, we excluded patients showing glial healing in 2 or more layers, which may result in inability to differentiate between layers in OCT images.

All patients underwent 23-gauge pars plana vitrectomy and internal limiting membrane (ILM) peeling with forceps in an area of 2-3 optic disc diameters around the MH. Sulfur hexafluoride (SF6) or perfluoropropane (C3F8) gas tamponade were used and patients were informed to remain in a face-down position for at least 3 days after surgery. Cataract surgery was not performed at the time of vitrectomy in any patient.

Visual acuity was measured and SD-OCT was performed the day before MH surgery and 1 month and 12 months postoperatively. Best corrected visual acuity (BCVA) was converted to the logarithm of the minimal angle of resolution (logMAR) equivalent. SD-OCT images were exported to the Java-based image processing computer software, ImageJ.[13,15] ImageJ is a reliable tool with high inter- and intra-observer reproducibility and has been used in several recent studies in the field of ophthalmology.[10,16,17,18] The "plot profile" function of ImageJ was used by a single masked physician (F.Y.) to analyze OCT images (Figure 1).[10,13,15] A vertical straight line passing through the center of the fovea was drawn from the vitreous cavity to the choroid to obtain reflectivity graph and reflectivity values along the line (Figure 1).[10,15] In a normal OCT image, the histologic order of reflectivity is RPE layer, EZ (formerly called the photoreceptor inner segment/outer segment [IS/OS] junction), and ELM, respectively. In studies regarding reflectivity of retina, the outermost highly reflective band is thought to represent RPE[19,20], so the highest value was accepted as the reflectivity of the RPE layer, and relative reflectivity of the EZ or ELM was calculated by dividing EZ or ELM reflectivity by RPE reflectivity according to this formula:

Relative reflectivity (arbitrary unit) = (reflectivity of EZ or ELM)/(reflectivity of RPE) x100.[10]

Statistical Analysis

All statistical analyses were performed using IBM SPSS for Windows version 20.0 (IBM Corp., Armonk, NY, USA). The normality of data distribution was tested with Kolmogorov-Smirnov test. Continuous variables were expressed as mean ± standard deviation (SD) and categorical variables as counts and percentages. The significance of differences between the time points was analyzed using paired-samples t-test for normally distributed variables and Wilcoxon signed-rank test

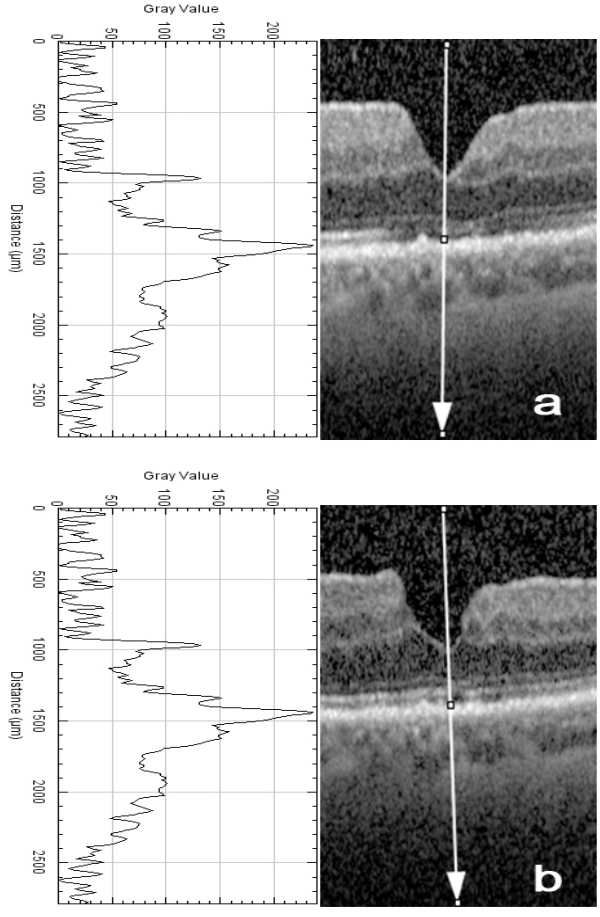


Figure 1. Peaks of the retinal pigment epithelium (RPE), ellipsoid zone (EZ), and external limiting membrane (ELM) on reflectivity graph (left) and gray-scale optical coherence tomography images (right) from postoperative 1 month (a) and 12 months (b) obtained from an image processing program (ImageJ). ImageJ gives reflectivity values along a line (vertical white arrow) and creates reflectivity graph

for nonnormally distributed variables. Pearson and Spearman correlation analysis was used to determine associations between continuous variables. A two-sided p value <0.05 was considered statistically significant.

Results

Twenty-four eyes of 24 consecutive idiopathic full-thickness MH patients (14 male, 10 female) with a mean age of 64.46±10.90 years were included in the study (Table 1). The MHs were classified as stage 2 in 13 eyes and stage 3 in 11 eyes (Table 1). The mean BCVA (logMAR ± SD) was 0.52±0.17 before surgery and increased to 0.35±0.15 at postoperative 12 months (p<0.001). The mean BCVA at postoperative 1 month was 0.51±0.22 and increased to 0.35±0.15 at postoperative 12 months (p=0.006) (Table 1). Eyes with any findings of exhibited glial healing in the RPE, EZ, and ELM layer excluded from statistical analysis (1 patient, 6 patients, and 3 patients, respectively).

In this retrospective study, we performed image analysis and determined the reflectivity of RPE, EZ, and ELM of all subjects. Absolute and relative EZ reflectivity showed a highly significant increase at postoperative 12 months compared to 1 month (p<0.001 and p<0.001, respectively) (Table 2). However, there were no differences between RPE and ELM reflectivities at postoperative 1 month and 12 months.

In addition, changes in absolute and relative reflectivity parameters according to BCVA improvement were analyzed (Table 3). The changes in absolute and relative EZ reflectivity from postoperative 1 month to 12 months after MH surgery were correlated with the change in BCVA from preoperative to postoperative 12 months (p=0.012 and p=0.020, respectively). However, changes in absolute and relative ELM reflectivity from postoperative 1 month to 12 months were not correlated with change in BCVA from preoperative to postoperative 12 months (p=0.337 and p=0.573). Change in absolute RPE reflectivity from postoperative 1 month to 12 months was not correlated with the pre- to postoperative change in BCVA (p=0.369). Changes in absolute and relative reflectivity measurements from postoperative 1 month to 12 months were not correlated with BCVA improvement from postoperative 1 month to 12 months. Absolute and relative reflectivity measurements at postoperative 1 month were not correlated with BCVA at postoperative 12 months.

Preoperative MH diameter was not correlated with absolute or relative reflectivities at postoperative 1 month and 12 months or with the changes in reflectivity from postoperative 1 month to 12 months. In the grade 2 and 3 MH patient groups, only absolute and relative EZ reflectivities showed a statistically significant increase from postoperative 1 month to 12 months (p=0.017 and p=0.003, respectively). Absolute RPE reflectivity

Table 1. Demographic data of macular hole (MH) patients (n=24)

Gender	
Male, n (%)	14 (58.3%)
Female, n (%)	10 (41.7%)
Age (years, mean ± SD)	64.46±10.90
MH stage	
Stage 2	13 (54.2%)
Stage 3	11 (45.8%)
Gas tamponade type	
C3F8	13 (54.2%)
SF6	11 (45.8%)
BCVA (logMAR, mean ± SD)	
Preoperative	0.52±0.17
Postoperative 1 month	0.51±0.22
Postoperative 12 months	0.35±0.15

SD: Standard deviation, BCVA: Best corrected visual acuity

Table 2. Comparison of retinal pigment epithelium (RPE), ellipsoid zone (EZ), and external limiting membrane (ELM) reflectivities at postoperative 1 and 12 months

	1 month	12 months	P value
Absolute RPE reflectivity (arbitrary unit, mean ± SD)	215.04±17.02	213.13±14.94	0.677
Absolute EZ reflectivity (arbitrary unit, mean ± SD)	122.86±29.94	159.23±24.97	**<0.001**
Absolute ELM reflectivity (arbitrary unit, mean ± SD)	96.23±28.51	106.04±24.15	0.418
Relative EZ reflectivity (arbitrary unit, mean ± SD)	58.11±11.39	75.42±9.27	**<0.001**
Relative ELM reflectivity (arbitrary unit, mean ± SD)	44.98±12.38	49.08±11.27	0.497

SD: Standard deviation

Table 3. Correlation of preoperative to postoperative month-12 BCVA changes with retinal pigment epithelium (RPE), ellipsoid zone (EZ), and external limiting membrane (ELM) reflectivity from postoperative month 1 to month 12

	Absolute EZ reflectivity change	Relative EZ reflectivity change	Absolute ELM reflectivity change	Relative ELM reflectivity change	Absolute RPE reflectivity change
BCVA change	**p=0.012** r=0.578	**p=0.020** r=0.543	p=0.337 r=0.221	p=0.573 r=0.131	p=0.369 r=0.196

and absolute and relative ELM reflectivities did not show significant differences between postoperative 1 month and 12 months in two groups (p=0.855, p=0.431 and p=0.439, respectively).

Discussion

Idiopathic MH is a pathological condition that causes disruption of the retinal layers alignment. The EZ, which signifies the photoreceptor inner segment ellipsoid with densely packed mitochondria[21], reflects photoreceptor integrity and function and is seen as a highly reflective continuous band just above the RPE in ultra-high-resolution OCT.[22] In recent years, some authors have emphasized EZ integrity as a prognostic factor for the increase in visual acuity after vitrectomy in some retinal diseases.[8,23,24,25,26,27,28,29] Baba et al.[7] showed the importance of normal EZ for visual improvement after MH surgery. In a study by Shimozono et al.[30] including 30 eyes of 30 patients with idiopathic MH that underwent successful vitrectomy, photoreceptor OS restoration was described as an important factor for visual recovery after MH surgery. Michalewska et al.[31] revealed resolved photoreceptor layer defects at postoperative 12 months in 70.5% of MH surgery patients. In addition, Kim et al.[32] used a photoreceptor layer map to show gradually decreased hyporeflectivity with improvement in visual acuity after MH surgery.

In the current study, we measured the reflectivity of the RPE, EZ, and ELM on SD-OCT scans using ImageJ image processing software to understand the effects of vitrectomy on the functionality of these layers in MH patients. We observed significant increases in EZ reflectivity (both absolute and relative) at postoperative 12 months compared to postoperative 1 month, whereas RPE and ELM reflectivity did not show a difference between postoperative 1 month and 12 months. Some studies showed that decreased EZ reflectivity is associated with poor photoreceptor function.[19,20] Our results also showed a significant positive correlation between EZ reflectivity and BCVA improvement.

Schumann et al.[33] reviewed patients with lamellar MH and macular pseudohole according to EZ and ELM integrity or discontinuity. They postulated that integrity of the ELM appeared to be more critical for visual improvement than integrity of the EZ. Chang et al.[34] retrospectively reviewed 60 eyes of 56 patients that underwent successful vitrectomy and ILM peeling for idiopathic MH and concluded that postoperative visual acuity was correlated with restored ELM and EZ line. Furthermore, in a retrospective study, eyes with both ELM and EZ disruption showed significantly lower BCVA measurements at postoperative 6 weeks than those with only EZ disruption, suggesting that ELM integrity is a critical factor for photoreceptor layer healing and visual improvement.[35] However, in the present study we did not find any correlation between RPE or ELM reflectivity and visual acuity improvement.

Other studies also showed that recovery of the macular contour, ELM, and EZ affected the recovery of vision after MH surgery.[36,37] Kim et al.[38] reported that the EZ recovered postoperatively in 19 patients (73.1%) and that better preoperative BCVA, smaller basal hole diameter, and shorter axial length were observed in eyes with recovered EZ. In another study, smaller defects in the EZ and absence of an ELM defect were found to be associated with better postoperative BCVA.[39]

Study Limitations

This study has some limitations, including the small sample size and its retrospective, non-randomized design. Potential transmission artifacts or some degrees of gliosis could influence the results of the current study.

Conclusion

In conclusion, EZ reflectivity seems to be essential for visual function and may be a predictor of functional and anatomical improvement after vitrectomy in MH patients.

Ethics

Ethics Committee Approval: The local ethics committee approved this study, and we followed the tenets of the Declaration of Helsinki.

Informed Consent: Obtained.

Peer-review: Externally and intenally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: L.K., Concept: B.Y.T., L.K., Design: B.Y.T., L.K., S.S., F.Y., Data Collection or Processing: B.Y.T., E.K., F.Y., Analysis or Interpretation: L.K., B.Ö., Literature Search: B.Y.T., S.S., F.Y., B.Ö., Writing: B.Y.T., F.Y., S.S.

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

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

References

1. Casuso LA, Scott IU, Flynn HW Jr, Gass JD, Smiddy WE, Lewis ML, Schiffman J. Long-term follow-up of unoperated macular holes. Ophthalmology. 2001;108:1150-1155.
2. Kelly NE, Wendel RT. Vitreous surgery for idiopathic macular holes. Results of a pilot study. Arch Ophthalmol. 1991;109:654-659.
3. Freeman WR, Azen SP, Kim JW, el-Haig W, Mishell DR 3rd, Bailey I. Vitrectomy for the treatment of full-thickness stage 3 or 4 macular holes. Results of a multicentered randomized clinical trial. The vitrectomy for treatment of macular hole study group. Arch Ophthalmol. 1997;115:11-21.
4. Leonard RE 2nd, Smiddy WE, Flynn HW Jr, Feuer W. Long-term visual outcomes in patients with successful macular hole surgery. Ophthalmology. 1997;104:1648-1652.
5. Lee JE, Lee SU, Jea SY, Choi HY, Oum BS. Reorganization of photoreceptor layer on optical coherence tomography concurrent with visual improvement after macular hole surgery. Korean J Ophthalmol. 2008;22:137-142.
6. Villate N, Lee JE, Venkatraman A, Smiddy WE. Photoreceptor layer features in eyes with closed macular holes: optical coherence tomography findings and correlation with visual outcomes. Am J Ophthalmol. 2005;139:280-289.
7. Baba T, Yamamoto S, Arai M, Arai E, Sugawara T, Mitamura Y, Mizunoya S. Correlation of visual recovery and presence of photoreceptor inner/outer segment junction in optical coherence images after successful macular hole repair. Retina. 2008;28:453-458.

8. Inoue M, Watanabe Y, Arakawa A, Sato S, Kobayashi S, Kadonosono K. Spectral-domain optical coherence tomography images of inner/outer segment junctions and macular hole surgery outcomes. Graefes Arch Clin Exp Ophthalmol. 2009;247:325-330.
9. Christensen UC, Kroyer K, Sander B, Larsen M, la Cour M. Prognostic significance of delayed structural recovery after macular hole surgery. Ophthalmology. 2009;116:2430-2436.
10. Toprak I, Yaylalı V, Yildirim C. Decreased photoreceptor inner segment/outer segment junction reflectivity in patients with idiopathic epimacular membrane. Eye (Lond). 2014;28:1126-1130.
11. Bizheva K, Pflug R, Hermann B, Povazay B, Sattmann H, Qiu P, Anger E, Reitsamer H, Popov S, Taylor JR, Unterhuber A, Ahnelt P, Drexler W. Optophysiology: depth-resolved probing of retinal physiology with functional ultrahigh-resolution optical coherence tomography. Proc Natl Acad Sci U S A. 2006;103:5066-5071.
12. Hood DC, Zhang X, Ramachandran R, Talamini CL, Raza A, Greenberg JP, Sherman J, Tsang SH, Birch DG. The inner segment/outer segment border seen on optical coherence tomography is less intense in patients with diminished cone function. Invest Ophthalmol Vis Sci. 2011;52:9703-9709.
13. Rasband W. Image J Medical Imaging Software. National Institutes of Health: Bethesda, MD, USA. Available at http://rsb.info.nih.gov/ij/. Last accessed 19 January 2018.
14. Gass JD. Reappraisal of biomicroscopic classification of stages of development of a macular hole. Am J Ophthalmol. 1995;119:752-759.
15. Murakami T, Nishijima K, Akagi T, Uji A, Horii T, Ueda-Arakawa N, Muraoka Y, Yoshimura N. Optical coherence tomographic reflectivity of photoreceptors beneath cystoid spaces in diabetic macular edema. Invest Ophthalmol Vis Sci. 2012;53:1506-1511.
16. Higaki M, Nozaki M, Yoshida M, Ogura Y. Less Expansion of Short-Pulse Laser Scars in Panretinal Photocoagulation for Diabetic Retinopathy. J Ophthalmol. 2018:9371895.
17. Liu H, Yang D, Ma T, Shi W, Zhu Q, Kang J, Wang N. Measurement and Associations of the Optic Nerve Subarachnoid Space in Normal Tension and Primary Open-Angle Glaucoma. Am J Ophthalmol. 2018;186:128-137.
18. Bladen JC, Moosajee M, Tracey-White D, Beaconsfield M, O'Toole EA, Philpott MP. Analysis of hedgehog signaling in periocular sebaceous carcinoma. Graefes Arch Clin Exp Ophthalmol. 2018;256:853-860.
19. Drexler W, Sattmann H, Hermann B, Ko TH, Stur M, Unterhuber A, Scholda C, Findl O, Wirtitsch M, Fujimoto JG, Fercher AF. Enhanced visualization of macular pathology with the use of ultrahigh-resolution optical coherence tomography. Arch Ophthalmol. 2003; 121:695-706.
20. Gloesmann M, Hermann B, Schubert C, Sattmann H, Ahnelt PK, Drexler W. Histologic correlation of pig retina radial stratification with ultrahigh-resolution optical coherence tomography. Invest Ophthalmol Vis Sci. 2003;44:1696-1703.
21. Spaide RF, Curcio CA. Anatomical correlates to the bands seen in the outer retina by optical coherence tomography: literature review and model. Retina. 2011;31:1609-1619.
22. Ko TH, Fujimoto JG, Duker JS, Paunescu LA, Drexler W, Baumal CR, Puliafito CA, Reichel E, Rogers AH, Schuman JS. Comparison of ultrahigh- and standard- resolution optical coherence tomography for imaging macular hole pathology and repair. Ophthalmology. 2004;111:2033-2043.
23. Sakamoto A, Nishijima K, Kita M, Oh H, Tsujikawa A, Yoshimura N. Association between foveal photoreceptor status and visual acuity after resolution of diabetic macular edema by pars plana vitrectomy. Graefes Arch Clin Exp Ophthalmol. 2009;247:1325-1330.
24. Oh J, Smiddy WE, Flynn Jr HW, Gregori G, Lujan B. Photoreceptor inner/outer segment defect imaging by spectral domain OCT and visual prognosis after macular hole surgery. Invest Ophthalmol Vis Sci. 2010;51:1651-1658.
25. 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.
26. Scholda C, Wirtitsch M, Hermann B, Unterhuber A, Ergun E, Sattmann H, Ko TH, Fujimoto JG, Fercher AF, Stur M, Schmidt-Erfurth U, Drexler W. Ultrahigh resolution optical coherence tomography of macular holes. Retina. 2006;26:1034-1041.
27. Oster SF, Mojana F, Brar M, Yuson RMS, Cheng L, Freeman WR. Disruption of the photoreceptor inner segment/outer segment layer on spectral domain-optical coherence tomography is a predictor of poor visual acuity in patients with epiretinal membranes. Retina. 2010;30:713-718.
28. Michalewska Z, Michalewski J, Cisiecki S, Adelman R, Nawrocki J. Correlation between foveal structure and visual outcome following macular hole surgery: a spectral optical coherence tomography study. Graefes Arch Clin Exp Ophthalmol. 2008;246:823-830.
29. Kunikata H, Abe T, Kinukawa J, Nishida K. Preoperative factors predictive of postoperative decimal visual acuity ≥1.0 following surgical treatment for idiopathic epiretinal membrane. Clin Ophthalmol. 2011;5:147-154.
30. Shimozono M, Oishi A, Hata M, Kurimoto Y. Restoration of the photoreceptor outer segment and visual outcomes after macular hole closure: spectral-domain optical coherence tomography analysis. Graefes Arch Clin Exp Ophthalmol. 2011;249:1469-1476.
31. Michalewska Z, Michalewski J, Nawrocki J. Continuous changes in macular morphology after macular hole closure visualized with spectral optical coherence tomography. Graefes Arch Clin Exp Ophthalmol. 2010;248:1249-1255.
32. Kim NM, Park HJ, Koo GH, Lee JE, Oum BS. Photoreceptor layer assessed in tissue layer image using spectral-domain optical coherence tomography after surgical closure of macular hole. Retina. 2011;31:1483-1492.
33. Schumann RG, Compera D, Schaumberger MM, Wolf A, Fazekas C, Mayer WJ, Kampik A, Haritoglou C. Epiretinal membrane characteristics correlate with photoreceptor layer defects in lamellar macular holes and macular pseudoholes. Retina. 2015;35:727-735.
34. Chang YC, Lin WN, Chen KJ, Wu HJ, Lee CL, Chen CH, Wu KY, Wu WC. Correlation Between the Dynamic Postoperative Visual Outcome and the Restoration of Foveal Microstructures After Macular Hole Surgery. Am J Ophthalmol. 2015;160:100-106.
35. Landa G, Gentile RC, Garcia PMT, Muldoon TO, Rosen RB. External limiting membrane and visual outcome in macular hole repair: spectral domain OCT analysis. Eye (Lond). 2012;26:61-69.
36. Sano M, Shimoda Y, Hashimoto H, Kishi S. Restored photoreceptor outer segment and visual recovery after macular hole closure. Am J Ophthalmol. 2009;147:313-318.
37. Itoh Y, Inoue M, Rii T, Hiraoka T, Hirakata A. Correlation between length of foveal cone outer segment tips line defect and visual acuity after macular hole closure. Ophthalmology. 2012;119:1438-1446.
38. Kim SH, Kim HK, Yang JY, Lee SC, Kim SS. Visual Recovery after Macular Hole Surgery and Related Prognostic Factors. Korean J Ophthalmol. 2018;32:140-146.
39. Geenen C, Murphy DC, Sandinha MT, Rees J, Steel DHW. Significance of preoperative external limiting membrane height on visual prognosis in patients undergoing macular hole surgery. Retina. 2019;39:1392-1398.

DOI: 10.4274/tjo.galenos.2020.82504
Turk J Ophthalmol 2020;50:288-292

Original Article

Causes of Blindness in the Adult Population in Somalia

Mustafa Kalaycı

Somali Mogadishu-Turkey Recep Tayyip Erdogan Training and Research Hospital, Clinic of Ophthalmology, Mogadishu, Somalia

Abstract

Objectives: To evaluate the causes and frequency of blindness among the adult Somali population according to the World Health Organization (WHO) criteria.

Materials and Methods: The data of 2,605 patients over 18 years old who presented to our tertiary hospital in Mogadishu (the capital of Somalia) were evaluated. Patients with best corrected visual acuity of less than 3/60 in both eyes were categorized as bilaterally blind and those with best corrected visual acuity of less than 3/60 in one eye but 3/60 or better in the other eye were classified as monocularly blind, as per the WHO classification.

Results: Of 2,605 patients, 1,251 (48%) were female and 1,354 (52%) were male. Among these, 256 patients were determined to have blindness in one or both eyes and were included in the study. The patients ranged in age from 19 to 85, and the mean age was 52.4±14.6 years. The overall blindness rate in the Somali population was 9.8%. In the monocularly blind group, the most common factor was trauma complication (23.6%), followed by cataract (19%) and diabetic retinopathy (13.2%). In the bilaterally blind group, the most common factors were cataract (26.9%), diabetic retinopathy (21.1%), and glaucoma (15.4%).

Conclusion: Trauma is the leading cause of blindness due to the security conditions in the country. Establishing and increasing the number of free public health centers in Somalia can reduce the frequency of blindness.

Keywords: Blindness, World Health Organization, Somalia, trauma, cataract

Introduction

Blindness is an important public health problem with economic and social dimensions. Blindness and low vision are indicators of the general health status of a society. Globally, 285 million people suffer from visual impairment, 39 million of whom have a level of vision below the threshold for blindness.[1] Approximately 90% of blind people live in developing countries.[2] In addition, 80% of blindness occurs due to preventable or treatable causes. The most common cause of blindness worldwide is diabetic retinopathy.[3] Diabetes is a common disease worldwide that causes ocular damage, including diabetic retinopathy.

The prevalence and causes of blindness and low vision vary in different societies based on their level of development. According to data from the World Health Organization (WHO), the prevalence of blindness is 7.3/1,000 in Africa, 3.5/1,000 in America, 8.5/1,000 in the Eastern Mediterranean Region, and 3.0/1,000 in Europe.[4]

Address for Correspondence: Mustafa Kalaycı, M.D., Somali Mogadishu-Turkey Recep Tayyip Erdogan Training and Research Hospital, Clinic of Ophthalmology, Mogadishu, Somalia Phone:+90 532 728 09 63 E-mail: drkalayci07@hotmail.com **ORCID-ID:** orcid.org/0000-0001-8056-6634

Received: 05.01.2020 **Accepted:** 13.04.2020

Cite this article as: Kalaycı M. Causes of Blindness in the Adult Population in Somalia. Turk J Ophthalmol. 2020;50:288-292

The appropriate allocation of resources is important for effective delivery of health services in underdeveloped and developing countries. In this respect, data on the causes of vision loss may be helpful in planning and utilizing resources appropriately. To be able to prevent blindness, appropriate data must first be collected.

Somalia is an underdeveloped country in Sub-Saharan Africa with a population of 14 million. To date, there has been no study on the prevalence of blindness in Somalia.

This hospital-based study was conducted at Somalia Mogadishu-Turkey Recep Tayyip Erdogan Training and Research Hospital and aimed to evaluate the causes and frequency of blindness among Somali adults.

Materials and Methods

Patient Data

The files of 2605 patients over 18 years of age who presented to the Somalia Mogadishu-Turkey Recep Tayyip Erdogan Training and Research Hospital, Clinic of Eye between January 2019 and January 2020 were analyzed retrospectively. Of these, 256 patients determined to have monocular or bilateral blindness were included in the study. Approval for the study was obtained from the Somalia Mogadishu-Turkey Recep Tayyip Erdogan Education and Research Hospital Local Ethics Committee.

The demographic data and medical and family histories of all patients were recorded. Best corrected visual acuity (BCVA) was evaluated using a standard Snellen chart. Intraocular pressure (IOP) was measured using a pneumatic tonometer. Values 21 mmHg or higher with the pneumatic tonometer were measured again with a Goldmann applanation tonometer. Anterior segment examinations were performed with slit-lamp biomicroscope. Detailed dilated fundus examinations were performed and when necessary, tests and imaging such as computerized visual field test, optical coherence tomography, ocular ultrasonography, magnetic resonance imaging (MRI), computed tomography, blood tests, fasting blood glucose, and hemoglobin A1C were requested.

According to the WHO criteria, patients with BCVA worse than 3/60 in both eyes were classified as bilaterally blind while patients with BCVA worse than 3/60 in one eye and better than 3/60 in the fellow eye were classified as monocularly blind.[5]

In most cases, blindness was associated with a single cause. In cases with more than one cause, the factor with the greatest impact in the development of blindness was selected as the main cause, in accordance with the WHO recommendation.[6]

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics version 23.0 software (IBM Corp., Armonk, NY, USA). Mean, standard deviation, and minimum-maximum values were determined for continuous variables. Frequency analysis was performed.

Results

Of the 256 patients, 120 (46.8%) were women and 136 (53.2%) were men. The patients were between 19 and 85 years of age, with a mean age of 52.4±14.6 years. Both monocular and bilateral blindness increased with age (Table 1). This finding was statistically significant ($p<0.05$).

In this hospital-centered study, the overall blindness rate was found to be 9.8% in the adult Somali population. The number of blind women was 120 (8%) and the number of blind men was 136 (10%). Blindness was bilateral in 104 patients (4%) and monocular in 152 patients (5.8%).

In the monocular blindness group, the most common cause was trauma complication (n=36, 23.6%), followed by cataract (n=29, 19%) and diabetic retinopathy (20, 13.2%) (Table 2).

For bilateral blindness, the most common causes were cataract (n=28, 26.9%), diabetic retinopathy (n=22, 21.1%), and glaucoma (n=16, 15.4%) (Table 3).

In the bilateral blindness group, vision loss was caused by retinitis pigmentosa in 2 patients (1.9%) and degenerative myopia in 2 patients (1.9%), while in the monocular group, the cause of vision loss was deep amblyopia in 3 patients (2%) and pterygium in 2 patients (1.4%).

Table 1. Blindness distribution by age

Age group (years)	Blind population	Total population	%
18-40	56	734	7.6
40-60	86	925	9.2
>60	114	946	12
Total	256	2.605	9.8

Table 2. Causes of unilateral blindness

Cause	Female	Male	Total	%
Complication of trauma (gun, shrapnel, etc.)	8	28	36	23.6
Cataract	16	13	29	19.0
Diabetic retinopathy	11	9	20	13.2
Corneal leucoma (microbial and dystrophies)	6	8	14	9.2
Glaucoma	5	7	12	7.9
Age-related macular degeneration	4	6	10	6.6
Retinal detachment	3	5	8	5.3
Uncorrected aphakia	4	3	7	4.6
Phthisis/evisceration	2	2	4	2.6
Uveitis	3	1	4	2.6
Deep amblyopia	2	1	3	2.0
Optic atrophy	2	1	3	2.0
Pterygium	0	2	2	1.4
Total	66	86	152	100

Table 3. Causes of bilateral blindness				
Cause	**Female**	**Male**	**Total**	**%**
Cataract	16	13	28	26.9
Diabetic retinopathy	12	10	22	21.1
Glaucoma	9	7	16	15.4
Age-related macular degeneration	4	6	10	9.7
Uncorrected aphakia	5	3	8	7.8
Corneal leucoma (microbial and dystrophies)	4	3	7	6.7
Trauma complication	1	3	4	3.8
Optic atrophy	2	1	3	2.9
Phthisis/evisceration	1	1	2	1.9
Retinitis pigmentosa	1	1	2	1.9
Degenerative myopia	0	2	2	1.9
Total	54	50	104	100

Discussion

The prevalence of blindness among adults was determined to be 9.8% in this study. This rate was reported as 7.3% in Ethiopia, 5.8% in Mali, 13.7% in Jordan, 10.9% in South Africa, and 7.8% in Kenya, and may vary between countries based on socioeconomic level, ethnic diversity, the healthcare system, the number and quality of eye care professionals, as well as whether or not there are institutions that support them.[7,8,9,10]

In our study, it was found that the prevalence of blindness increased with age. The higher frequency of glaucoma, cataract, and age-related retinal diseases in adults aged 60 and older may explain the higher rate of blindness in this group. Our findings were similar to those in other countries.[11,12,13]

Trauma complications were found to be the most common cause of monocular blindness. This may be a result of the terrorist acts and state of chaos that have persisted in the country for years. Based on our observations, this high rate may be due to the frequent bomb explosions in Somalia (twice a month on average) and the fact that nearly everyone owns a weapon and attempts to settle even minor arguments with firearms or non-firearm weapons. It was also observed in this study that trauma was more common among men. In Somalia, the fact that men are more active and work outside make them vulnerable to trauma. Similar findings were reported in a study related to ocular trauma patterns conducted in Nepal and a study conducted in the Bursa region of Turkey by Argun Kivanc et al.[14,15] Both studies showed that the agriculture and construction sectors generally employ men and that ocular trauma is more common among workers in these sectors.[15] Most of the male patients in our study group were also working in these areas, and our findings were similar to those reported in these two studies.

Furthermore, the majority of the Somalian population lives in rural areas and earns a living from agriculture and animal husbandry. Because patients also pay their own healthcare costs, it has been observed that early presentation to health services after ocular trauma is uncommon among agricultural workers. This seems to be another reason for the high rate of trauma-related blindness.

As ours is the only tertiary care hospital in Somalia, the country's complicated ophthalmological cases are referred to our clinic. It has been observed that patients living far from the capital who present to local doctors after ocular trauma are referred to our clinic for surgical treatment. Referred patients are able to present to our clinic a few days later. No matter how quickly these patients are treated in our clinic, their vision may remain below the blindness threshold because of late presentation.

According to WHO data, the leading cause of blindness worldwide is cataract (51%).[6] Blindness is defined as having a level of vision not exceeding 3/60 despite all treatments. Today, however, cataract is a surgically treatable condition. WHO's inclusion of cataract patients in the classification of blindness required us to evaluate these cases in our study. Cataract was the most common cause of bilateral blindness (26.9%) and the second most common cause of monocular blindness (19%) in our study. This finding was similar to those in developing countries. A rate of 23.4% was reported in Ethiopia, 36.5% in Nigeria, 19.2% in Mali, and 34.9% in Mongolia.[10,16,17,18] Based on our observations, patients present very late to ophthalmology clinics due to the lack of a publicly funded healthcare system in Somalia, resulting in them having to pay the full cost of cataract surgery themselves, and the low income in the general population. These reasons may explain why cataract is the most common cause of bilateral blindness.

In our study, diabetic retinopathy emerged as another common cause of blindness. We believe factors that may increase the impact of diabetic retinopathy as a cause of blindness in Somalia include the lack of intraocular injection therapy for diabetic macular edema, the inability to diagnose and treat with methods such as fundus fluorescein angiography and argon laser photocoagulation, as well as patients' systemic comorbidities such as hypertension and kidney failure, and poor blood glucose control.

Another cause of blindness resulting from retinal damage in our study was age-related macular degeneration (6.6% unilateral, 9.7% bilateral). Blindness due to age-related macular degeneration and diabetic retinopathy is on the rise in both developed and developing countries. In Turkey, Özen Tunay et al.[19] determined in their study of the geriatric age group that age-related macular degeneration was the most common cause of low vision in presenile and senile groups. As development continues and the average lifespan becomes longer in Somalia, we believe there will be an increase in vision loss associated with retinal diseases in the near future.

Glaucoma was found to be the third most common cause of bilateral blindness (15.4%). Glaucoma is a common cause

of blindness in both developed and developing countries.[20,21] In previous studies, blindness due to glaucoma was reported at rates of 7.1% in Pakistan, 15.4% in Sweden, 7.7% in China, 5% in Iceland, and 17% in Saudi Arabia.[3,21,22,23,24]

There are no previous studies reporting the prevalence of glaucoma in the Somali population. However, according to our clinical observations, glaucoma patients tend to present to the outpatient clinic at a late stage. We have also observed that awareness of glaucoma is low. Insufficient access to medicines (largely due to financial incapacity) and low awareness among patients are thought to contribute to blindness caused by glaucoma.

Although this study provides data regarding monocular and bilateral blindness from all regions of Somalia, it may not be able to determine the actual prevalence due to its hospital-centered design. We believe that society-based studies are necessary to establish the exact prevalence.

Conclusion

Trauma is the most important cause of blindness due to national security conditions. The lack of a national healthcare system in Somalia is a notable factor in patients' late presentation to healthcare clinics for their medical problems and increases the rate of blindness. Considering that 80% of blindness is preventable and treatable according to WHO data, primary healthcare services should be established in Somalia and these centers should be encouraged to conduct screening programs. Public hospitals with free service should be established to reduce the growing problem of blindness. These centers should include treatment and follow-up clinics for low-income patients with diseases such as cataract, glaucoma, and diabetic retinopathy.

Ethics

Ethics Committee Approval: Approval for the study was obtained from the Somalia Mogadishu-Turkey Recep Tayyip Erdogan Training and Research Hospital Local Ethics Committee.

Peer-review: Externally peer reviewed.

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

References

1. Wolfram C, Schuster AK, Elflein HM, Nickels S, Schulz A, Wild PS, Beutel ME, Blettner M, Münzel T, Lackner KJ, Pfeiffer N. The Prevalence of Visual Impairment in the Adult Population. Dtsch Arztebl Int. 2019;116:289-295.
2. Ramke J, Kuper H, Limburg H, Kinloch J, Zhu W, Lansingh VC, Congdon N, Foster A, Gilbert CE. Avoidable Waste in Ophthalmic Epidemiology: A Review of Blindness Prevalence Surveys in Low and Middle Income Countries 2000-2014. Ophthalmic Epidemiol. 2018;25:13-20.
3. Alghamdi HF. Causes of irreversible unilateral or bilateral blindness in the Al Baha region of the Kingdom of Saudi Arabia. Saudi J Ophthalmol. 2016;30:189-193.
4. Şahlı E, İdil A. Az Görmeye Genel Yaklaşım: Az Görenin Muayene ve Rehabilitasyonu. Turk J Ophthalmol. 2019;49:89-98.
5. Thylefors B, Négrel AD, Pararajasegaram R, Dadzie KY. Global data on blindness. Bull World Health Organ. 1995;73:115-121.
6. Resnikoff S, Pascolini D, Etya'ale D, Kocur I, Pararajasegaram R, Pokharel GP, Mariotti SP. Global data on visual impairment in the year 2002. Bull World Health Organ. 2004;82:844-851.
7. Cherinet FM, Tekalign SY, Anbesse DH, Bizuneh ZY. Prevalence and associated factors of low vision and blindness among patients attending St. Paul's Hospital Millennium Medical College, Addis Ababa, Ethiopia. BMC Ophthalmol. 2018;18:232.
8. Maake MM, Oduntan OA. Prevalence and causes of visual impairment in patients seen at Nkhensani Hospital Eye Clinic, South Africa. Afr J Prim Health Care Fam Med. 2015;7:728.
9. Harrell J, Larson ND, Menza E, Mboti A. A Clinic-based Survey of Blindness in Kenya. Community Eye Health. 2001;14:68-69.
10. Al-Bdour MD, Al-Till MI, Abu-Khader IB. Causes of blindness among adult Jordanians: a hospital-based study. Eur J Ophthalmol. 2002;12:5-10.
11. Bourne RRA, Flaxman SR, Braithwaite T, Cicinelli MV, Das A, Jonas JB, Keeffe J, Kempen JH, Leasher J, Limburg H, Naidoo K, Pesudovs K, Resnikoff S, Silvester A, Stevens GA, Tahhan N, Wong TY, Taylor HR; Vision Loss Expert Group. Magnitude, temporal trends, and projections of the global prevalence of blindness and distance and near vision impairment: a systematic review and meta-analysis. Lancet Glob Health. 2017;5:888-897.
12. Hsu WM, Cheng CY, Liu JH, Tsai SY, Chou P. Prevalence and causes of visual impairment in an elderly Chinese population in Taiwan: the Shihpai Eye Study. Ophthalmology. 2004;111:62-69.
13. Pascolini D, Mariotti SP. Global estimates of visual impairment: 2010. Br J Ophthalmol. 2012;96:614-618.
14. Kinderan YV, Shrestha E, Maharjan IM, Karmacharya S. Pattern of ocular trauma in the western region of Nepal. Nepal J Ophthalmol. 2012;4:5-9.
15. Argun Kıvanç S, Akova Budak B, Skrijelj E, Tok Çevik M. Türkiye'nin En Çok Endüstrileşmiş Bölgesindeki İşe Bağlı Açık Glob Yaralanmalarının Demografik Özellikleri ve Klinik Sonuçları. Turk J Ophthalmol. 2017;47:18-23.
16. Isawumi M, Ubah Jn, Olomola Bv, Afolabi Om. Blindness and Visual Impairment among Adults in a Tertiary Eye Clinic, in Osogbo S W Nigeria. Ann Med Health Sci Res. 2014;4:594-597.
17. Traoré J, Boitte JP, Omgbwa EA, Momo Zefack G, Perez D. Importance du handicap visuel dans une population de consultants en ophtalmologie: a propos de 828 cas à l'Institut d'Ophtalmologie tropicale de l'Afrique de Bamako [Extent of visual impairment in a population attending an ophthalmology center in Africa. Findings in 828 cases at the Tropical Ophthalmology Institute of Africa in Bamako, Mali]. Med Trop (Mars). 2006;66:477-480.
18. Zhang G, Tham YC, Gong H, Ren F, Morige J, Dai W, Cheng CY, Zhang H, Liu L. Blindness, low vision and cataract surgery outcome among adults in Hohhot of Inner Mongolia: a Rapid Assessment of Avoidable Blindness (RAAB) study. Br J Ophthalmol. 2018;102:1653-1657.
19. Özen Tunay Z, Idil A, Seza Petriçli İ, Özdemir Ö. Geriatrik Yaş Grubunda Az Görme Rehabilitasyonu. Turk J Ophthalmol. 2016;46:118-122.
20. Koç F, Erden V, Sefi-Yurdakul N. Causes of low vision and blindness in a Turkish adult population: the Izmir eye study. East Mediterr Health J. 2018;24:161-168.
21. Dineen B, Bourne RR, Jadoon Z, Shah SP, Khan MA, Foster A, Gilbert CE, Khan MD; Pakistan National Eye Survey Study Group. Causes of blindness and visual impairment in Pakistan. The Pakistan national blindness and visual impairment survey. Br J Ophthalmol. 2007;91:1005-1010.

22. Peters D, Bengtsson B, Heijl A. Lifetime risk of blindness in open-angle glaucoma. Am J Ophthalmol. 2013;156:724-730.
23. Xu L, Wang Y, Li Y, Wang Y, Cui T, Li J, Jonas JB. Causes of blindness and visual impairment in urban and rural areas in Beijing: the Beijing Eye Study. Ophthalmology. 2006;113:1134.
24. Gunnlaugsdottir E, Arnarsson A, Jonasson F. Prevalence and causes of visual impairment and blindness in Icelanders aged 50 years and older: the Reykjavik Eye Study. Acta Ophthalmol. 2008;86:778-785.

DOI: 10.4274/tjo.galenos.2020.38096
Turk J Ophthalmol 2020;50:293-303

Review

Current Management of Conjunctival Melanoma Part 1: Clinical Features, Diagnosis and Histopathology

İrem Koç, Hayyam Kıratlı

Hacettepe University Faculty of Medicine, Department of Ophthalmology, Ocular Oncology Service, Ankara, Turkey

Abstract

Conjunctival melanoma is a rare disease which makes up approximately 5% of ocular melanomas. The lesion may occur de novo or originate from a pre-existing nevus or primary acquired melanosis. Biomicroscopy is of paramount importance in diagnosis and follow-up of the disease, while other diagnostic modalities serve as supplementary tools. Many clinical and histopathological risk factors have been reported for prognosis. This review aims to address the clinical findings, differential diagnosis, diagnostic tools, prognostic factors, and staging of this disease.

Keywords: Conjunctival melanoma, diagnosis, prognosis

Introduction

Primary melanoma of the eye can occur in four different anatomical compartments of the globe: the orbit, eyelids, conjunctiva, and uvea (subdivided as the iris, ciliary body, and choroid). Conjunctival melanoma (CM) is considered an ocular surface neoplasia and accounts for 1-7% of all ocular melanomas, with an incidence rate nearly one-tenth of that of uveal melanoma in whites.[1] CM, which can arise from primary acquired melanosis (PAM), from an existing conjunctival nevus, or de novo, is derived from a malignant proliferation of melanocytes of neural crest origin that normally reside in the basal layer of the conjunctival epithelium.[2]

CM differs substantially in histopathology, genetic profile, and management from other ocular melanomas and is handled as a separate entity in clinical practice. Even so, in terms of histopathogenesis, molecular biology, and biological behavior such as distant metastatic pattern, CM lies biologically closer to mucosal and cutaneous melanomas than does a uveal melanoma.[3] The pattern of metastasis usually presents with spread to the regional lymph nodes first in CM and cutaneous melanoma, while uveal melanoma primarily tends to cause hematogenous metastasis to the liver.[4] Another common trait between CM and cutaneous melanoma is that they are derived from melanocytes of neural crest origin, which migrate toward epithelium, whereas the melanocytes that form uveal melanoma cells migrate into deep mesodermal tissue.

CM is a potentially sight- and life-threatening tumor if left untreated, with a 10-year mortality rate up to 30%.[4] Spread of the uncontrolled disease can manifest as local recurrence, involvement of distant conjunctiva, or distant metastasis through regional lymph nodes via involvement of blood vessels or lymphatics located in the substantia propria of the conjunctiva.[1] All considered, CM requires appropriate management in line with the recent advances in our understanding of this disease.

Address for Correspondence: İrem Koç, M.D., Hacettepe University Faculty of Medicine, Department of Ophthalmology, Ocular Oncology Service, Ankara, Turkey
Phone:+90 533 424 20 00 E-mail: kocirem@gmail.com **ORCID-ID:** orcid.org/0000-0001-9370-6173
Received: 04.03.2020 **Accepted:** 07.04.2020

Cite this article as: Koç İ, Kıratlı H. Current Management of Conjunctival Melanoma Part 1: Clinical Features, Diagnosis and Histopathology. Turk J Ophthalmol. 2020;50:293-303

Epidemiology

The current epidemiological data for CM shows an incidence of 0.2-0.8 per million with a race predilection favoring non-Hispanic whites, and even though it is a rare disease, there is an upwards trend in incidence which is mostly attributed to ultraviolet radiation exposure.[5] It is a disease of middle-aged individuals 55 to 65 years old, and is even rarer in childhood, where less than 1 in 20 conjunctival tumors are malignant. There is no proven sex predilection for CM. In large series of conjunctival specimens in tertiary referral centers, CM constitutes 12-25% of all excised conjunctival tumors and 23-25% of all excised melanocytic conjunctival lesions.[6] Population-based studies report a lower ratio, including a recent study from Olmsted County, Minnesota reporting 6 melanoma cases out of 504 patients with a conjunctival tumor.[7] Table 1 shows the incidences reported for CM in recent population-based studies involving Caucasian populations in the Western world.[3,7,8,9,10,11,12]

Clinical Findings

CM clinically presents as an elevated macule, plaque, nodule, or diffuse infiltration with varying pigmentation from light brown to dark brown, and in rare cases as an amelanotic mass (Figure 1). Recurrent lesions tend to be lighter compared to primary CM.[13] Any immobile, melanocytic conjunctival lesion with prominent vascularity should raise suspicion for CM. Nearly one third of CMs can be multifocal.[14] The most common location for CM is the peribulbar conjunctiva near the limbus, especially temporally.[4] Benign tumors are rarely seen in the extrabulbar conjunctiva (palpebral and forniceal conjunctiva)

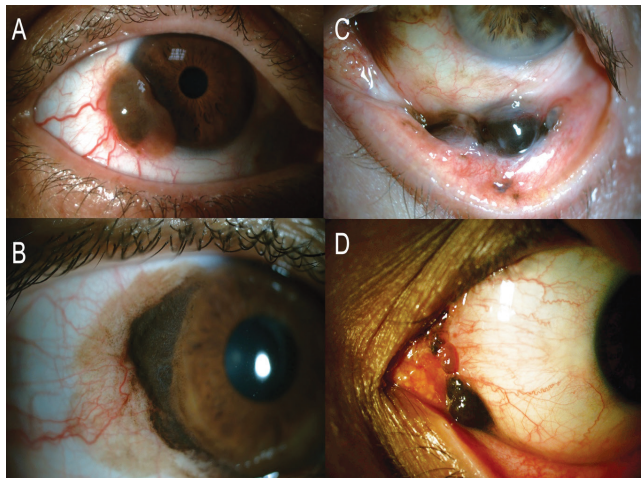


Figure 1. Anterior segment photography of various clinical presentations. A) A limbal, vascularized melanotic mass later proved to be CM. Note the finely vascularized amelanotic base and dilated conjunctival feeder vessels. B) A large limbal CM surrounded by diffuse PAM, which suggests PAM as the origin. C) Forniceal location of CM. D) CM involving the plica semilunaris and caruncle.

Table 1. Recent population-based studies of CM involving Caucasian populations in the Western World

Study group	Reported incidence rate	Details	Study population (years)	Location
Isager et al.[8]	For men: 0.78 (CI 0.74 to 0.82), for women: 0.65 (CI 0.61 to 0.68) per 100,000 person-years	Stable incidence for choroid, ciliary body and conjunctival melanomas, M=F	1943-1997	Denmark
Larsen[3]	As high as 2.12 per 1,000,000 (CI 1.23 to 3.65)	Increasing incidence over time, M=F, epibulbar> extrabulbar>caruncular, more frequent in sun-exposed areas	1960-2012	Denmark
Dalvin et al.[7]	1.5 per 1,000,000 (CI 0.3 to 2.8)	Analysis of incidence over time was not possible due to small number of patients, M=F	1980 -2015	Olmsted County, Minnesota
Missotten et al.[9]	0.05 per 100,000	Similar to the previously reported incidence of 0.05/100,000 in the Netherlands	1950-2002	The Netherlands (70% of CMs in the Netherlands)
Tuomalaa et al.[10]	0.51 per 1,000,000	Age-adjusted incidence increased from 0.4 to 0.8 during the study period. Similar increase curve in incidence of cutaneous melanoma.	1967-2000	Finland
Triay et al.[11]	In men: 0.74 per 1,000,000 In women: 0.45 per 1,000,000	Overall age-standardized incidence of CM showed a sevenfold increase (from 0.08 cases/million to 0.56 cases/million)	1960-2005	Sweden
Ghazawi et al.[12]	0.32 cases per 1,000,000 (0.35 and 0.29 per 1,000,000 for men and women, respectively)	North to south gradient of increasing incidence is consistent with literature for cutaneous melanoma. Incidence was stable over the studied years.	1992-2010	Canada

CI: Confidence interval, M: Male, F: Female

and caruncle, so any pigmented lesion in this area should raise suspicion for CM.

Differential Diagnosis

The differential diagnosis of CM includes other melanocytic lesions of the conjunctiva including conjunctival nevus, congenital melanosis, primary or secondary acquired melanosis, extraocular extension of uveal melanoma, metastatic CM of cutaneous origin,[15] pigmented squamous cell carcinoma or papilloma, sebaceous carcinoma, and oncocytoma. A variety of non-melanocytic entities such as Axenfeld nerve loop, pyogenic granuloma, infected epithelial inclusion cyst, post-surgical hematoma, mycosis, mascaroma, argyrosis, pinguecula, and foreign body are the other entities that can mimic CM. In all patients (including pediatric cases), older age, larger mean basal diameter, thicker tumors, hemorrhage, and absence of cysts favor CM rather than conjunctival nevus.[6] The co-occurrence of an intraocular tumor and a pigmented conjunctival lesion with spared conjunctival epithelium should initially suggest an extraocular extension of the intraocular tumor, because CM only invades the globe in the most advanced cases unless there is a facilitating wound such as previous sclerectomy or cataract incision.[16] Of the entities considered for differential diagnosis, PAM is of particular clinical importance and will be addressed separately below.

Primary Acquired Melanosis

PAM is considered the benign counterpart of CM and is the precursor lesion in 25-75% of CMs, while nearly 50% of PAM with atypia progress to CM.[17] PAM usually presents as unilateral patchy or diffuse superficial pigmentation of the epibulbar conjunctiva with or without waxing and waning (Figure 2). The rest of CM cases not associated with PAM arise from preexisting nevi or de novo, with only 1% of conjunctival nevi found to progress to CM after 7 years of follow-up.[2,15] Additionally, dysplastic nevus syndrome is another possible predisposing condition for CM, although a risk prediction or prognostication for CM or a direct link between the two diseases has yet to be determined. Studies of time trends in CM incidence have revealed that CM lesions have been detected at lower thicknesses and diameters over time, which suggests earlier diagnosis, but tumors as large as 40 mm in largest basal diameter and 15 mm in thickness are still reported in large series.[6]

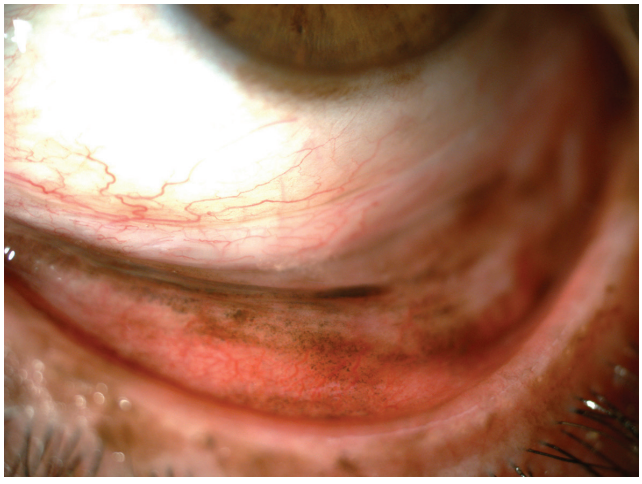


Figure 2. Eversion of the lower eyelid reveals diffuse PAM, especially in the tarsal conjunctiva. Note the additional limbal pigmentation.

In general, CM presents nearly a decade later than PAM, which correlates with the process of transformation into melanoma. Similarly, patients with PAM without atypia were found to be younger than those having PAM with atypia, though a similar pattern of progression among the latter two has yet to be determined in humans.[17] The differentiation of PAM with atypia and without atypia is based on histopathology only; however, clinical clues favoring CM versus PAM have been defined as: thickness more than 1 mm, lack of pigment, presence of feeder or intrinsic vessels, cysts, hemorrhage, older age, and tarsal location.[6]

The terminology for what is called PAM today has shifted over time, initially from precancerous melanosis to benign acquired melanosis, then to melanoma in situ,[18] and today PAM represents acquired melanosis with or without atypia.[16,17] Some centers have replaced the term PAM with conjunctival melanocytic intraepithelial neoplasm (C-MIN) with an additional histological grading system based on horizontal epithelial involvement, vertical depth of melanocytic infiltration, and degree of cellular atypia, where the lowest C-MIN score of 0 corresponds to melanosis, 1 corresponds to "PAM with mild atypia", 2 or 3 corresponds to "PAM with moderate atypia", 4 corresponds to "PAM with severe atypia", and a score of 5 or more corresponds to CM in situ.[19] In both cases, either PAM or C-MIN, the lesions are described clinically as flat, usually unilateral, patchy or diffuse, unifocal or multifocal, noncystic melanocytic lesions of the conjunctiva generally seen in Caucasians.

Based on current knowledge, it is now considered overtreatment to perform orbital exenteration, whereas this was once considered the main approach for these lesions.[18] The contemporary approach to PAM treatment lacks standardization and consists of close observation, excision alone or combined with cryotherapy, and topical chemotherapy with mitomycin C, 5-fluorouracil, or interferon-alpha-2-beta.[19] Additional mapping biopsies before commencing treatment may aid in determining the need for brachytherapy in tumors with a high C-MIN score, the extent of the disease (particularly in amelanotic disease),[19] and the degree of atypia at different locations, as the lesion may be multifocal. However, incisional or needle biopsies for CM should be avoided because these procedures are associated with tumor recurrence and iatrogenic seeding.[1] Impression cytology (IC) is also not recommended in melanocytic proliferations of the conjunctiva.[20] Our approach to PAM/C-MIN consists of total excision where possible and several incisional biopsies combined with topical 0.04% mitomycin C drops 4 times a day for 2 weeks followed by a 2-week drop-free period, for at least 2 cycles, targeting residual or resistant areas in more extensive cases. Extensive PAM or PAM with atypia should be approached

with vigilance, as PAM with atypia has a 13% risk of conversion to CM as opposed to 0% in PAM without atypia, and each clock hour increase in the extent of the lesion increases the likelihood of CM 1.7 times.[21] Histologically, PAM with atypia is considered to pose a higher risk of progression to melanoma with increasing number of epithelioid melanocytes and when there is intraepithelial pagetoid spread.[16] Additionally, the risk of progression to CM increases with increasing clinical extent of PAM.[21]

Histopathology

Detecting the atypical melanocytes of CM can be challenging, particularly when composed purely of small polyhedral cells. The pathological diagnosis of CM is made when atypical melanocytes are seen to invade the substantia propria, with loss of maturation and loss of normal polarity.[15] CM can be composed of 4 different cell types in variable proportions: small polyhedral cells, epithelioid cells, balloon cells, and spindle cells.[17] Features that favor melanoma rather than nevus histopathologically are intraepithelial component of PAM with atypia displaying pagetoid growth, intraepithelial radial extension beyond the lateral edge of invasion of the substantia propria, inflammation at the base of the lesion, mitotic activity, loss of normal polarity, and production of tyrosinase at the base of the lesion.[16] Invasion of the substantia propria is required for definitive diagnosis of CM; however, in both PAM and CM, atypical melanocytes can show nesting in the epithelial junction and pagetoid spread into the epithelium, where prominent atypical features such as nuclear pleomorphism, prominent nucleoli, atypical mitoses, and abundant cytoplasm favor CM.[16]

Diagnostic Tools

As for all conjunctival lesions raising suspicion for malignancy, the gold standard for CM diagnosis relies on histopathology.[22] However, there are some adjuvant diagnostic tools which aid in differential diagnosis.

a) Slit-lamp Biomicroscopy Documentation and Follow-up

Photographic documentation of the conjunctival melanocytic lesion should be carried out initially and at follow-up visits together with clinical mapping, expression of extent in clock minutes, and schematic drawing introduced by Damato et al.[23] A thorough slit-lamp examination and documentation of the following should be made at every visit: the eyelid skin, whole conjunctival surfaces including palpebral conjunctiva with eversion, forniceal conjunctiva, tarsal conjunctiva, caruncle, plica, puncta, and all other visible portions of bulbar and nonbulbar conjunctiva. Care should be taken to note corneal involvement, if any. Adherence of the tumor to the underlying structures should be tested using a cotton-tipped swab as it is both helpful in differential diagnosis and surgical planning. The preferred approach is to excise the lesion in total when CM is suspected; however, serial photographic and schematic documentation is crucial when monitoring a PAM lesion since it is not possible to clinically determine which PAM lesions will transform into CM.

b) Impression Cytology

There are few studies on IC of pigmented conjunctival lesions, including CM.[24,25] Of these, Paridaens et al.[25] reported 74% agreement between IC and histopathology in a 24-patient series including 9 cases of CM. Eight cases of CM were suitable for IC evaluation, and in 7 out of 8 cases IC confirmed later biopsy-proven CM, and 4 out of 7 cases of PAM with atypia were diagnosed accurately with IC.[25] Keijser et al.[24] reported 85% sensitivity, 78% specificity, 59% positive predictive value, and 93% negative predictive value for IC for conjunctival pigmented lesions in a study of 294 smears and 157 histological samples from 182 patients. They suggested prompt excision for grade 3 and 4 lesions in IC, but CM also developed within 6 months after IC in 35% of grade 0 lesions (insufficient material for diagnosis), 6% of grade 1 lesions (normal conjunctival cells), and 7% of grade 2 lesions (melanocytes with mild atypia).[24] In the light of these findings, because IC only evaluates superficial epithelial cells, leaving out deeper lesion components, and morphological changes could be induced in the samples with brush cytology, IC is not recommended in the current or 8th edition of the American Joint Committee on Cancer (AJCC) guideline.[20]

c) Dermoscopy

Dermoscopy is a method of in vivo microscopic visualization of particularly pigmented skin lesions. Recently in a series of dermoscopic visualizations of 147 conjunctival lesions, 8 were CM with brown pigmentation, and the defined dermoscopic pattern for these was irregularly distributed dots confluent in a structureless pattern.[26] In differentiation of CM from PAM, PAM lesions in this series had a diffuse distribution of dots, and as an indication of uninvolved episclera and sclera in the pigmented conjunctival lesions, they observed and described a "flag sign" of multiple epithelial folds of the pigmented lesion at the edge of the lesion.[26] Whether dermoscopy and digital surface dermoscopy would be complementary imaging for slit-lamp biomicroscopy remains controversial due to small sample sizes.

d) Pump-probe Microscopy

Pump-probe microscopy uses a two-colored pulse laser source to distinguish between different types of melanins with high spatial resolution. Wilson et al.[27] demonstrated qualitative and quantitative differentiation of melanin composition in conjunctival nevi, PAM, and CM.[27] The authors believed this imaging method aided in the detection of recurrences and evaluation of surgical margins by taking advantage of biological and photochemical properties.[27] Similarly, Robles et al.[28] reported 92.3% and 97.5% sensitivity and specificity, respectively, in the differentiation of invasive pigmented conjunctival lesions from noninvasive counterparts with this method.[28]

e) Anterior Segment Optical Coherence Tomography (AS-OCT)

Anterior segment optical coherence tomography is superior to ultrasound biomicroscopy (UBM) imaging in terms of

visualization of anterior chamber anatomy and imaging of the anterior border of the lesion, but it fails to demonstrate posterior layers of larger and pigmented tumors due to optical shadowing. With high-resolution OCT, which has increased scan depth and axial resolution, conjunctival nevi and CM are shown to display intensely hyperreflective basal epithelial layers, and CM is differentiated from nevi by the intense posterior shadowing seen with most CMs.[29]

f) *In vivo* Confocal Microscopy (IVCM)

In vivo confocal microscopy is an anterior segment imaging modality which utilizes near-infrared laser to collect the reflection at the same point as the light source. Its use is limited in CM since it provides no sense of depth or thickness, which is crucial in management of the disease. In CM, IVCM can display atypical, highly reflective cells with prominent nuclei and large nucleoli, such as in extrascleral extension of uveal melanoma. It can also be helpful to differentiate between PAM with and without atypia, as PAM with atypia shows a large network of dendritic cells and hyperreflective granules throughout the epithelium, while these are confined to the basal layer in PAM without atypia. As a diagnostic tool for CM, IVCM is reported to have 100% sensitivity and 78% specificity for diagnosis of conjunctival malignant tumors.[30] With IVCM, the presence of hyperreflective Langerhans cells mimicking malignant melanocytes is considered the main cause for misdiagnosis of malignant conjunctival tumors.[30]

g) Ultrasound Biomicroscopy (UBM)

The use of UBM in CM as a diagnostic tool involves defining the extent and thickness of the disease, visualizing the tumor margins, and ruling out intraocular invasion of CM or extraocular extension of uveal melanoma. Even though UBM provides better resolution of pigmented conjunctival lesions with less optical shadowing and offers a larger field of view compared to AS-OCT, the depth of penetration is still limited to 4-5 mm due to high-frequency transducers.

h) Photoacoustic Imaging

Photoacoustic imaging in vivo was recently described as a noninvasive tool for CM detection and growth monitoring in an animal model of CM in albino mice.[31] The principle relies on the photoacoustic signal intensity of melanin and the purpose is to perform a photoacoustic tomography. The authors concluded that the photoacoustic signal correlated well with total and melanotic tumor volume.[31] Still, this imaging method needs to be further confirmed in different clinical settings in human eyes with tumors of variable pigmentation and melanin content.

i) Metastatic Screening and Systemic Work-up

Upon clinical examination of CM, suspicion of deep invasion of the sclera or intraocular, orbital, or sinus invasion should prompt computer tomography (CT) or magnetic resonance imaging (MRI).[20] Anterior chamber angle invasion should readily be examined with gonioscopy and UBM is helpful in visualization of the anterior portion of the globe including the ciliary body and most anterior part of the sclera. Bowman's membrane acts as a natural barrier against deeper invasion of the cornea, so care should be taken to leave the membrane intact during surgical excision. Invasion of the nasolacrimal passage and any other surrounding tissue by CM is also possible with pagetoid spread. Because the substantia propria of the conjunctiva is loose connective tissue rich in blood vessels and lymphatics, metastasis of CM can occur via lymphatic or hematogenous routes. Primary sites for lymphatic metastasis are regional draining lymph nodes of head and neck, including the preauricular, posterior auricular, submandibular, and cervical lymph nodes.[32] Hematogenous dissemination can occur in virtually any part of the body but the most common sites for distant hematogenous metastasis are the lungs, brain, liver, and bones.[32,33] Distant metastases without involvement of regional lymphatics are not uncommon.[33] Accordingly, metastatic follow-up with annual chest X-ray and cranial MRI can be recommended in CM. The metastatic screening protocol of CM consists of clinical evaluation of the head and neck lymph nodes, liver function tests, liver ultrasound, chest X-ray, sentinel lymph node biopsy for lesions >2 mm with ulceration, and questioning nose bleeding, epiphora, change in smell sensation, and nasal obstruction, all repeated semi-anually.[34] The role of positron emission tomography/computed tomography (PET/CT) has been limited in CM. Currently it is not suggested as a preoperative metastasis screening modality but rather a helpful tool in follow-up or restaging of selected patients.

j) Sentinel Lymph Node Biopsy (SLNB)

In CM, the concept of regional metastasis in draining lymph nodes as a precursor of distant metastasis is partially invalidated by the fact that distant metastasis can occur without any clinical involvement of the lymph nodes.[3,33] Still, the micrometastatic state of the regional lymph nodes remains to be tested in these cases. The estimated cumulative incidence of 10-year lymph node metastasis in CM is between 11% and 28%, and 45% of those who develop metastasis of CM have initial metastasis to lymph nodes.[32] The rationale of SLNB is detection of lymphatic metastasis before it is clinically overt, assuming the patient will benefit from lymph node excision in terms of survival. In 2008, Tuomaala and Kivelä[35] proposed a guideline to determine the CMs deserving SLNB, in which they suggested performing SLNB on tumors with >2 mm thickness and nonlimbal location. Their suggestion was based on the evidence that the cumulative incidence of initial or systemic metastasis of tumors measuring no more than 2 mm in thickness was 5% at 10 years and nearly 20% at 5 years for tumors with >2 mm thickness, and the cumulative incidence of initial or systemic metastasis of limbal tumors was less than 10% at 10 years and nearly 20% for nonlimbal tumors at 5 years.[35] They performed SLNB at the time of excisional surgery.[35] In 2015, Aziz et al.[36] expanded the high-risk clinical and pathological characteristics that warrant SLNB to nonlimbal location, thickness >2 mm, ulceration on pathology, and >1 mitotic figures. Histopathologically, ulceration means the loss of epithelium over the tumor and is shown to be related to both lymph node and distant metastases.

Therefore, SLNB should also be considered in tumors showing ulceration even when the thickness is <2 mm. Intraoperative SLN assessment is recommended by some groups based on the proposal of better visualization of lymph nodes intraoperatively, but objected to by others to avoid a possible iatrogenic tumor dissemination, or to allow time for detailed histopathological evaluation for high-risk factors.[36,37] When a positive SLN is detected, neck dissection should be planned and depending on the extent of the disease, adjuvant therapy in the form of radiation treatment, chemotherapy, high-dose interferon, or biochemotherapy may be offered.[33] The positivity rate with SLNB in CM is 11% to 16%, and the reported false-negativity rate (i.e., the development of nodal metastasis during follow-up despite exclusion of micrometastasis with SLNB) is as low as 8%. However, a consensus is lacking on the definition of false-negativity in terms of duration of follow-up.[37] A recent study favoring SLNB was performed by Esmaeli et al.[38] where 31 of 88 consecutive patients underwent SLNB and positive SLN was significantly associated with worse disease-free survival. The authors concluded that SLN positivity was a strong predictor of prognosis and therefore SLNB is helpful in the classification of high-risk patients and nomination of those who will receive adjuvant treatment.[38]

Prognosis

To date, a large number of population-based or clinical studies have reported local recurrence rates, 5-year and 10-year survival rates, risk factors for local recurrence, and risk factors for distant metastasis. These factors, described mostly in the last decade, can be classified as clinical and histopathological.

a) Clinical

Local recurrence rates, mortality rates, and clinical factors associated with disease prognosis are listed in Table 2.[2,3,9,10,14,32,39,40,41,42,43,44,45,46] A recent publication of 70 patients associated light iris color and low tumor pigmentation, and low tumor pigmentation was found to be related to metastasis formation and death in both uni- and multivariate analyses.[47] Recurrence was associated with low tumor pigmentation in multivariate but not univariate analysis.[47] This was confirmed by a larger series of 444 CM patients, including 177 recurrent cases, in which low primary tumor pigmentation was linked to higher recurrence rate, recurrences with low pigmentation, and greater risk of metastases and death; however, recurrences with low pigmentation did not carry risk for increased metastases or death.[13]

b) Histopathological

Histopathological criteria for CM associated with worse prognosis and increased mortality are presence of tumor-associated lymphangiogenesis, lymphocytic infiltration of the tumor, tumor thickness more than 2 mm, presence of surface ulceration, increasing depth of invasion, absence of complete surgical clearance, mitotic figure count >5/10 high-power fields, pagetoid growth pattern, and absence of focal inflammation.[17] Origin of the CM has no direct effect on prognosis but CM arising from PAM has a tendency to recur.[17] The recurrence rate after excision of PAM with tumor-free surgical margins has been reported to be 26% in 5 years and 65% in 15 years.[2]

On a molecular level, chemokines and chemokine receptors have been studied as potential trophic factors for metastatic spread of several malignancies, including conjunctival melanoma.[48] Immunoreactive scores for chemokine receptors CXCR4 and CCR10 were shown to be related to progression of melanocytic conjunctival lesions towards CM with significant differences in nevi versus melanoma, and CXCR4 upregulation was found to be related to metastatic potential of CM.[48]

Staging

In order to clinically and histopathologically classify CM, a few decades ago the Clark-McGovern classification of cutaneous melanoma was adapted with partial success and certain limitations, mainly because the conjunctiva lacks a papillary dermis, unlike skin, and vertical growth of the lesion cannot be assessed properly. On a macroscopic level, the disease can be classified as focal/nodular or diffuse/widespread. Unlike CM without PAM, CM with PAM mostly exhibits other risk factors for metastasis such as melanocytic atypia and palpebral conjunctiva involvement; therefore, CM with and without PAM should be classified separately.

The most recent AJCC tumor (T), node (N), metastasis (M) classification system offers a classification for CM based on tumor location and size (T), lymph node status (N), and presence of metastasis (M) (Table 3).[20] In this classification system, lower T grades correlate with less extensive disease, and according to the 7th edition of the AJCC TNM classification, CM survival was found to correlate with local recurrence, lymph node metastasis, and death, with T1 tumors representing less risk than T2 and T3 disease.[49] The term Tis, standing for melanoma in situ, was first introduced in the 7th edition, together with separation of caruncular tumors from the rest of the nonbulbar locations, and further modifications made in the latest 8th edition include regarding Tis as a pathological diagnosis, reclassification of the depth of substantia propria invasion with a threshold of 2 mm in pathologic staging, and removal of biopsy criteria from the N0 category.[20] It is also advised that the term PAM should also be used clinically and the underlying process, whether melanosis or melanocytosis, together with the extent should be reported pathologically.[20]

Validation of the 8th edition of the AJCC classification of CM was conducted in a large-scale, multicenter international study including 288 eyes of 288 patients. The study confirmed higher mortality rates in cT2 and cT3 tumors than in cT1 as well as higher mortality rates in pT2 and pT3 tumors compared to pT1.[50] Furthermore, tumor thickness, ulceration, and tumor invasion but not caruncle or plica involvement were identified as independent risk factors for mortality.[50] Despite having a large cohort for such a rare cancer, this study lacked subgroup analysis and considered metastasis equivalent to mortality.

Table 2. Local recurrence, metastasis, and survival rates, prognostic factors of CM reported in the literature

Study group	Year	Reported local recurrence rates	Reported rates for metastasis	Reported mortality rates	Details	Unfavorable prognostic indicators for survival (S) or metastasis (M) (RM: Regional metastasis is used when specified in the study)	Unfavorable prognostic indicators for local recurrence (LR)
Larsen[3]	2016	48%	NA	NA	139 patients median age: 67 (14-100) years	• Extrabulbar location (S) • Local invasion (M) • T3 compared to T1 and T2 (M) • Fewer melanoma-related deaths in T1 • Local recurrence (M,S) • Incisional biopsy (M) • No adjuvant treatment (M,S) • Tumor thickness >2 mm (S), only in univariate analysis	• No adjuvant treatment • T-stage was not associated with LR
Sheng et al.[39]	2015	30%, 5-year recurrence-free survival: 58.3%	45%, 5-year metastasis-free survival: 51.3%	5-year overall survival: 65.5%	53 patients median follow-up: 37 (3-101) months	• Higher T stage (M,S) • Greater tumor thickness (M) • Local resection (M,S) • No adjuvant therapy (M,S) • Increase in involved quadrants (M)	• Higher T-stage • Greater tumor thickness • Local resection • No adjuvant therapy
Anastassiou et al.[40]	2002	49%	NA	24.6% died of disease-related causes, 5-year tumor-related mortality: 32%	69 patients median age: 60 (14-80) years median follow-up: 67 (15-360) months	• Location: palpebral conjunctiva, caruncle, plica or fornices (S) • Invasion deeper than substantia propria (S) • Incomplete excision (S) • Tumor with a nodular component • (Adjuvant therapy was not associated with M or S)	• Irregular pigmentation • Incomplete excision • Invasion deeper than substantia propria • Epithelioid tumor cells
Yousef and Finger[14]	2012	33% in 1-5 years	19%	12% of disease related causes, 2% of myocardial infarction	42 patients median age: 61 (9-90) years	• Thickness >0.5 mm (M) • Invasion of orbit, eyelid or sinuses (M) • CM rather than melanoma in situ (M) • Tumor recurrence (M) • Increasing clinical and pathological T stages (M)	• Tumors involving >1 quadrant • Thickness >0.5 mm • Increasing clinical and pathological T-stages • Tumor multifocality • Previously treated lesions
Shields et al.[2]	2011	NA	5- and 10-year rates: 19%, 25% for PAM origin; 10%, 26% for nevus origin; 35%, 49% for de novo CM	5- and 10-year rates: 5%, 9% for PAM origin; 0%, 9% for nevus origin; 17%, 35% for de novo CM	382 consecutive cases, 74% of PAM, 7% of nevus, 19% de novo origin median age: 62 years 40% pre-treated median follow-up: 52 months	• Tumors arising de novo (M,S) • Nodular tumor (M,S) • Palpebral location (M) • Orbital invasion (M) • Fornix location (S)	NA
Missotten et al.[9]	2005	112 patients in median 6.8 year-follow-up (0.1-51.5) 62.6%	21% regional metastasis, 25% distant metastasis (mean 4.37 years)	Tumor-related survival at 5, 10 and 15 years: 86.3%, 72%, 67%	194 patients median age: 58 years 30% orbital exenteration rate	• Increasing tumor thickness (RM,S) • Increasing tumor diameter (RM) • Non-epibulbar tumors (S) • Multifocal tumor (S)	• Non-epibulbar tumors • Less LR with excision + adjuvant radiotherapy • (LR was not affected by skip metastasis)
Tuomaala et al.[10]	2002	5-year cumulative proportion of LR: 0.36	NA	Melanoma-related 5- and 10-year mortalities: 0.20, 0.38	85 patients median age: 60 (20-90) years	• Non-limbal location (S) • Increasing tumor thickness (S) • Local recurrence (S) • Increasing largest basal diameter (S)	• Non-limbal location predicted shorter time to LR

Table 2 contiuned

Tuomaala and Kivelä[32]	2004	NA	20 patients (45% of them had RM first) 10-year incidence of RM: 11%, DM: 18%	NA	85 patients Median time from RM to DM: 1 year Median time from diagnosis to metastasis: 2.6 years Median time to RM: 2.3 years Median time to DM: 3.4 years	• Tumor thickness >2 mm (RM,DM) • Non-limbal tumors (DM) • (Initial RM had better survival than initial DM)	NA
Tuomaala et al.[41]	2007	36% 5- and 10-year cumulative probabilities: 34%, 36%	NA	Tumor-related death: 30% 5- and 10-year survival probabilities: 83%, 67%	70 tumors of 85 patients Median age: 60 (20-90) years	• Non-limbal location (S) • Recurrence (S) • Increase in tumor thickness (S)	• Shorter time to recurrence with: • Absence of epithelioid cells • Smaller mean diameter of 10 largest nucleoli • Increasing mitotic count • More frequent recurrence when in palpebral conjunctiva
Esmaeli et al.[42]	2012	NA	Regional metastasis: 16%, distant metastasis: 20%	23%	46 consecutive cases Median age: 62 years Median follow-up: 40 months	• Tumor thickness >2 mm (RM,S) • Histologic ulceration (RM,S) • Mitotic figure >1/mm (RM,S) • Vascular invasion (S) • Epithelioid cell type (S) • Microsatellitosis (S)	NA
Damato and Coupland[43]	2009	6 out of 40 developed recurrence	NA	11 patients died (4 metastasis-related death, 7 unrelated causes)	56 CM patients (40 primary). Mean age: 61 (24-88) years Median follow-up: 2.7 years for primary tumors	• Inadequate surgery (S)	• Medial tumors • Treatment without radiotherapy • Inadequate surgery
Werschnik and Lommatzsch[44]	2002	%52	11.8% regional metastasis, 20% distant metastasis	10-year survival rate: 62.5% based on all-cause mortality, 77.7% based on melanoma-related death	85 patients Mean age: 55.1 years	• •Patient age >55 years (S) • Higher TNM category (S) • Non-limbal location (S)	• Non-limbal location • Higher TNM grade • Excision alone (without adjuvant therapy)
Paridaens et al.[45]	1994	44.9% were recurrence-free	11.3% regional metastasis	5- and 10-year survival rates: 82.9%, 69.3%	256 consecutive cases	• Non-epibulbar tumors (S) • Mixed cell type (S) • Lymphatic invasion (S) • Multifocality in epibulbar tumors (S) • >4 mm thickness in non-epibulbar tumors (S)	NA
Abt et al.[46]	2019	NA	NA	5- and 10-year survival rates: 71.3%, 49.6%	Population-based retrospective study of 644 conjunctival melanoma cases Mean age at diagnosis: 62.1 years Mean follow-up: 6.4 years Mean survival time: 77.2 months	• Older age (S) • Male sex (S) • T4 tumors (S) • N1 tumors (S)	NA

NA: Not available, S: Survival, M: Metastasis, RM: Regional metastasis, DM: Distant metastasis, LR: Local recurrence, TNM: Tumor, node, metastasis

Table 3. TNM definitions according to 8th American Joint Committee on Cancer (AJCC) Classification for CM.[20]	
Clinical tumor category (c)	**Clinical tumor criteria**
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1 T1a T1b T1c T1d	Tumor of the bulbar conjunctiva <1 quadrant ≥1 to <2 quadrants ≥2 to <3 quadrants ≥3 quadrants
T2 T2a T2b T2c T2d	Tumor of the nonbulbar (forniceal, palpebral, tarsal) conjunctiva, and tumor involving the caruncle Non-caruncular, and ≤1 quadrant of the non-bulbar conjunctiva involved Non-caruncular, and >1 quadrant of the non-bulbar conjunctiva involved Caruncular, and ≤1 quadrant of the non-bulbar conjunctiva involved Caruncular, and >1 quadrant of the non-bulbar conjunctiva involved
T3 T3a T3b T3c T3d	Tumor of any size with local invasion Globe Eyelid Orbit Nasolacrimal duct and/or lacrimal sac and/or paranasal sinuses
T4	Tumor of any size with invasion of the central nervous system
N category	**N criteria**
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
M category	**M criteria**
M0	No distant metastasis
M1	Distant metastasis
Pathological tumor category (p)	**Pathological tumor kriteria**
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Melanoma confined to conjunctival epithelium
T1 T1a T1b	Tumor of the bulbar conjunctiva Tumor of the bulbar conjunctiva with invasion of the substantia propria, not more than 2.0 mm in thickness Tumor of the bulbar conjunctiva with invasion of the substantia propria, more than 2.0 mm in thickness
T2 T2a T2b	Tumor of the non-bulbar (forniceal, palpebral, tarsal) conjunctiva. and tumor involving the caruncle Tumor of the non-bulbar conjunctiva with invasion of the substantia propria, not more than 2.0 mm in thickness Tumor of the non-bulbar conjunctiva with invasion of the substantia propria, more than 2.0 mm in thickness
T3 T3a T3b T3c T3d	Tumor of any size with local invasion Globe Eyelid Orbit Nasolacrimal duct and/or lacrimal sac and/or paranasal sinuses
T4	Tumor of any size with invasion of the paranasal sinuses and/or central nervous system

Esmaeli[51] further emphasized pathologic factors such as tumor thickness and ulceration as prognostic predictors and suggested incorporating these factors into the AJCC classification. A detailed subgroup analysis of cumulative mortality between pT1a, pT1b, pT2a, and pT2b was also recommended in order to study the exact effect of tumor thickness on mortality.[51] Other authors have expanded the factors to be incorporated into future AJCC classifications by adding positive SLNB as a prognostic factor.[36,49] Tumor thickness and histologic ulceration were reported as the strongest predictors for nodal metastasis, distant metastasis, and melanoma-related death, rather than bulbar versus nonbulbar location and caruncular versus noncaruncular location.[38] This is in part due to the discrepancy between clinical and pathological classification of T-categories, where Tis can correspond to a broad range of clinical T-categories, T1, T2, and even T3.[38] This problem is overcome by excluding Tis from

metastasis analyses, which made it possible to purely study the effects of thickness and ulceration, as Tis lesions are not expected to cause distant metastases or death.[38] Overall, it is likely that tumor thickness and ulceration will be more distinctively incorporated in future AJCC classifications, similar to that of cutaneous melanoma.

Conclusion

Even though CM is regarded as a rare entity, it can have a severe impact on overall survival. Notably, the incidence rates are reported to show an increasing trend in some series. Biomicroscopy is indispensable in diagnosis, determination of additional features, and follow-up of the disease, whereas other imaging modalities can be used with their own limitations as adjunct tools. Metastatic work-up and SLNB should be conducted for the indications proposed in the literature. Staging is still in progress as new prognostic factors are defined to develop more precise indicators for overall survival.

Ethics

Peer-review: Externally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: H.K., İ.K., Concept: H.K., İ.K., Design: İ.K., Data Collection or Processing: İ.K., Analysis or Interpretation: İ.K., Literature Search: İ.K., Writing: H.K., İ.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. Lim LA, Madigan MC, Conway RM. Conjunctival melanoma: a review of conceptual and treatment advances. Clin Ophthalmol. 2013;6:521-531.
2. Shields CL, Markowitz JS, Belinsky I, Schwartzstein H, George NS, Lally SE, Mashayekhi A, Shields JA. Conjunctival melanoma: outcomes based on tumor origin in 382 consecutive cases. Ophthalmology. 2011;118:389-395.
3. Larsen AC. Conjunctival malignant melanoma in Denmark. Epidemiology, treatment, and prognosis with special emphasis on tumorigenesis and genetic profile. Acta Ophthalmol. 2016;94:1-27.
4. Seregard S. Conjunctival melanoma. Surv Ophthalmol. 1998;42:321-350.
5. Yu GP, Hu DN, McCormic S, Finger PT. Conjunctival melanoma: is it increasing in the United States? Am J Ophthalmol. 2003;135:800-806.
6. Shields CL, Alset AE, Boal NS, Casey MG, Knapp AN, Sugarman JA, Schoen MA, Gordon PS, Douglass AM, Sioufi K, Say EA, Shields JA. Conjunctival tumors in 5002 cases. Comparative analysis of benign versus malignant counterparts. The 2016 James D. Allen lecture. Am J Ophthalmol. 2017;173:106-133.
7. Dalvin LA, Salomão DR, Patel SV. Population-based incidence of conjunctival tumours in Olmsted County, Minnesota. Br J Ophthalmol. 2018;102:1728-1734.
8. Isager P, Østerlind A, Engholm G, Heegaard S, Lindegaard J, Overgaard J, Storm HH. Uveal and conjunctival malignant melanoma in Denmark, 1943-97: incidence and validation study. Ophthalmic Epidemiol. 2005;12:223-232.
9. Missotten GS, Keijser S, De Keizer RJ, De Wolff-Rouendaal D. Conjunctival melanoma in the Netherlands: a nationwide study. Invest Ophthalmol Vis Sci. 2005;46:75-82.
10. Tuomaala S, Eskelin S, Tarkkanen A, Kivelä T. Population-based assessment of clinical characteristics predicting outcome of conjunctival melanoma in whites. Invest Ophthalmol Vis Sci. 2002;43:3399-3408.
11. Triay E, Bergman L, Nilsson B, All-Ericsson C, Seregard S. Time trends in the incidence of conjunctival melanoma in Sweden. Br J Ophthalmol. 2009;93:1524-1528.
12. Ghazawi FM, Darwich R, Le M, Jfri A, Rahme E, Burnier JV, Sasseville D, Burnier MN Jr, Litvinov IV. Incidence trends of conjunctival malignant melanoma in Canada. Br J Ophthalmol. 2019;104:23-25.
13. Brouwer NJ, Marinkovic M, Luyten GPM, Shields CL, Jager MJ. Pigmentation of conjunctival melanoma recurrences and outcome. Graefes Arch Clin Exp Ophthalmol. 2019;257:1783-1788.
14. Yousef YA, Finger PT. Predictive value of the seventh edition American Joint Committee on Cancer staging system for conjunctival melanoma. Arch Ophthalmol. 2012;130:599-606.
15. Brownstein S. Malignant melanoma of the conjunctiva. Cancer Control. 2004;11:310-316.
16. Jakobiec FA, Folberg R, Iwamoto T. Clinicopathologic characteristics of premalignant and malignant melanocytic lesions of the conjunctiva. Ophthalmology. 1989;96:147-166.
17. Folberg R, McLean IW, Zimmerman LE. Malignant melanoma of the conjunctiva. Hum Pathol. 1985;16:136-143.
18. Zimmerman LE. Criteria for management of melanosis. Arch Ophthalmol. 1966;76:307-308.
19. Kenawy N, Lake SL, Coupland SE, Damato BE. Conjunctival melanoma and melanocytic intra-epithelial neoplasia. Eye (Lond). 2013;27:142-152.
20. Coupland SE, Barnhill R, Conway RM, Damato BE, Esmaeli B, Albert DM, Auw-Hädrich C, Chévez-Barrios P, Grossniklaus HE, Heegaard S, Holbach LM, Kivelä T, Pavlick AC, Pe'er C, Shields C, Singh AD, Wittekind CW, Williams MD, Prieto VG, Finger PT. Conjunctival melanoma. In: Amin MB, Edge SB, Greene FL, Byrd DR, Brookland RK, Washington MK, Gershenwald JE, Compton CC, Hess KR, Sullivan DC, Jessup JM, Birerley JD, Gaspar LE, Schilsky RL, Balch CM, Winchester DP, Asare EA, Madera M, Gress DM, Meyer LR, eds. AJCC Cancer Staging Manual (8th ed). Switzerland; Springer; 2017:795-803.
21. Shields JA, Shields CL, Mashayekhi A, Marr BP, Benavides R, Thangappan A, Phan L, Eagle RC Jr. Primary acquired melanosis of the conjunctiva. Risks for progression to melanoma in 311 eyes The 2006 Lorenz E Zimmerman Lecture. Ophthalmology. 2008;115:511-519.
22. Kocaoglu FA. Biopsy in ocular oncology. Turk J Ophthalmol. 2014;44:49-54.
23. Damato B, Coupland SE. Clinical mapping of conjunctival melanomas. Br J Ophthalmol. 2008;92:1545-1549.
24. Keijser S, van Luijk CM, Missotten GS, Veselic-Charvat M, de Wolff-Rouendaal D, de Keizer RJ. Predictive value of exfoliative cytology in pigmented conjunctival lesions. Acta Ophthalmol Scand. 2006;84:188-191.
25. Paridaens AD, McCartney AC, Curling OM, Lyons CJ, Hungerford JL. Impression cytology of conjunctival melanosis and melanoma. Br J Ophthalmol. 1992;76:198-201.
26. Cinotti E, La Rocca A, Labeille B, Grivet D, Tognetti L, Lambert V, Kaspi M, Nami N, Fimiani M, Perrot JL, Rubegni P. Dermoscopy for the diagnosis of conjunctival lesions. Dermatol Clin. 2018;36:439-449.
27. Wilson JW, Vajzovic L, Robles FE, Cummings TJ, Mruthyunjaya P, Warren WS. Imaging microscopic pigment chemistry in conjunctival melanocytic lesions using pump-probe laser microscopy. Invest Ophthalmol Vis Sci. 2013;54:6867-6876.
28. Robles FE, Wilson JW, Warren WS. Quantifying melanin spatial distribution using pump-probe microscopy and a 2-D morphological autocorrelation transformation for melanoma diagnosis. J Biomed Opt. 2013;18:120502.
29. Nanji AA, Sayyad FE, Galor A, Dubovy S, Karp CL. High-resolution optical coherence tomography as an adjunctive tool in the diagnosis of corneal and conjunctival pathology. Ocul Surf. 2015;13:226-235.
30. Cinotti E, Singer A, Labeille B, Grivet D, Rubegni P, Douchet C, Cambazard F, Thuret G, Gain P, Perrot JL. Handheld in vivo reflectance confocal microscopy for the diagnosis of eyelid margin and conjunctival tumors. JAMA Ophthalmol. 2017;135:845-851.
31. Khattak S, Gupta N, Zhou X, Pires L, Wilson BC, Yucel YH. Non-invasive

dynamic assessment of conjunctival melanomas by photoacoustic imaging. Exp Eye Res. 2019;179:157-167.
32. Tuomaala S, Kivelä T. Metastatic pattern and survival in disseminated conjunctival melanoma: implications for sentinel lymph node biopsy. Opthalmology. 2004;111:816-821.
33. Esmaeli B. Wang X. Youssef A, Gershenwald JE. Patterns of regional and distant metastasis in patients with conjunctival melanoma: experience at a cancer center over four decades. Ophthalmology. 2001;108:2101-2105.
34. Missotten GS, de Wolff-Rouendaal D, de Keizer RJ. Screening for conjunctival melanoma metastasis: literature review. Bull Soc Belge Ophtalmol. 2007;306:23-30.
35. Tuomaala S, Kivelä T. Sentinel lymph node biopsy guidelines for conjunctival melanoma. Melanoma Res. 2008;18:235.
36. Aziz HA, Gastman BR, Singh AD. Management of conjunctival melanoma: critical assessment of sentinel lymph node biopsy. Ocul Oncol Pathol. 2015;1:266-273.
37. Cohen VML, Tsimpida M, Hungerford JL, Jan H, Cerio R, Moir G. Prospective study of sentinel lymph node biopsy for conjunctival melanoma. Br J Ophthalmol. 2013;97:1525-1529.
38. Esmaeli B, Rubin ML, Xu S, Goepfert RP, Curry JL, Prieto VG, Ning J, Tetzlaff MT. Greater tumor thickness, ulceration, and positive sentinel lymph node are associated with worse prognosis in patients with conjunctival melanoma: implications for future AJCC classifications. Am J Surg Pathol. 2019;43:1701-1710.
39. Sheng X, Li S, Chi Z, Si L, Cui C, Mao L, Lian B, Tang B, Wang X, Yan X, Kong Y, Dai J, Guo J. Prognostic factors for conjunctival melanoma: a study in ethnic Chinese patients. Br J Ophthalmol. 2015;99:990-996.
40. Anastassiou G, Heiligenhaus A, Bechrakis N, Bader E, Bornfeld N, Steuhl KP. Prognostic value of clinical and histopathological parameters in conjunctival melanomas: a retrospective study. Br J Ophthalmol. 2002;86:163-167.
41. Tuomaala S, Toivonen P, Al-Jamal R, Kivelä T. Prognostic significance of histopathology of primary conjunctival melanoma in Caucasians. Curr Eye Res. 2007;32:939-952.
42. Esmaeli B, Roberts D, Ross M, Fellman M, Cruz H, Kim SK, Prieto VG. Histologic features of conjunctival melanoma predictive of metastasis and death (an American Ophthalmological thesis). Trans Am Ophthalmol Soc. 2012;110:64-73.
43. Damato B, Coupland SE. An audit of conjunctival melanoma treatment in Liverpool. Eye (Lond). 2009;23:801-809.
44. Werschnik C, Lommatzsch PK. Long-term follow-up of patients with conjunctival melanoma. Am J Clin Oncol. 2002;25:248-255.
45. Paridaens AD, Minassian DC, McCartney AC, Hungerford JL. Prognostic factors in primary malignant melanoma of the conjunctiva: a clinicopathological study of 256 cases. Br J Ophthalmol. 1994;78:252-259.
46. Abt NB, Zhao J, Huang Y, Eghrari AO. Prognostic factors and survival for malignant conjunctival melanoma and squamous cell carcinoma over four decades. Am J Otolaryngol. 2019;40:577-582.
47. Brouwer NJ, Marinkovic M, Luyten GPM, Shields CL, Jager MJ. Lack of tumour pigmentation in conjunctival melanoma is associated with light iris colour and worse prognosis. Br J Ophthalmol. 2019;103:332-337.
48. van Ipenburg JA, de Waard NE, Naus NC, Jager MJ, Paridaens D, Verdijk RM. Chemokine receptor expression pattern correlates to progression of conjunctival melanocytic lesions. Invest Ophthalmol Vis Sci. 2019;60:2950-2957.
49. Shields CL, Kaliki S, Al-Dahmash S, Lally SE, Shields JA. American Joint Committee on Cancer (AJCC) clinical classification predicts conjunctival melanoma outcomes. Ophthalmic Plast Reconstr Surg. 2012;5:313-323.
50. Jain P, Finger PT, Damato B, Coupland SE, Heimann H, Kenawy N, Brouwer NJ, Marinkovic M, Van Duinen SG, Caujolle JP, Maschi C, Seregard S, Pelayes D, Folgar M, Yousef YA, Krema H, Gallie B, Calle-Vasquez A; American Joint Committee on Cancer Ophthalmic Oncology Task Force. Multicenter, international assessment of the eighth edition of the American Joint Committee on Cancer Cancer Staging Manual for conjunctival melanoma. JAMA Ophthalmol. 2019;137:905-911.
51. Esmaeli B. Inclusion of histologic ulceration and tumor thickness in future American Joint Committee on Cancer T category definitions for conjunctival melanoma. JAMA Ophthalmol. 2019;137:912-913.

DOI: 10.4274/tjo.galenos.2020.47568
Turk J Ophthalmol 2020;50:304-307

Case Report

Cytomegalovirus Endotheliitis After Penetrating Keratoplasty

Tuna Çelik Büyüktepe*, Nilüfer Yalçındağ**

*Dr. Nafiz Körez Sincan State Hospital, Clinic of Ophthalmology, Ankara, Turkey
**Ankara University Faculty of Medicine, Department of Ophthalmology, Ankara, Turkey

Abstract

Cytomegalovirus (CMV)-related corneal endotheliitis is an inflammation of the corneal endothelium caused by CMV. It may occur de novo or after ocular surgery in otherwise healthy individuals. In patients who have undergone keratoplasty, the differential diagnosis of viral endotheliitis and immune-related graft rejection is challenging due to the similar clinical findings. Here we report a patient who underwent penetrating keratoplasty and was using local and systemic immunosuppressive agents due to previous history of graft rejection. At postoperative year 4, ophthalmologic examination revealed localized corneal edema, coin-shaped keratic precipitates, and increased intraocular pressure, consistent with viral endotheliitis. Polymerase chain reaction revealed CMV-DNA amplification in the aqueous humor sample. Valganciclovir treatment was started and the symptoms improved in 2 months. It should be kept in mind that local or systemic immunosuppressants used after keratoplasty may trigger CMV reactivation. Anti-CMV treatment should be initiated immediately in patients with coin-shaped keratic precipitates.

Keywords: Penetrating keratoplasty, cytomegalovirus, viral endotheliitis, graft rejection

Introduction

Viral endotheliitis is endothelial inflammation and damage characterized by corneal edema, keratic precipitates (KPs), mild anterior chamber reaction, and elevated intraocular pressure (IOP).[1] The main causative agents are herpes simplex virus (HSV), varicella zoster virus (VZV), mumps virus, and cytomegalovirus (CMV).[2]

CMV-associated endotheliitis can occur de novo or secondary to ocular surgery in immunocompetent individuals.[3] Although KPs with typical location and appearance (coin-shaped) facilitate the differential diagnosis, it is mainly confirmed by isolation of viral antibodies or DNA in the aqueous humor by polymerase chain reaction (PCR).[4] CMV endotheliitis after keratoplasty may be misdiagnosed as graft rejection; therefore, deciding on the treatment protocol can be challenging. Corneal vascularization accompanying stromal edema, different KP pattern, and quick response to steroid therapy are clinical signs of immune-related graft rejection.[5]

This report describes a case of CMV endotheliitis that occurred at postoperative 4 years after partial penetrating keratoplasty (PPK) in a patient with a history of graft rejection and under immunosuppressive therapy. The aim is to provide information to differentiate two clinical entities which are frequently confused and raise our colleagues' awareness of CMV endotheliitis.

Address for Correspondence: Tuna Çelik Büyüktepe, M.D., Dr. Nafiz Körez Sincan State Hospital, Clinic of Ophthalmology, Ankara, Turkey
Phone:+90 506 631 81 07 E-mail: tuna_clk@yahoo.co.uk **ORCID-ID:** orcid.org/0000-0002-2383-0029
Received: 29.12.2019 **Accepted:** 06.04.2020

Cite this article as: Çelik Büyüktepe T, Yalçındağ N. Cytomegalovirus Endotheliitis After Penetrating Keratoplasty. Turk J Ophthalmol. 2020;50:304-307

Case Report

A 42-year-old man presented to our hospital with complaint of low vision in both eyes. His past medical history revealed severe ocular itching and redness in childhood suggesting ocular allergy, and his vision had declined over the last 12 years. On ophthalmological examination, his best corrected visual acuity (BCVA) was counting fingers from 2 meters in the right eye and 0.2 in the left eye. On anterior segment examination, total corneal opacity was observed in the right eye (Figure 1) and near total opacity in the left eye. Intraocular pressure (IOP) was 15 mmHg in the right eye and 14 mmHg in the left eye. Because posterior segment evaluation of the right eye was limited by dense corneal opacity, ocular ultrasonography was performed and revealed no pathology. Fundoscopy of the left eye was normal.

The patient was diagnosed as having vernal keratoconjunctivitis-associated corneal scar and underwent PPK in the right eye. After uncomplicated PPK surgery, the patient received topical ofloxacin drops 5 times a day, dexamethasone drops 5 times a day, chloramphenicol ointment twice a day, and 200 mg oral cyclosporine-A. In the early postoperative period, the graft was clear, BCVA was 0.5, and IOP was 14 mmHg (Figure 2). The corneal sutures were removed at postoperative 12 months. Decreased vision (0.4), graft edema, and medium-sized KP in the graft center were first observed at 18-month follow-up. Suspecting immune-mediated graft rejection, the topical steroid dose was increased and intravenous pulse methylprednisolone (250 mg 4 times a day for 3 days) was added to the current immunosuppressant treatment. At 1 week after pulse steroid therapy, the KPs dissappeared, graft edema resolved, and BCVA increased to 0.5.

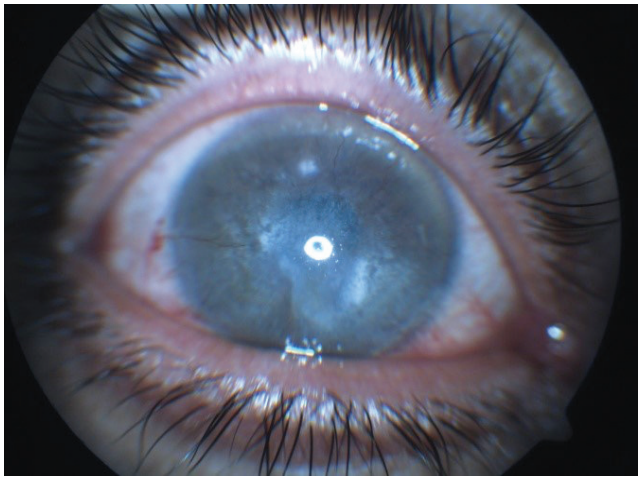


Figure 1. An anterior segment photograph of the patient before keratoplasty shows vernal keratoconjunctivitis scar

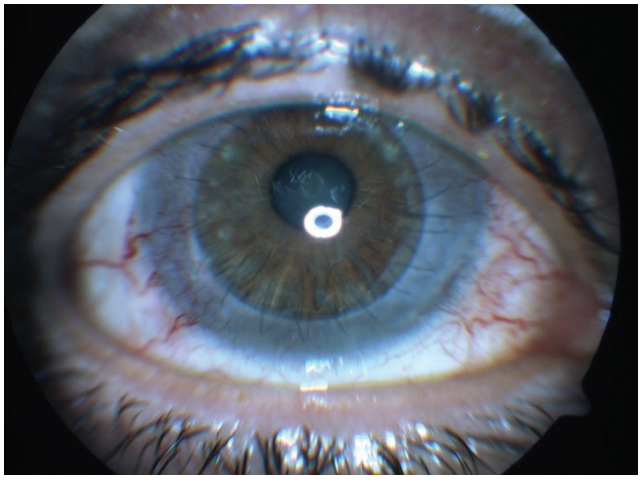


Figure 2. The graft is clear in the early period after partial penetrating keratoplasty

At postoperative year 4, the cyclosporine therapy was discontinued gradually. Three months later, his BCVA had declined again to 0.4. On anterior segment examination, coin-shaped KPs and corneal edema were observed in the paracentral area of the graft cornea (Figure 3). Additionally, mild anterior chamber reaction (+1) was present and IOP was elevated to 30 mmHg. Viral endotheliitis was suspected and etiological agents were investigated by performing anterior chamber paracentesis and PCR analysis. CMV-DNA was isolated in the aqueous humor. The patient was started on oral valganciclovir 900 mg twice a day, topical dexamethasone drops 5 times a day, ganciclovir gel 5 times a day, and topical dorzolamide-timolol drop twice a day. After 2 months of follow-up, graft edema and anterior chamber reaction had resolved and IOP was under control with topical antiglaucomatous treatment.

Discussion

Ocular CMV infection, especially retinitis, occurs in patients with a suppressed T-cell-related immune response due to acquired immunodeficiency syndrome (AIDS) or organ transplantation.[6] On the other hand, in immunocompetent patients, mainly the anterior segment is affected in the form of anterior uveitis or endotheliitis. CMV-associated endotheliitis presents with corneal endothelial damage due to the intense viral load in the aqueous fluid. Clinical findings include local stromal edema,

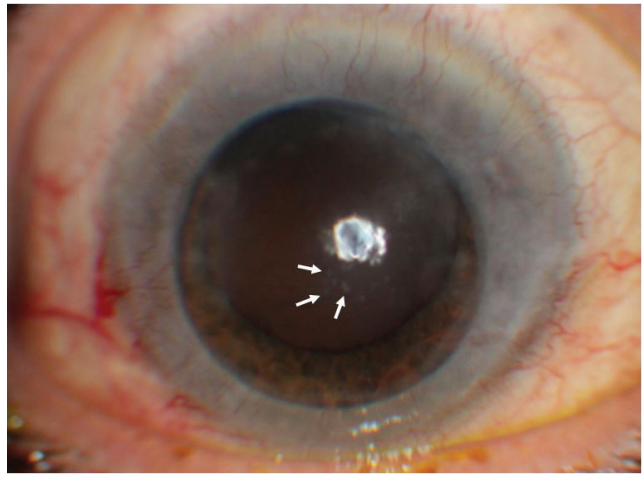


Figure 3. At postoperative 4 years, the patient under ongoing local and systemic immunosuppressive therapy developed coin-shaped keratic precipitates (arrows) in the central cornea and edema in the surrounding stroma

mild anterior chamber reaction, KP, elevated IOP, and stromal iris atrophy. Antiviral agents are used in treatment.[7]

Various cases of CMV endotheliitis after keratoplasty have been reported in the literature.[8,9,10] In such cases, differential diagnosis of corneal graft rejection and viral infection can be challenging due to the similar clinical findings of both diseases. Furthermore, CMV infection can lead to endothelial inflammation and trigger graft rejection.[11] Microbiological examination of the aqueous humor is diagnostic for CMV endetheliitis after PPK.[12] However, in cases where PCR cannot be performed, the typical pattern of KPs may also be helpful for differential diagnosis. Conversely, in immune-related graft rejection, KPs form a line along the edema margins called a "Khodadoust line". In CMV-related endotheliitis, KPs are usually coin-shaped and located in the center of the edema. Additionally, CMV-associated endotheliitis is often accompanied by anterior uveitis and elevated IOP. Immunosuppressive agents are effective in the treatment of immune-related graft rejection, whereas antiviral therapies such as ganciclovir or foscarnet can provide clinical improvement in CMV-associated endotheliitis.[1] Our patient developed epithelial defect and corneal edema at postoperative 18 months under topical steroid and systemic cyclosporine treatment, and was diagnosed as graft rejection. At that time, the absence of anterior chamber reaction or typical endothelial plaque, normal IOP, symptom relief after intensive steroid administration without antiviral therapy, and the long-term disease-free period ruled out the diagnosis of CMV endotheliitis. However, at postoperative 4 years, CMV endotheliitis was suspected due to localized stromal edema accompanied by coin-shaped KPs and anterior chamber reaction, and the diagnosis was confirmed by PCR.

The source of CMV infection is uncertain in patients who underwent keratoplasty. It may arise from the donor tissue or be caused by reactivation of a preexisting CMV infection in the host.[1] Although donors are routinely evaluated for hepatitis virus and human immunodeficiency virus (HIV) serology before corneal transplantation, CMV serology is usually unknown. Therefore, transmission may occur from a CMV-positive donor cornea to a CMV-negative host. However, it was thought to occur rarely.[13] Additionally, although the mean incubation period for donor-derived viral endotheliitis after corneal transplantation is not certain yet, systemic CMV infection is known to begin within 6 weeks to 6 months.[14] Similarly, in CMV retinitis the symptoms usually appear early at post-transplantation 9 months.[6] Therefore, CMV-associated endotheliitis is expected to present clinical signs and symptoms at early post-transplantation period. Another possible mechanism of CMV infection is reactivation of latent CMV virus in the host tissue. The topical or systemic immunosuppressive therapy used after keratoplasty may lead to CMV reactivation and endotheliitis.[1] In our patient, the preoperative CMV serology was unknown. Still, disease onset at postoperative year 4 and the patient's long-term use of immunosuppressive therapy suggest CMV reactivation. There was no evidence of retinitis or systemic CMV infection in our patient's ocular or systemic evaluations.

The ocular response to viral infections is mediated mainly by the cellular immune system. Zheng et al.[15] first inoculated rabbit eyes with an inactivated HSV, and then infected intracamerally with live HSV. They observed corneal endotheliitis and suspected anterior chamber-associated immune deviation in its pathogenesis. Accordingly, suppression of cellular immunity and T-cell-mediated delayed-type hypersensitivity results in loss of the antiviral protection, and the endothelial cells are damaged by the virus.[15] Similarly, Koizumi et al.[7] also reported that anterior chamber-associated immune deviation may play a role in CMV reactivation. The reason for CMV reactivation in the anterior chamber can be local and/or systemic immunosuppressive therapy.[1,6] Our patient also developed CMV endotheliitis after immunosuppressive therapy. In the literature, topical steroid use has been reported in 96% of patients with CMV endotheliitis, suggesting that local immunosuppression may also trigger CMV reactivation.[1]

In conclusion, CMV-associated corneal endotheliitis can occur in healthy individuals without systemic symptoms due to viral reactivation. In keratouveitis patients with corneal edema, coin-shaped KPs, and elevated IOP, CMV should be considered as a potential cause of viral endotheliitis in addition to HSVs and VZV. The isolation of viral DNA by PCR is very useful in differential diagnosis, and ganciclovir therapy should be initiated without delay.

Ethics

Informed Consent: Consent was obtained from the patient.

Peer-review: Externally peer reviewed.

Authorship Contributions

Surgical and Medical Procedures: N.Y., Concept: T.Ç.B., N.Y., Design: T.Ç.B., N.Y., Data Collection or Processing: T.Ç.B., Analysis or Interpretation: T.Ç.B., Literature Search: T.Ç.B., Writing: T.Ç.B., N.Y.

Conflict of Interest: The authors declare no conflicts of interest.

Financial Disclosure: The authors report receiving no financial support.

References

1. Koizumi N, Inatomi T, Suzuki T, Shiraishi A, Ohashi Y, Kandori M, Miyazaki D, Inoue Y, Soma T, Nishida K, Takase H, Sugita S, Mochizuki M, Kinoshita S; Japan Corneal Endotheliitis Study Group. Clinical features and management of cytomegalovirus corneal endotheliitis: analysis of 106 cases from the Japan corneal endotheliitis study. Br J Ophthalmol. 2015;99:54-58.
2. Moshirfar M, Murri MS, Shah TJ, Skanchy DF, Tuckfield JQ, Ronquillo YC, Birdsong OC, Hofstedt D, Hoopes PC. A Review of Corneal Endotheliitis and Endotheliopathy: Differential Diagnosis, Evaluation, and Treatment. Ophthalmol Ther. 2019;8:195-213.
3. Oray M, Tugal Tutkun İ. Sitomegalovirüs Ön Üveitlerinde Güncel Tanı ve Tedavi Yaklaşımı. Turkiye Klinikleri Ophthalmology-Special Topics. 2019;12:10-16.
4. Yesilirmak N, Akova AY, Eroğlu FC. Sitomegalovirüs Enfeksiyonuna Bağlı Gelişen Keratoüveit Tablosunda Klinik Bulgular Prognoz ve Tedavi Yaklaşımı. MN Oftalmoloji. 2011;18:3.
5. Chee SP, Jap A, Ling EC, Ti SE. Cytomegalovirus-positive corneal stromal edema with keratic precipitates after penetrating keratoplasty: a case-control study. Cornea. 2013;32:1094-1098.

6. Carmichael A. Cytomegalovirus and the eye. Eye. 2012;26:237-240.
7. Koizumi N, Suzuki T, Uno T, Chihara H, Shiraishi A, Hara Y, Inatomi T, Sotozono C, Kawasaki S, Yamasaki K, Mochida C, Ohashi Y, Kinoshita S. Cytomegalovirus as an etiologic factor in corneal endotheliitis. Ophthalmology. 2008;115:292-297.
8. Wehrly SR, Manning FJ, Proia AD, Burchette JL, Foulks GN. Cytomegalovirus keratitis after penetrating keratoplasty. Cornea. 1995;14:628-633.
9. Suzuki T, Hara Y, Uno T, Ohashi Y. DNA of cytomegalovirus detected by PCR in aqueous of patient with corneal endotheliitis after penetrating keratoplasty. Cornea. 2007;26:370-372.
10. Sonoyama H, Araki-Sasaki K, Osakabe Y, Nakamura M, Amano S, Koizumi N, Kinoshita S, Ideta H. Detection of cytomegalovirus DNA from cytomegalovirus corneal endotheliitis after penetrating keratoplasty. Cornea. 2010;29:683-685.
11. Shahrudin NA, Mohd Zahidin AZ, Md Noh UK, Wan Abdul Halim WH, Md Din N. CMV endotheliitis: a cause for recurrent failed corneal transplant. GMS Ophthalmol Cases. 2017;7:Doc31.
12. Miyazaki D, Shimizu D, Shimizu Y, Inoue Y, Inoue T, Higaki S, Ueta M, Sugita S; Real-time PCR for ocular cytomegalovirus infection study group. Diagnostic efficacy of real-time PCR for ocular cytomegalovirus infections. Graefes Arch Clin Exp Ophthalmol. 2018;256:2413-2420.
13. Holland EJ, Bennett SR, Brannian R, Osborne JC, Goeken JA, Krachmer JH. The risk of cytomegalovirus transmission by penetrating keratoplasty. Am J Ophthalmol. 1988;105:357-360.
14. Fishman JA, Rubin RH. Infection in organ-transplant recipients. N Engl J Med. 1998;338:1741-1751.
15. Zheng X, Yamaguchi M, Goto T, Okamoto S, Ohashi Y. Experimental corneal endotheliitis in rabbit. Invest Ophthalmol Vis Sci. 2000;41:377-385.

DOI: 10.4274/tjo.galenos.2020.94580
Turk J Ophthalmol 2020;50:308-312

Case Report

Unintentional Staining of the Anterior Vitreous With Trypan Blue During Cataract Surgery

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

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

Abstract

During phacoemulsification and intraocular lens (IOL) implantation surgery, the trypan blue dye used to stain the anterior capsule passed into vitreous cavity and stained the anterior capsule and anterior vitreous in 6 patients. There was history of trauma in 2 patients, uveitis in 1 patient, mature cataract in 1 patient, and no risk factors in the other patients. IOL was implanted in-the-bag without problem in 5 patients. In the patient with iris and zonular defects due to trauma, a sutured IOL was implanted in the same session. The migration of trypan blue into the vitreous cavity through damaged or intact lens zonules is a rare but important complication that makes subsequent surgical steps substantially more difficult.

Keywords: Trypan blue, phacoemulsification, vitreous

Introduction

Trypan blue is a dye that facilitates anterior lens capsule visualization and capsule manipulation during cataract surgery.[1,2] Trypan blue staining of the posterior capsule and anterior vitreous is uncommon; reports in the literature indicate that it may occur in eyes with ocular trauma, history of ocular surgery, or pseudoexfoliation.[3,4,5,6,7] Migration of dye to the posterior chamber and vitreous cavity through areas of zonular weakness has been implicated as the probable cause of anterior vitreous and posterior capsule staining.

The aim of this study was to present cases in which complete loss of the red reflex was observed due to trypan blue migrating to the posterior chamber and staining the posterior capsule and anterior vitreous during cataract surgery, and to evaluate this rare clinical picture.

Case Report

Six cases in which trypan blue stained the posterior capsule and anterior vitreous during cataract surgery performed in the ophthalmology department of Manisa Celal Bayar University Faculty of Medicine are presented (Table 1). Patient characteristics, surgical difficulties encountered, and features that facilitated the migration of trypan blue to the anterior vitreous are presented.

Address for Correspondence: Suzan Doğruya, M.D., Uşak University Training and Research Hospital, Clinic of Ophthalmology, Uşak, Turkey
Phone: +90 532 227 07 32 E-mail: sdogruya@hotmail.com **ORCID-ID:** orcid.org/0000-0002-6822-9077
Received: 04.12.2019 **Accepted:** 29.04.2020

Cite this article as: 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

Table 1. Characteristics of the patients in whom trypan blue used for capsule staining during cataract surgery dyed the anterior vitreous and posterior capsule (the fact that none of the patients used prostate medication was emphasized in the text and therefore was not included in the table). Clearance times could not be determined because the patients were followed up on an outpatient basis and were not hospitalized

Parameter	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Age, sex	62, F	39, M	62, F	76, M	61, M	60, M
Eye (right-left) Visual acuity	Left: CF30 cm	Right: 0.2	Left: CF50 cm	Left: 0.2	Left: LP	Left: CF20 cm
Risk factor	Uveitic eye	Trauma	None	None	Trauma	None
IOL power Axial length	22.0 D 22.5 mm	16.5 D 25.2 mm	22.0 D 22.6 mm	21.5 D 23.1 mm	22.0 D 23.2 mm	22.0 D 22.8 mm
Biomicroscopic risk factor	Posterior synechia, small pupil	Normal	Normal	Normal	Superior iris defect	Mature white cataract
Outcome	Phakic PC-IOL	Phakic PC-IOL	Phakic PC-IOL	Phakic PC-IOL	Sutured IOL, Anterior vitrectomy	Phakic PC-IOL
Postop VA (Snellen)	0.5	0.9	0.5	0.4	0.6	0.8
Iris retractor	Yes	None	None	None	None	None

F: Female, M: Male, CF: Counting fingers, LP: Light perception, IOL: Intraocular lens, D: Diopter, PC: Posterior chamber, VA: Visual acuity

Case 1

A 62-year-old woman had preoperative visual acuity of counting fingers from 30 cm, posterior synechia secondary to previous uveitic episodes, and nuclear cataract in the left eye (Figure 1). During cataract surgery, the anterior chamber was filled with dispersive-cohesive viscoelastic and iris retractors were used to provide pupil dilation and the capsule was stained with 0.06% trypan blue under viscoelastic. Anterior capsulorhexis was performed. No signs of zonular defect were encountered during the operative stages. While emulsifying the nucleus fragments, complete loss of the red reflex was observed (Figure 2). No anterior chamber shallowness or ocular rigidity that would suggest suprachoroidal hemorrhage was detected. Cortex aspiration was completed with the irrigation/aspiration cannula and a foldable IOL was implanted in the capsular sac (Figure 3a, b). The posterior capsule and anterior vitreous staining observed on biomicroscopic examination on postoperative day 1 decreased on day 2 and disappeared completely in the following days.

Case 2

A 39-year-old man had visual acuity of 0.2 in his right eye and extensive corticonuclear cataract on anterior segment examination. His history included information about ocular trauma. During cataract surgery, 0.06% trypan blue was administered to the anterior chamber under air and irrigated, and the anterior chamber was filled with a dispersive-cohesive viscoelastic substance. The red reflex was not observed during nucleus phacoemulsification, but the operative stages were completed without any problems. The IOL was inserted into the capsular sac without difficulty (Figure 4). The trypan blue staining disappeared with a few days after the operation without causing any surgical complications or problems in postoperative follow-up.

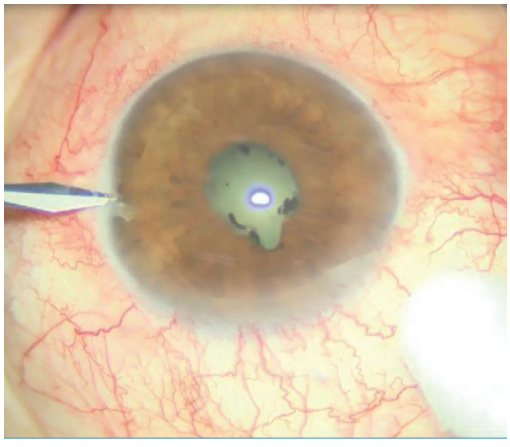


Figure 1. Posterior synechia, small pupil, and cataract reflex are observed in the peroperative initial appearance of our uveitic patient (patient 1)

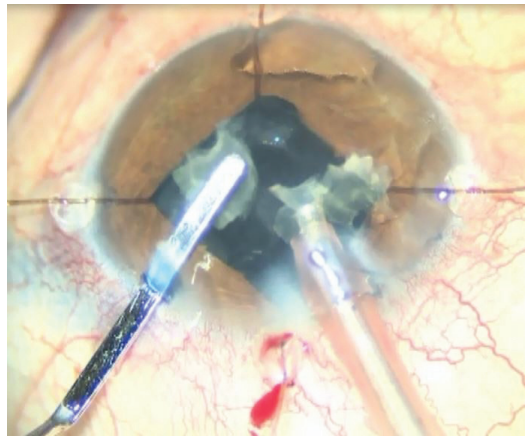


Figure 2. Disappearance of the fundus reflex is observed during phacoemulsification with iris retractors

Of the other cases, only the patient with ocular trauma (patient 5) exhibited atrophy in the upper half of the iris and zonular defect detected by ultrasound biomicroscopic imaging (UBM) in the preoperative evaluation performed due to the trauma (Figure 5). Trypan blue staining of the posterior capsule was attributed to the zonular defect in this patient.

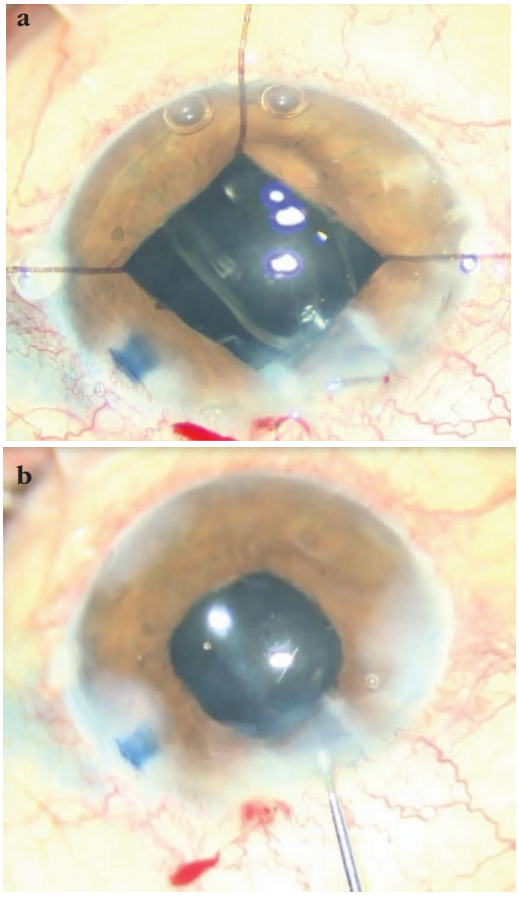


Figure 3. Intraocular lens placement (a) and appearance at the end of the operation (b)

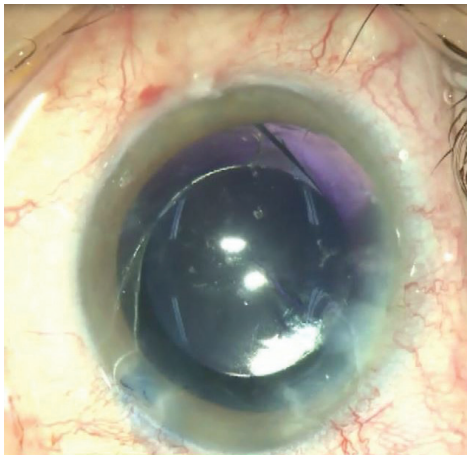


Figure 4. Trypan blue staining of the posterior capsule and anterior vitreous is observed (patient 2)

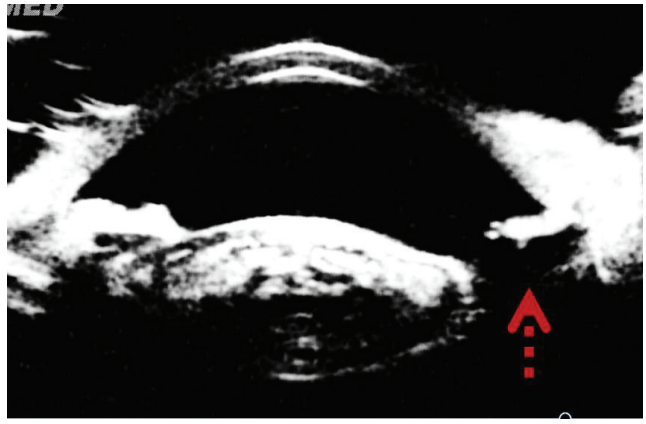


Figure 5. Ultrasound biomicroscopy reveals iris and zonular defects and lens opacity (patient 5). The red arrow indicates the area of zonular damage

In the uveitic patient, trypan blue staining was performed under viscoelastic. In the other patients, trypan blue was administered to the anterior chamber under air, irrigated, and the anterior chamber was filled with dispersive-cohesive viscoelastic (DisCoVisc OVD, Alcon, TX, USA). The patients showed no signs of phacodonesis, iridodonesis, or pseudoexfoliation.

In all patients, red reflex was absent on biomicroscopic examination on the first postoperative day, but the staining cleared rapidly. One week later, there was no sign of staining in the posterior segment and the retina could be evaluated easily. Postoperative UBM in 3 patients (patients 1-3) revealed no evidence of zonular damage.

Discussion

In case reports of inadvertent posterior capsule staining in the literature, this phenomenon occured in eyes with pseudoexfoliation, ocular trauma, or ocular surgery history, and it was suggested that zonular weakness may be responsible.[3,4,5,6,7] However, two published case reports demonstrated that trypan blue staining of the posterior capsule is also possible even in eyes without history of surgery or trauma; regarding the etiology, the administration of additional viscoelastic was posited to increase intraocular pressure and force the posterior migration of the dye through intact zonules.[8,9] In addition, the intraoperative use of iris retractors to dilate the pupil or stabilize a floppy iris may cause inadvertent staining of the posterior capsule. The authors proposed that this was because iris retractors lift the iris, thereby facilitating the passage of trypan blue through the intact zonules to the posterior chamber.[10] Anterior vitreous staining with trypan blue may occur in cases without pre- or intraoperative zonular dialysis but with peripheral iridotomy or conditions that may damage the anterior hyaloid surface or zonular apparatus.[11]

In our patient with uveitis and synechiae (patient 1), the use of an iris retractor due to small pupil may have facilitated trypan blue migration to the posterior chamber. In our patients with

history of trauma (patients 2 and 5), trypan blue staining of the anterior vitreous occured due to zonular damage. The absence of known risk factors in the other two patients (patients 3 and 4) suggests that the surgical method may also have caused dye migration through the intact zonules. In our patient with mature cataract (patient 6), although we noted no risk factors during surgery, staining of the anterior vitreous suggests abnormality in the zonular apparatus. None of our patients had a history of using prostate medication, so our patient group did not include iris atrophy and floppy iris.

Different methods have been recommended for more effective trypan blue staining of the anterior capsule with less toxicity to the endothelium. The purpose of staining under air is to protect the corneal endothelium. Alternative methods have been developed, such as staining the anterior capsule with trypan blue under viscoelastic, attaching iris retractors parallel to the iris plane without allowing iris elevation, injecting viscoelastic to the peripheral iridolenticular area to act as a barrier, and using a mixture of viscoelastic and trypan blue.[5,7,12,13,14]

The main purpose of staining under air is to prevent dye contact with the corneal endothelium and the potential toxic effects that can result. Better dyeing can be achieved under air because viscoelastic can block the dye from touching the anterior capsule. However, air bubbles are not stable and anterior chamber loss may occur while introducing the cannula into the anterior chamber for dye injection. A small amount of viscoelastic can be injected through the side port to prevent the air bubble escaping from the anterior chamber. The anterior capsule can also be stained with trypan blue under viscoelastic. Another alternative staining method may be to use a mixture of viscoelastic and trypan blue.

We chose to use a dispersive-cohesive viscoelastic agent in our patients because we anticipated that these may be difficult cases. Due to the greater space-maintaining property of this agent, it is possible it displaced the stain posteriorly. The longer dwell time in the anterior chamber and the stronger coating of the tissues and endothelial protection increased the success of our surgery.

In cataract surgery, it may be necessary to use iris retractors and trypan blue simultaneously. In this case, the retractors should be positioned parallel to the iris plane and iris tenting should be avoided. By injecting trypan blue under viscoelastic, which creates a confined space in the anterior chamber, the posterior migration of the dye under the iris can be prevented. The creation of a viscoelastic barrier to the peripheral iridolenticular space may also prevent posterior migration of dye. However, the desired degree of staining may not be achieved if sufficient contact with the anterior capsule is not ensured.

Retinal toxicity was not observed in our patients. However, it should not be forgotten that trypan blue in high concentrations (above 0.5%) may have toxic effects on the retina.[3,7,15,16]

In conclusion, trypan blue staining of the posterior capsule and anterior vitreous can occur during phacoemulsification in eyes with risk factors related to cataract surgery as well as in eyes with no zonular pathology. Trypan blue in the posterior segment causes no detectable early or late problems other than increasing the risk of surgical complications by interfering with visualization of the posterior capsule and capsulorhexis intraoperatively, and it disappears after the first day.

Ethics

Informed Consent: Obtained.

Peer-review: Externally peer reviewed.

Authorship Contributions

Concept: Ö.R.K., H.M., S.D., Ş.A., A.A.Y., E.K., Design: Ö.R.K., H.M., S.D., Ş.A., A.A.Y., E.K., Data Collection or Processing: Ö.R.K., H.M., S.D., Ş.A., A.A.Y., E.K., Analysis or Interpretation: Ö.R.K., H.M., S.D., Ş.A., A.A.Y., E.K., Literature Search: Ö.R.K., H.M., S.D., Ş.A., A.A.Y., E.K., Writing: Ö.R.K., H.M., S.D., Ş.A., A.A.Y., E.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. Jacobs DS, Cox TA, Wagoner MD, Ariyasu RG, Karp CL; American Academy of Ophthalmology; Ophthalmic Technology Assessment Committee Anterior Segment Panel. Capsule staining as an adjunct to cataract surgery: a report from the American Academy of Ophthalmology. Ophthalmology. 2006;113:707-713.
2. Sharma N, Bhartiya P, Sinha R, Vajpayee RB. Trypan blue assisted phacoemulsification by residents in training. Clin Exp Ophthalmol. 2002;30:386-387.
3. Bacsal KME, Chee SP. Trypan blue-associated retinal toxicity post complicated cataract surgery. Eye (Lond). 2006;20:1310-1311.
4. Chowdhury PK, Raj SM, Vasavada AR. Inadvertent staining of the vitreous with trypan blue. J Cataract Refract Surg. 2004;30:274-276.
5. Gaur A, Kayarkar VV. Inadvertent vitreous staining. J Cataract Refract Surg. 2005;31:649.
6. Birchall W, Raynor MK, Turner GS. Inadvertent staining of the posterior lens capsule with trypan blue dye during phacoemulsification. Arch Ophthalmol. 2001;119:1082-1083.
7. Kheirkhah A, Nazari R, Roohipour R. Inadvertent vitreous staining with trypan blue in pseudoexfoliation syndrome. Arch Ophthalmol. 2010;128:1372-1373.
8. Marques FF, Soccol FM, Marques DMV, Rehder JRCL. [Unintentional staining of lens posterior capsule with trypan blue during extracapsular cataract extraction: case report]. Arq Bras Oftalmol. 2006;69:111-113.
9. Pelit A. Unintentional staining of the posterior lens capsule with trypan blue dye during phacoemulsification: case report. Int Ophthalmol. 2012;32:187-189.
10. Burkholder BM, Srikumaran D, Nanji A, Lee B, Weinberg RS. Inadvertent trypan blue posterior capsule staining during cataract surgery. Am J Ophthalmol. 2013;155:625-628.
11. Wang BZ, Forward H, Farber L, Chiu D, Chandra A. Surgical blues: vitreous staining with trypan blue during cataract surgery. Clin Exp Ophthalmol. 2014;42:788-789.

12. Marques DMV, Marques FF, Osher RH. Three-step technique for staining the anterior lens capsule with indocyanine green or trypan blue. J Cataract Refract Surg. 2004;30:13-16.
13. Khokhar S, Pangtey MS, Panda A, Sethi HS. Painting technique for staining the anterior lens capsule. J Cataract Refract Surg. 2003;29:435-436.
14. Kayikiçioğlu O, Erakgün T, Güler C. Trypan blue mixed with sodium hyaluronate for capsulorhexis. J Cataract Refract Surg. 2001;27:970.
15. Kwok AKH, Yeung CK, Lai TYY, Chan KP, Pang CP. Effects of trypan blue on cell viability and gene expression in human retinal pigment epithelial cells. Br J Ophthalmol. 2004;88:1590-1594.
16. Rezai KA, Farrokh-Siar L, Gasyna EM, Ernest JT. Trypan blue induces apoptosis in human retinal pigment epithelial cells. Am J Ophthalmol. 2004;138:492-495.

DOI: 10.4274/tjo.galenos.2020.86300
Turk J Ophthalmol 2020;50:313-316

Case Report

Optical Coherence Tomography Angiography Findings in Long-Term Follow-up of Leber's Hereditary Optic Neuropathy: Report of Two Cases

Pınar Bingöl Kızıltunç*, Feyza Tüntaş Bilen**, Huban Atilla*

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

Abstract

Leber's hereditary optic neuropathy (LHON) is thought to be a neurovascular disease due to presence of vascular changes in asymptomatic patients. Here we present 2 patients in whom optical coherence tomography angiography (OCTA) imaging demonstrated capillary drop-out areas and decreased radial peripapillary capillary (RPC) density in the quadrants that had thinner retinal nerve fiber layer (RNFL) in OCT images. Progressive decrease in RNFL and RPC density were shown in each patient at month 12 and 30 of follow-up. Following up patients with OCTA imaging in the future will provide insight into the pathogenesis and prognosis of LHON.

Keywords: Leber's hereditary optic neuropathy, optical coherence tomography, optical coherence tomography angiography, retinal nerve fiber layer

Introduction

Leber's hereditary optic neuropathy (LHON) is a maternally inherited mitochondrial DNA-related disease.[1] Optic disc hyperemia, vascular tortuosity, and peripapillary telangiectatic vessels are characteristic findings in asymptomatic patients and patients with early-stage disease. Increased vessel tortuosity and capillary size at the optic disc suggest that the disease is a neurovascular disorder.[2] Recently, the development of optical coherence tomography angiography (OCTA) has enabled noninvasive evaluation of the ocular microvasculature. With this method, the peripapillary retinal and vascular circulation can be evaluated three-dimensionally. Evaluation of vascular changes in LHON using OCTA may help us to understand the pathophysiology of the disease, assess disease progression, and monitor the efficacy of treatment. Here we presented the optical coherence tomography (OCT) and OCTA findings of 2 patients with LHON.

Case Report

Case 1

A 28-year-old man with no relevant history was referred to our clinic with loss of vision in both eyes, starting first in his right eye and 1 week later in the left eye. His best corrected visual acuity (BCVA) was counting fingers at 25 cm in the right eye and 1/20 in the left eye. Optic discs were pale in both eyes. OCT showed thinner retinal nerve fiber layer (RNFL) in all quadrants in the right eye and consistent with the OCT findings, there were areas of capillary drop-out and decreased radial

Address for Correspondence: Pınar Bingöl Kızıltunç, M.D., Ankara University Faculty of Medicine, Department of Ophthalmology, Ankara, Turkey
Phone:+90 544 821 41 53 E-mail: pinarbingol84@gmail.com **ORCID-ID:** orcid.org/0000-0003-4394-7926
Received: 29.10.2019 **Accepted:** 07.04.2020

Cite this article as: Bingöl Kızıltunç P, Tüntaş Bilen F, Atilla H. Optical Coherence Tomography Angiography Findings in Long-Term Follow-up of Leber's Hereditary Optic Neuropathy: Report of Two Cases. Turk J Ophthalmol. 2020;50:313-316

peripapillary capillary (RPC) density in all quadrants on OCTA (AngioVue RTVue XR Avanti with AngioVue, OptoVue, Inc, Fremont, CA). The RNFL was thinner in the inferior and temporal quadrants and, similar to OCT findings, capillary drop-out areas and decreased RPC density were detected in the inferior and temporal quadrants in the left eye (Figure 1). Genetic testing confirmed the diagnosis with G11778A mutation. Idebenone treatment (900 mg/day) was given orally. Progressive decreases in RNFL and RPC density were shown at month 12 of follow-up (Figure 1).

Case 2

An 8-year-old boy with family history of LHON in his maternal uncle was examined. Ophthalmologic examination revealed normal findings. Although the family was informed, they did not consent to genetic evaluation. Two years later, the patient presented with loss of vision in his left eye. BCVA was 20/20 in the right eye and counting fingers at 1 meter in the left eye. Optic discs were normal in the right eye and pale temporally in the left eye. He was diagnosed as having LHON with G11778A mutation and idebenone (450 mg/day) treatment was given orally. At 6-month follow-up, the right eye was also affected. Visual acuities were 2/20 in the right eye and counting fingers at 1 m in the left eye, and both optic discs were pale temporally. The patient was followed up with idebenone therapy OCT and OCTA imaging for 30 months. Visual acuity was counting fingers at 1 m and there was optic disc pallor in the both eyes at the last visit. Although his right eye was not affected in the first visit, drop-out areas were determined by OCTA imaging. Decreased RNFL thickness and RPC density and increased capillary drop-out were shown by OCT and OCTA in the follow-up period (Figure 2).

Discussion

Since OCTA imaging is a noninvasive and easy method to evaluate vascular structures, different studies evaluated vascular changes in LHON patients and demonstrated RPC defects.[3,4] Balducci et al.[4] reported decreases in RPC mostly in the temporal region in patients at different stages.

Our case reports have importance for evaluating RPC density and capillary drop-out areas in LHON over long-term follow-up and we were also able to compare OCTA findings in patient 2 before and after involvement. In both cases, in parallel to the decrease in RNFL, RPC density decreased and peripapillary capillary drop-out areas increased.

In our first case, both eyes were affected when the patient presented to our clinic. A decrease in RNFL was observed in all quadrants in the right eye, which was involved first, while the left eye was affected later and the decrease in RNFL was shown

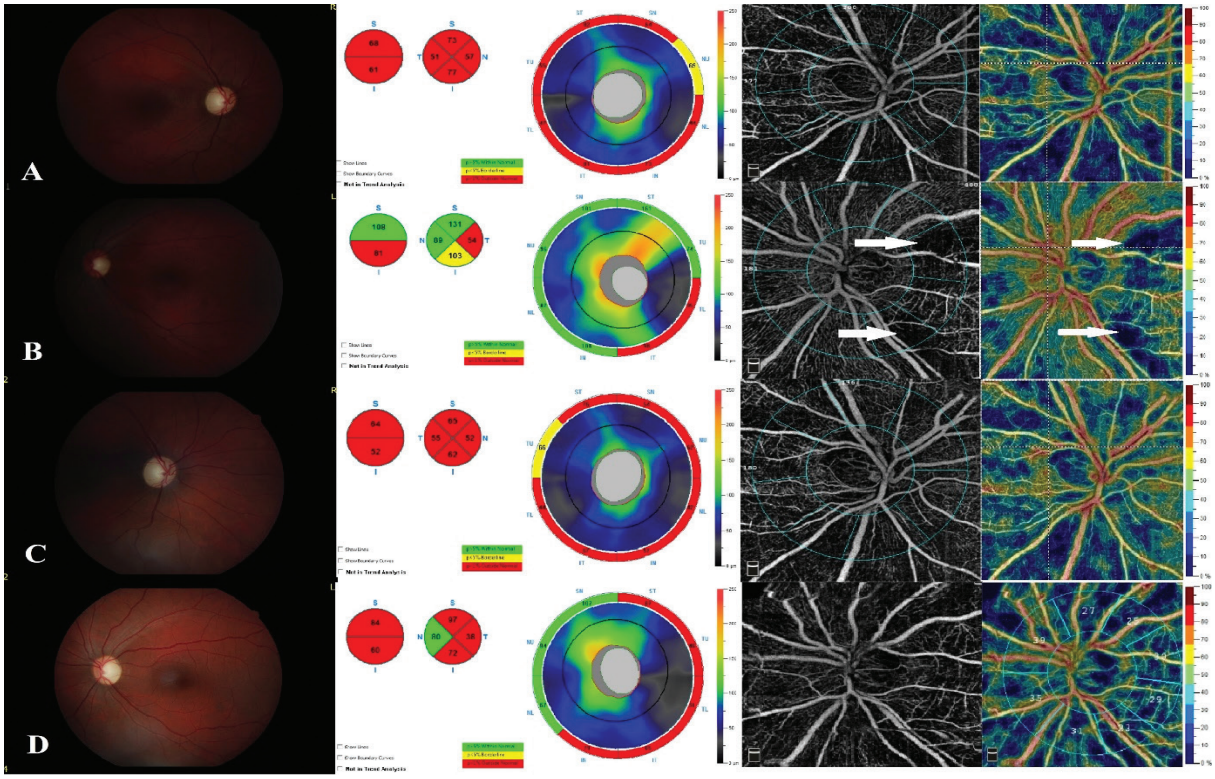


Figure 1. Fundus photos, optic disc OCT and OCTA findings of patient 1. A, B) Findings of the right (A) and left (B) eye at initial examination. From left to right: Optic disc pallor is seen in fundus photograph; decrease in thickness of RNFL on OCT; peripapillary capillary drop-out areas (arrows) and decrease in RPC density on OCTA. C, D) Findings of right (C) and left (D) eye at 12-month follow-up examination. From left to right: optic disc pallor is seen in fundus photograph; marked decrease in thickness of RNFL on OCT; increased peripapillary capillary drop-out areas and marked decrease in RPC density on OCTA

RNFL: Retinal nerve fiber layer, OCT: Optical coherence tomography, OCTA: Optical coherence tomography angiography, RPC: Radial peripapillary capillary

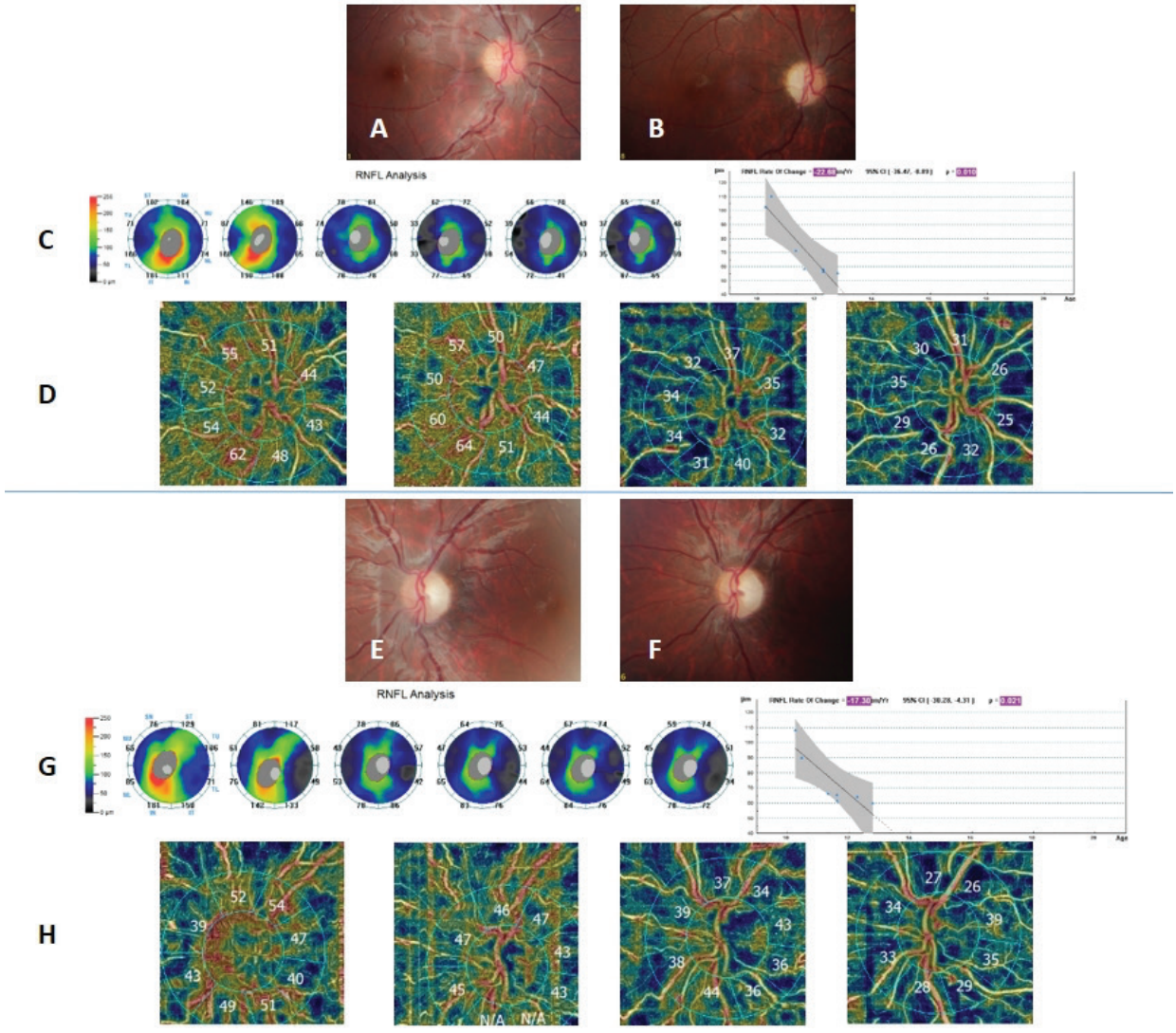


Figure 2. Progressive changes in the optic disc during a 30-month follow-up period in both eyes of patient 2. A) Normal optic disc findings of the right eye in the first examination; B) Optic disc pallor in the right eye in the last examination; C) Progressive decrease in the RNFL in the right eye on OCT; D) Progressive decrease in RPC density in the right eye on OCTA. E,F) Optic disc pallor in the first and last examination in the left eye; G) Progressive decrease in RNFL in the left eye on OCT; H) Progressive decrease in RPC density in the left eye on OCTA

RNFL: Retinal nerve fiber layer, OCT: Optical coherence tomography, OCTA: Optical coherence tomography angiography, RPC: Radial peripapillary capillary

only in the temporal and inferior quadrants. Decrease in RPC density was correlated with loss of RNFL. RPC density was decreased in all quadrants in the right eye and in the temporal and inferior quadrant in the left eye in the first evaluation. In the early stage of LHON, it is known that the smaller caliber fibers of papillomacular bundle are lost, and then loss of fibers progresses and all fibers of the optic nerve can be affected.[5,6] In accordance with this knowledge, loss of RNFL and RPC density were detected in the inferior and temporal quadrant in the left eye in the early stage of disease. In the follow-up period, both RNFL and RPC density decreased progressively in all quadrants.

In the second case, we were able to evaluate the OCT and OCTA findings of the right eye before involvement and we detected drop-out areas. Before visual acuity decreased in the right eye, we showed that there were drop-out areas. This finding is important in terms of demonstrating OCTA changes in asymptomatic carriers. In the acute phase of the right eye, RNFL thickness increased and visual acuity decreased without any change in RPC density. Decrease in RPC density followed the decrease of RNFL. In LHON, it has been shown that RNFL thickness increases in the early acute phase (within 12 weeks of symptom onset) and decreases gradually in the late acute (12 to

24 weeks after symptom onset) and chronic (24 weeks or more after symptom onset) phases.[7] The increase in thickness can be explained by impaired axoplasmic transport and a compensatory increase of mitochondrial biogenesis. It is followed by progressive thinning as atrophy develops in the later stages. Decrease in RPC density can be associated with the thinning of RNFL. When the RNFL get thinner, the required metabolic activity is reduced and this can explain the progressive decrease of RPC density in LHON as the disease progresses and RNFL get thinner.

In the follow-up period of our patients, although the decrease in RPC density progressed, visual acuity was stable. This may be explained by macular microvascular changes. In LHON patients, not only the optic disc but also macular microvascular structures are affected. Borrelli et al.[8] determined that the severity of visual loss was associated with the density of macular superficial capillary plexus. A shortcoming of these case reports is that macular microvascular changes were not evaluated.

In conclusion, OCTA imaging is thought to be an important test for evaluating changes in LHON patients and asymptomatic carriers. In the future, following patients with treatment will help us to gain insight into the pathogenesis and prognosis of LHON.

Ethics

Informed Consent: Obtained.

Peer-review: Externally and internally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: H.A., Consept: H.A., Design: H.A., Data Collection or Processing: P.B.K., F.T.B., Analysis or Interpretation: P.B.K., H.A., F.T.B., Literature Search: P.B.K., F.T.B., Writing: P.B.K., F.T.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. Carelli V, Ross-Cisneros FN, Sadun AA. Mitochondrial dysfunction as a cause of optic neuropathies. Prog Retin Eye Res. 2004;23:53-89.
2. Nikoskelainen E, Hoyt WF, Nummelin K. Ophthalmoscopic findings in Leber's hereditary optic neuropathy. I. Fundus findings in asymptomatic family members. Arch Ophthalmol. 1982;100:1597-1602.
3. De Rojas JO, Rasool N, Chen RWS, Horowitz J, Odel JG. Optical coherence tomography angiography in Leber hereditary optic neuropathy. Neurology. 2016;87: 2065-2066.
4. Balducci N, Cascavilla ML, Ciardella A, La Morgia C, Triolo G, Parisi V, Bandello F, Sadun AA, Carelli V, Barboni P. Peripapillary vessel density changes in Leber's hereditary optic neuropathy: a new biomarker. Clin Exp Ophthalmol. 2018;46:1055-1062.
5. Sadun AA, Win PH, Ross-Cisneros FN, Walker SO, Carelli V. Leber's hereditary optic neuropathy differentially affects smaller axons in the optic nerve. Trans Am Ophthalmol Soc. 2000;98:223-232.
6. Barboni P, Carbonelli M, Savini G, Ramos Cdo V, Carta A, Berezovsky A, Salomao SR, Carelli V, Sadun AA. Natural history of Leber's hereditary optic neuropathy: longitudinal analysis of the retinal nerve fiber layer by optical coherence tomography. Ophthalmology. 2010;117:623-627.
7. Hedges TR, Gobuty M, Manfready RA, Erlich-Malona N, Monaco C, Mendoza-Santiesteban CE. The Optical Coherence Tomographic Profile of Leber Hereditary Optic Neuropathy. Neuroophthalmology. 2016;40:107-112.
8. Borrelli E, Balasubramanian S, Triolo G, Barboni P, Sadda SR, Sadun AA. Topographic Macular Microvascular Changes and Correlation With Visual Loss in Chronic Leber Hereditary Optic Neuropathy. Am J Ophthalmol. 2018;192:217-228.

DOI: 10.4274/tjo.galenos.2020.36360
Turk J Ophthalmol 2020;50:317-320

Case Report

Intracranial Mass Lesion in a Patient Being Followed up for Amblyopia

Ali Mert Koçer, Bayazıt İlhan, Anıl Güngör

Ulucanlar Ophthalmology Trainig and Research Hospital, Clinic of Ophthalmology, Ankara, Turkey

Abstract

A 12-year-old boy being followed up for amblyopia presented to our hospital with visual disturbance in the left eye. The patient's best corrected visual acuity on Snellen chart was 1.0 in the right eye and 0.3 in the left eye. Increased horizontal cup-to-disc ratio was detected on dilated fundus examination. Retinal nerve fiber layer measurement showed diffuse nerve fiber loss and visual field test showed bitemporal hemianopsia. Magnetic resonance imaging revealed a lesion that filled and widened the sella and suprasellar cistern and compressed the optic chiasm. The patient was operated with transcranial approach. The pathologic examination revealed craniopharyngioma.

Keywords: Amblyopia, craniopharyngioma, hemianopsia

Introduction

Amblyopia is poor best corrected visual acuity (BCVA) in one or both eyes due to low vision or abnormal binocular interaction without any detectable structural defect in the eye or visual pathways. Amblyopic vision loss can be corrected if treated at an early age. The most important factors in the development of amblyopia are the severity, timing of onset, and duration of visual impairment. Blurred vision is much more likely to develop into amblyopia in young children. Although variable, the risk of amblyopia is generally higher in the first 2-3 years of life, and the risk is reported to continue until the age of 12.

Anisometropia and strabismus are among the most common causes of amblyopia.[1] Blurred vision caused by uncorrected refractive error appears to be the main factor that prevents the development of central vision in anisometropic amblyopia. Anisometropia is generally defined as a difference in spherical/cylindrical refractive errors of 1.5-2 diopters (D) or more and is more common in hyperopic eyes than in myopia.[2]

Craniopharyngioma is a benign tumor that develops from the remnant of Rathke's pouch and is located in the sellar/parasellar region.[3] It shows a bimodal age distribution, with patients usually diagnosed between the ages of 5 and 14 or after the age of 50.[4] Although these tumors are slow-growing and benign, they can cause serious symptoms due to their proximity to important anatomical structures such as the pituitary gland, hypothalamus, and optic chiasm. Clinical manifestations may include endocrine disorders such as hypothyroidism, impotence, and amenorrhea; visual symptoms such as optic atrophy, visual field defect, and decreased vision; and symptoms related to increased intracranial pressure, such as headache, nausea, and vomiting.[5,6] The most frequent ocular signs are bitemporal hemianopsia and optic atrophy. Diagnosis of craniopharyngioma is based on neurological, visual, and endocrine symptoms and the

Address for Correspondence: Ali Mert Koçer, M.D., Ulucanlar Ophthalmology Trainig and Research Hospital, Clinic of Ophthalmology, Ankara, Turkey
Phone:+90 506 222 85 55 E-mail: alimertkocer@gmail.com **ORCID-ID:** orcid.org/0000-0001-6847-1560
Received: 14.12.2019 **Accepted:** 11.05.2020

Cite this article as: Koçer AM, İlhan B, Güngör A. Intracranial Mass Lesion in a Patient Being Followed up for Amblyopia. Turk J Ophthalmol. 2020;50:317-320

appearance of a calcific solid/cystic lesion on radiologic imaging. The diagnosis is confirmed by pathologic examination.

In this article, we present a patient under follow-up for amblyopia who was diagnosed as having craniopharyngioma after further examination in our clinic.

Case Report

A 12-year-old boy with no disease, history of trauma, or systemic symptoms presented to our hospital with low vision in his left eye. It was learned that the patient was under follow-up at another center for left amblyopia and had been treated with right eye closure for a period of time. His family history included no consanguineous marriage or illnesses that cause vision impairment. Written informed consent was obtained from the patient for the examination and tests. Autorefractometer measurements showed a spherical refraction error of -0.25 D in the right eye and -1.5 D in the left eye. His Snellen BCVA was 1.0 in the right eye and 0.3 in the left eye. Intraocular pressure was measured as 15 mmHg in both eyes. No afferent pupillary defect was detected. Color vision in both eyes was evaluated as normal using the Ishihara color vision test. Anterior segment examination findings were normal. On dilated fundus examination, both posterior poles appeared normal, whereas bilateral optic disc pallor and increased horizontal cup-to-disc (C/D) ratio were observed (Figure 1). Retinal nerve fiber layer (RNFL) thickness measurement (Spectralis, Heidelberg Engineering, Heidelberg, Germany) revealed nerve fiber loss around both optic discs (Figure 2). The macula appeared normal in both eyes on optical coherence tomography (Spectralis, Heidelberg Engineering, Heidelberg, Germany). Bitemporal hemianopsia that was more prominent on the left side was observed in 24-2 visual field test (Humphrey Field Analyzer; Carl Zeiss Meditec, Dublin, CA) (Figure 3). Suspecting the patient may have an intracranial lesion compressing the optic chiasm, cranial and pituitary magnetic resonance imaging (MRI) was requested. MRI demonstrated a nonenhancing lesion 24 x 23 x 32 mm in size filling and widening the sella and suprasellar cistern and compressing the optic chiasm. On T1- and T2-weighted images, the lower half of the mass was heterogeneous and the upper half was hypointense (Figure 4). Craniopharyngioma and hemorrhagic complicated adenoma were considered in the radiologic differential diagnosis. The patient underwent surgery via transcranial approach in the neurosurgery department. On pathologic examination of the specimen, diffuse hyalinization, calcification, xanthogranulomatous debris, and several foci of keratin adjacent to the adenohypophysis were observed and the lesion was diagnosed as craniopharyngioma. The patient was evaluated with visual field test until postoperative month 6 and no changes were detected in visual field or BCVA.

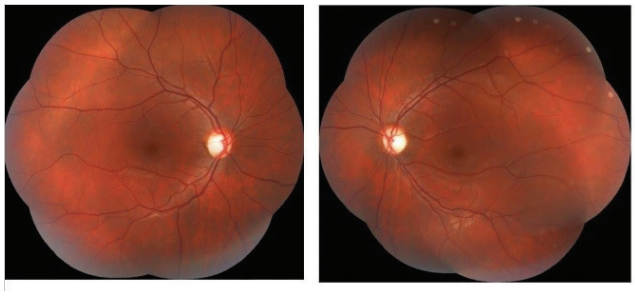


Figure 1. Bilateral fundus photographs show a normal macula and increased cup-to-disc ratio in the optic disc

Discussion

Amblyopia is unilateral or bilateral low best corrected visual acuity (BCVA) caused by poor vision or abnormal binocular

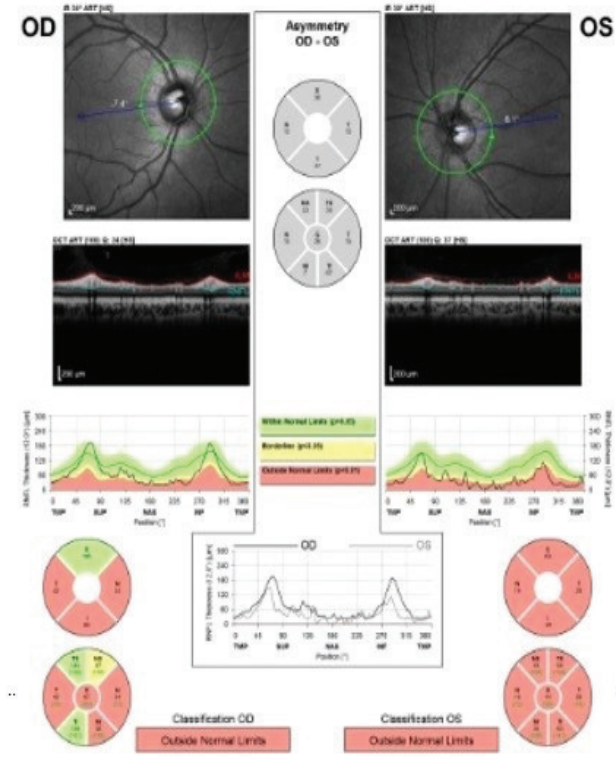


Figure 2. Retinal nerve fiber layer thickness measurement demonstrated diffuse retinal nerve fiber loss in both eyes

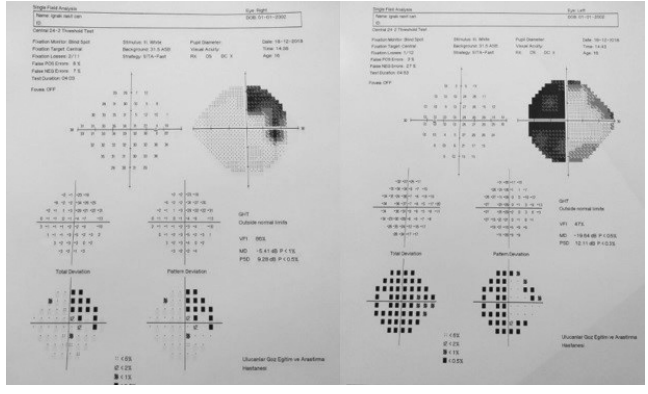


Figure 3. The 24-2 visual field test revealed visual field defect that was more prominent in the left eye and bitemporal hemianopsia

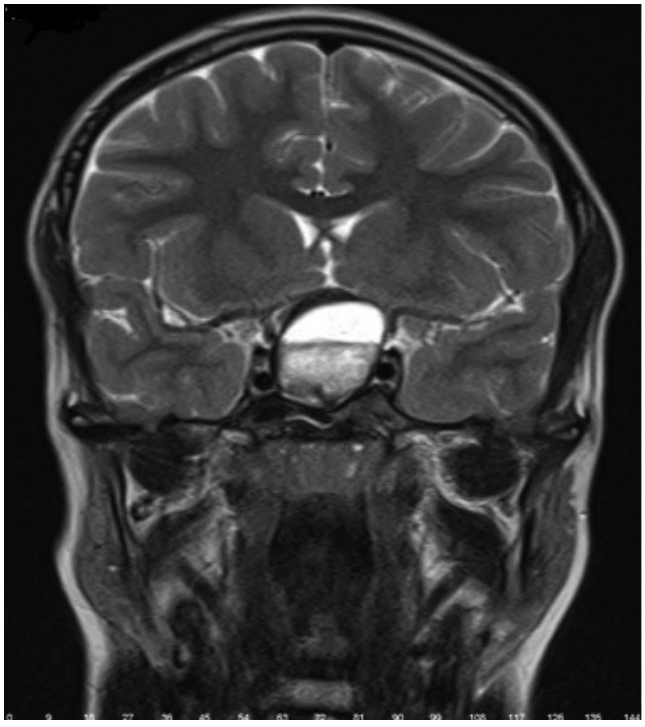


Figure 4. In the cranial magnetic resonance imaging coronal slice, a sellar/suprasellar intracranial mass was observed

interaction in the absence of a structural defect in the eye or visual pathways.[7] Excluding organic pathologies that can lead to optic neuropathy, such as intracranial masses, before making a diagnosis of amblyopia is critical in the follow-up and treatment approach. In the pediatric population, the most common intracranial masses include astrocytoma, ependymoma, and medullablastoma. In addition, considering that in many studies the most common symptom of craniopharyngioma was blurred vision and subsequent decrease in visual acuity, craniopharyngioma seems to be a pathology that should be considered in the differential diagnosis of intracranial masses.[8,9] Especially in patients with vision loss accompanied by symptoms such as headache, nausea/vomiting, growth retardation, delay in the development of secondary sex characteristics, polydipsia, and polyuria, it is important to perform a systemic examination and to consider an organic pathology as the cause of low vision. If there are no accompanying systemic symptoms, as in our patient, a careful fundus examination and the use of auxiliary imaging methods when necessary can provide important information about the cause of low vision. Although craniopharyngioma is a benign tumor, diagnosis and treatment are important due to its close proximity to important anatomical structures. These tumors are most commonly located in the sellar/parasellar region.[10] The tumor typically places pressure on the optic chiasm from the anterior and posterior, generally resulting in bitemporal hemianopsia visual field defect. In some cases, homonymous hemianopsia can also be seen.[11] Pituitary tumor, suprasellar aneurysm, third ventricular glioma, and tuberculum sellae meningioma are among the pathologies that cause bitemporal hemianopsia visual field defect and should be included in the differential diagnosis of craniopharyngioma.

The surgical treatment of craniopharyngioma involves resection of the tumor via a transcranial or transsphenoidal approach while preserving the optic and hypothalamic structures. Total resection or subtotal resection with or without radiotherapy is performed as appropriate according to parameters such as tumor size, growth pattern, and hypothalamus involvement.[12,13] Initial symptoms are visual in more than half of patients, and about 41-48% of patients may have some amount of visual gain after surgery.[14] Poor prognostic factors in postoperative visual gain are severe vision loss and prechiasmatic tumor location.[15] Although the transsphenoidal surgical approach is associated with better visual prognosis, it is only effective in intrasellar tumors. In addition, suprasellar positioning is seen in a larger proportion of craniopharyngioma patients.

Undergoing surgery via transcranial approach and having very low preoperative visual acuity seem to be poor prognostic factors in our case. Our patient showed no changes in visual field or BCVA in postoperative evaluations, demonstrating the importance of early diagnosis of intracranial masses causing optic neuropathy in terms of postoperative visual recovery. We believe that early diagnosis may have been possible in our patient with the detection of temporal optic disc pallor and increased C/D ratio, but the diagnosis was delayed because these changes were not detected in the early period. Furthermore, it should not be forgotten that patients diagnosed with intracranial mass may exhibit some amount of anisometropic amblyopia, as in the present case.

In conclusion, because diagnosis occurs later in children, visual morbidity is greater, and visual acuity generally remains low after treatment at more advanced stages, early diagnosis of tumors is important to minimize visual sequelae. The most important steps for early diagnosis are a detailed history, careful fundus examination, and visual field testing when necessary. In children with suspicious examination findings and inadequate cooperation, we recommend using additional tests before a diagnosis of amblyopia is made.

Ethics

Informed Consent: Obtained.

Peer-review: Externally peer reviewed.

Authorship Contributions

Concept: B.İ., Design: B.İ., Data Collection or Processing: A.G., Analysis or Interpretation: A.M.K., Literature Search: A.M.K., Writing: A.M.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. Atilla H. Amblyopia and treatment. Turkiye Klinikleri J Ophthalmol. 2010;3:1-8.
2. Koçak G, Duranoğlu Y. Amblyopia and treatment. Turk J Ophthalmol. 2014;44:228-236.
3. Garre ML, Cama A. Craniopharyngioma: modern concepts in pathogenesis and treatment. Curr Opin Pediatr. 2007;19:471-479.
4. Mollá E, Martí-Bonmatí L, Revert A, Arana E, Menor F, Dosdá R, Poyatos C. Craniopharyngiomas: identification of different semiological patterns with MRI. Eur Radiol. 2002;12:1829-1836.
5. Jagannathan J, Dumont AS, Jane JA Jr, Laws ER Jr. Pediatric sellar tumors: diagnostic procedures and management. Neurosurg Focus. 2005;18:6.
6. Karavitaki N, Cudlip S, Adams CB, Wass JA. Craniopharyngiomas. Endocr Rev. 2006;27:371-397.
7. DeSantis D. Amblyopia. Pediatr Clin North Am. 2014;61:505-518.
8. Adamson TE, Wiestler OD, Kleihues P, Yaşargil MG. Correlation of clinical and pathological features in surgically treated craniopharyngiomas. J Neurosurg. 1990;73:12-17.
9. Kennedy HB, Smith RJ. Eye signs in craniopharyngioma. Br J Ophthalmol. 1975;59:689-695.
10. Karavitaki N, Brufani C, Warner JT, Adams CB, Richards P, Ansorge O, Shine B, Turner HE, Wass JA. Craniopharyngiomas in children and adults: systematic analysis of 121 cases with long-term follow-up. Clin Endocrinol (Oxf). 2005;62:397-409.
11. Chen C, Okera S, Davies PE, Selva D, Crompton JL. Craniopharyngioma: a review of long-term visual outcome. Clin Exp Ophthalmol. 2003;31:220-228.
12. Spoudeas HA, Saran F, Pizer B. A multimodality approach to the treatment of craniopharyngiomas avoiding hypothalamic morbidity: a UK perspective. J Pediatr Endocrinol Metab. 2006;19(Suppl 1):447-451.
13. Puget S, Garnett M, Wray A, Grill J, Habrand JL, Bodaert N, Zerah M, Bezerra M, Renier D, Pierre-Kahn A, Sainte-Rose C. Pediatric craniopharyngiomas: classification and treatment according to the degree of hypothalamic involvement. J Neurosurg. 2007;106(1 Suppl):3-12.
14. Elliott RE, Jane JA Jr, Wisoff JH. Surgical management of craniopharyngiomas in children: meta-analysis and comparison of transcranial and transsphenoidal approaches. Neurosurgery. 2011;69:630-643.
15. Steno J, Bízik I, Steno A, Matejcík V. Craniopharyngiomas in children: how radical should the surgeon be? Childs Nerv Syst. 2011;27:41-54.

DOI: 10.4274/tjo.galenos.2020.58638
Turk J Ophthalmol 2020;50:321-323

Case Report

Multimodal Imaging of Isolated Foveal Hypoplasia: A Case Report

Cumali Değirmenci, Filiz Afrashi, Serhad Nalçacı, Onur Furundaoturan

Ege University Faculty of Medicine, Department of Ophthalmology, İzmir, Turkey

Abstract

Foveal hypoplasia is characterized by the lack of development of a normal fovea. It may be isolated or may occur secondary to ocular conditions. Optical coherence tomography (OCT), fluorescein angiography, fundus autofluorescence, and OCT angiography may be used for diagnosis. In this case report, we present a patient with foveal hypoplasia that was diagnosed with multimodal imaging.

Keywords: Albinism, foveal hypoplasia, optical coherence tomography, optical coherence tomography angiography

Introduction

Foveal hypoplasia is defined as the underdevelopment of the fovea and is characterized by nystagmus and low visual acuity. It is usually associated with optic nerve hypoplasia, familial exudative vitreoretinopathy (FEVR), Stickler syndrome, albinism, aniridia, and microphthalmia. It may also be isolated with no clear etiology. The visual acuity of patients with foveal hypoplasia varies from 20/20 to 20/50 and they have no foveal depression or pigmentation. Some authors have reported that foveal hypoplasia is related to mutations of genes such as P*AX6*, *OCA2,* and *GPR143* that are associated with albinism.[1,2]

The normal fovea is observed to have a central depression with loss of the inner retinal layer and lengthening of the outer segments of the photoreceptors on optical coherence tomography (OCT). Additionally, OCT angiography (OCTA) revealed that the fovea has a central avascular black gap. A staging system based on OCT was developed for patients with foveal hypoplasia.[3,4] The current study presents the multimodal imaging of a patient with foveal hypoplasia.

Case Report

A 19-year-old man presented to the clinic with complaints of non-progressive low visual acuity. The patient had no previous major illnesses and did not report any similar family history. On ophthalmic examination, his best corrected visual acuity (BCVA) was 0.40 logMAR with +5.50-1.50x135 in the right eye and 0.10 logMAR with +5.50-2.00x110 in the left eye. There was no manifest or latent strabismus, but latent nystagmus was found in both eyes. Examination of the anterior segment did not show any indicators of ocular albinism such as transillumination, and iris pigmentation was normal. Funduscopic examination revealed a normal optic disc and vessels but a lack of foveal pigmentation (Figure 1).

OCT images showed no foveal depression in either eye with continuity of the inner retinal layers. The outer segments of the photoreceptors were not lengthened. Fluorescein angiography showed the foveal avascular zone was absent. OCTA confirmed the lack of a foveal avascular zone along with absence of the central black gap. Fundus autofluorescence images also showed no hypoautofluorescence in the corresponding fovea (Figure 2, 3).

Address for Correspondence: Cumali Değirmenci, M.D., Ege University Faculty of Medicine, Department of Ophthalmology, İzmir, Turkey
Phone:+90 506 859 96 44 E-mail: cudegirmenci@yahoo.com **ORCID-ID:** orcid.org/0000-0002-8268-536X
Received: 19.03.2020 **Accepted:** 11.05.2020

Cite this article as: Değirmenci C, Afrashi F, Nalçacı S, Furundaoturan O. Multimodal Imaging of Isolated Foveal Hypoplasia: A Case Report. Turk J Ophthalmol. 2020;50:321-323

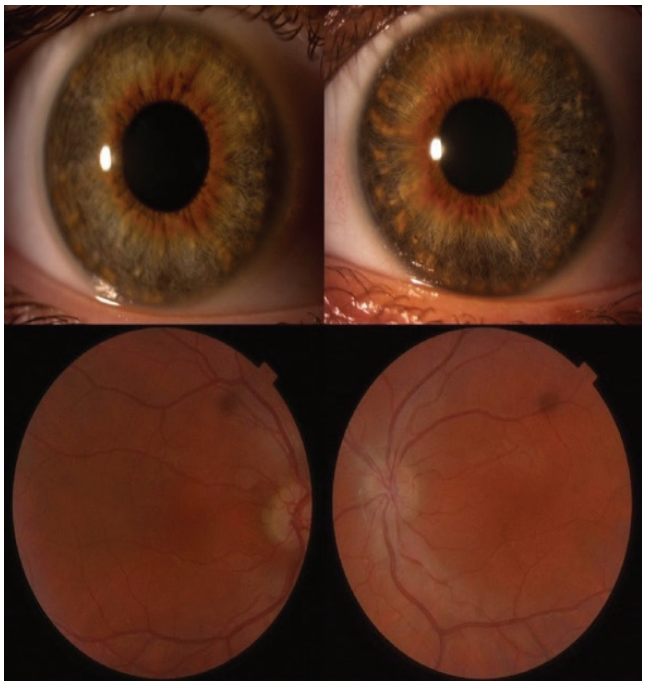


Figure 1. Normal anterior segment photos of the patient without any loss of pigmentation or iris transillumination (upper panels) and fundus images of the patient without foveal reflex (lower panels)

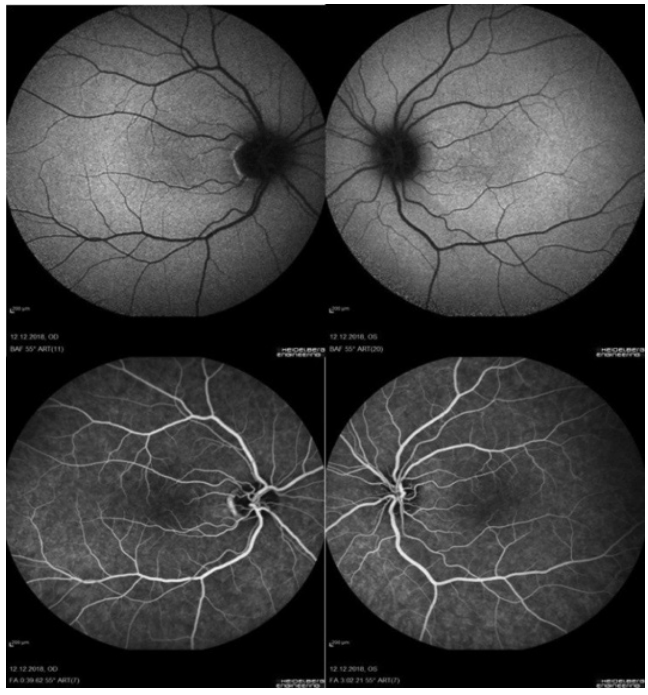


Figure 2. Fundus autofluorescence demonstrated a lack of foveal hypoautofluorescence in the central macula (upper panels) and fundus fluorescein angiography images did not show foveal avascular zone (lower panels)

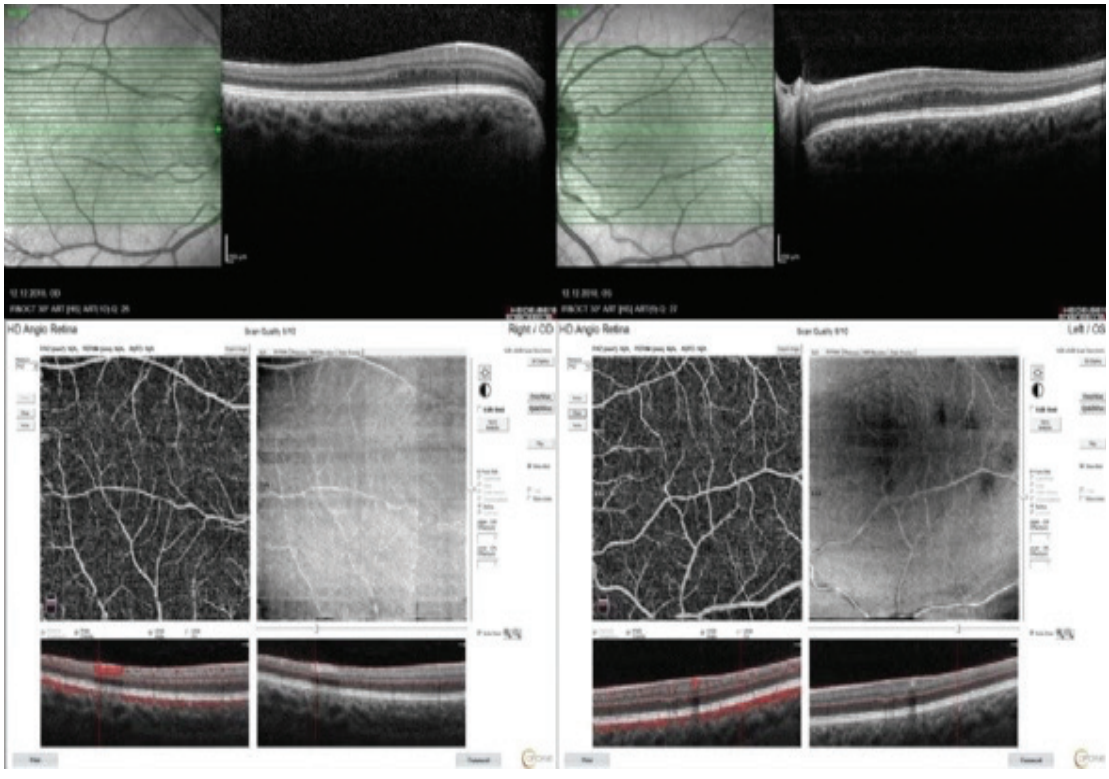


Figure 3. Optical coherence tomography showed no foveal depression (upper panels) and optical coherence tomography angiography images revealed the lack of foveal avascular zone (lower panels)

The patient was informed about this publication and written consent was obtained to publish collected images.

Discussion

In the current report, we present a patient with isolated foveal hypoplasia associated with an underdeveloped fovea and nystagmus without any etiology such as optic nerve hypoplasia, FEVR, Stickler syndrome, albinism, aniridia, microphthalmia, nanophthalmus, retinopathy of prematurity, incontinentia pigmenti, or achromatopsia.

Patients with foveal hypoplasia present with decreased visual acuity. Thomas et al.[2] proposed a grading system for foveal hypoplasia to predict the prognosis of visual acuity based on OCT scans. The authors suggested 3 key points for the arrest of foveal development, including incursion of the plexiform layer to the posterior of the foveola, partial displacement of the inner retinal layers, and lengthening of the outer segment of photoreceptors. In the current case, the patient had no foveal pit or lengthening of the outer segment of the photoreceptors; both of which correspond to the worst prognosis. Also, outer nuclear layer widening was not observed. Based on these findings, the patient had grade 4 foveal hypoplasia. However, the BCVA of the patient was 0.4 logMAR in the right eye and 0.1 logMAR in the left eye. It is possible that structural properties of the fovea and visual acuity may not be correlated; further investigations are needed to better understand this.[3]

Fluorescein angiography or fundus autofluorescence are techniques used to establish the lack of the foveal avascular zone and foveal hypoautofluorescence. OCTA is an easy, rapid, and noninvasive method for imaging the retinal microvasculature and can reveal the lack of foveal avascular zone in the superficial and deep capillary layers in foveal hypoplasia.[5,6,7] In the current case, the patient showed no foveal avascular zone in both eyes.

Although foveal hypoplasia can be determined and graded by OCT, different imaging techniques including fundus autofluorescence, fluorescein angiography, and OCTA can be used to perform further evaluation. It is recommended that patients with low visual acuity are evaluated with multimodal imaging methods.

Ethics

Informed Consent: Obtained.

Peer-review: Externally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: C.D., F.A., Consept: O.F., C.D., Design: C.D., F.A., S.N., Data Collection or Processing: O.F., C.D., Analysis or Interpretation: F.A., S.N., Literature Search: C.D., O.F., Writing: C.D.

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

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

References

1. Al-Saleh AA, Hellani A, Abu-Amero KK. Isolated foveal hypoplasia: report of a new case and detailed genetic investigation. Int Ophthalmol. 2011;31:117-120.
2. Thomas MG, Kumar A, Mohammad S, Proudlock FA, Engle EC, Andrews C, Chan WM, Thomas S, Gottlob I. Structural grading of foveal hypoplasia using spectral-domain optical coherence tomography a predictor of visual acuity? Ophthalmology. 2011;118:1653-1660.
3. Kirchner ID, Waldman CW, Sunness JS. A Series Of Five Patients With Foveal Hypoplasia Demonstrating Good Visual Acuity. Retin Cases Brief Rep. 2017;13:376-380.
4. Meyer CH, Lapolice DJ, Freedman SF. Foveal hypoplasia in oculocutaneous albinism demonstrated by optical coherence tomography. Am J Ophthalmol. 2002;133:409-410.
5. Sánchez-Vicente JL, Contreras-Díaz M, Llerena-Manzorro L, Rueda T, López-Herrero F, Molina-Socola FE, Muñoz-Morales A, Rodríguez de la Rúa-Franch E. Foveal Hypoplasia: Diagnosis Using Optical Coherence Tomography Angiography. Retin Cases Brief Rep. 2018;12:122-126.
6. Bazvand F, Karkhaneh R, Roohipoor R, Rajabi MB, Ebrahimiadib N, Davoudi S, Modjtahedi BS. Optical Coherence Tomography Angiography in Foveal Hypoplasia. Ophthalmic Surg Lasers Imaging Retina. 2016;47:1127-1131.
7. Pakzad-Vaezi K, Keane PA, Cardoso JN, Egan C, Tufail A. Optical coherence tomography angiography of foveal hypoplasia. Br J Ophthalmol. 2017;101:985-988.